Effective Health Care Program

Comparative Effectiveness Review
Number 28

Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA)

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10066-I

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AHRQ Publication No. 11-EHC039-EF
September 2011

This report is based on research conducted by the Duke Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10066-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Kemper AR, Coeytaux R, Sanders GD, Van Mater H, Williams JW, Gray RN, Irvine RJ, Kendrick A. Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA). Comparative Effectiveness Review No. 28. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 11-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA)

Structured Abstract

Objectives. To summarize the benefits and harms of disease-modifying antirheumatic drugs (DMARDs) compared to conventional treatment (non-steroidal anti-inflammatory drugs [NSAIDs] and/or intra-articular corticosteroids) with or without methotrexate, and of the various DMARDs compared to one another, in children with juvenile idiopathic arthritis (JIA); and to describe selected tools commonly used to measure clinical outcomes associated with JIA.

Data Sources. MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews. Additional studies were identified from the review of reference lists.

Review Methods. To evaluate efficacy, we included prospective trials that included a comparator and that lasted for at least 3 months. No comparator was required for reports of adverse events or of the clinical outcome measure tools.

Results. A total of 198 articles were included. There is some evidence that methotrexate is superior to conventional treatment (NSAIDs and/or intra-articular corticosteroids). Among children who have responded to a biologic DMARD, randomized discontinuation trials suggest that continued treatment decreases the risk of having a flare. Although these studies evaluated DMARDs with different mechanisms of action (abatacept, adalimumab, anakinra, etanercept, intravenous immunoglobulin, tocilizumab) and used varying comparators, followup periods, and descriptions of flare, the finding of a reduced risk of flare was precise and consistent. There are few direct comparisons of DMARDs, and insufficient evidence to determine if any specific drug or drug class has greater beneficial effects. Reported rates of adverse events are similar between DMARDs and placebo in nearly all published randomized controlled trials. This review identified 11 incident cases of cancer among several thousand children treated with one or more DMARD. The Childhood Health Assessment Questionnaire (CHAQ) was the most extensively evaluated instrument of those considered. While it demonstrated high reproducibility and internal consistency, it had only moderate correlations with indices of disease activity and quality of life, and poor to moderate responsiveness.

Conclusions. Few data are available to evaluate the comparative effectiveness of either specific DMARDs or general classes of DMARDs. However, based on the overall number, quality, and consistency of studies, there is moderate strength of evidence to support that DMARDs improve symptoms associated with JIA. Limited data suggest that short-term risk of cancer is low. Future trials are needed to evaluate the effectiveness of DMARDs against both conventional therapy and other DMARDs across categories of JIA, and registries are needed to better understand the risks of these drugs.

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Executive Summary

Background

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease in childhood, with an overall prevalence of 7 to 400 per 100,000 children. JIA is an important cause of chronic disease in childhood, with prevalence similar to type I diabetes mellitus. Several classification systems have been used over time to categorize the various categories of juvenile arthritis, including juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA), based upon clinical presentation and disease course. In 1995, the International League of Associations for Rheumatology (ILAR) proposed a new classification system, JIA, which consists of seven main categories. These categories are useful in examining potential differences in treatment response and prognosis. The main categories of JIA are:

- Systemic arthritis: Initial presentation includes spiking fever, rash, and arthritis; one-quarter of children who present in this way may have severe destructive disease.
- Oligoarthritis: Affects up to four joints within the first 6 months of illness; may be persistent (i.e., involving no more than four joints) or extended (i.e., involving more than four joints after the first 6 months of illness), and may be associated with uveitis.
- Rheumatoid-factor positive (RF+) polyarthritis: Affects five or more joints during the first 6 months of disease, and is more likely to result in destructive joint disease. May be associated with uveitis.
- Rheumatoid-factor negative (RF-) polyarthritis: Affects five or more joints during the first 6 months of disease. May be associated with uveitis.
- Enthesitis-related arthritis: May be associated with uveitis.
- Psoriatic arthritis: May be associated with uveitis.
- Undifferentiated: Arthritis lasting more than 6 weeks that does not meet the criteria for any of the above categories, or that meets the criteria for more than one category.

JIA can place a severe physical and psychological burden on affected children and can be a major stressor to their families. As is true for all chronic conditions in childhood, treatment of JIA may be enhanced through the use of a multidisciplinary team to address these issues. There is no cure for JIA, but over the past 25 years new therapies have provided great advances in treatment and symptom control. Previous treatments with nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen) and corticosteroids (systemic or intra-articular) were only partially effective in treating the symptoms of arthritis and reducing long-term complications (e.g., growth delay, erosive joint disease, persistently active disease, mortality). Treatment with the class of agents known as disease-modifying antirheumatic drugs (DMARDs) has become an increasingly important component of care because these drugs appear to lead to better disease control, with higher numbers of children achieving remission, and fewer children suffering long-term joint damage. DMARDs interfere with the making or working of immune cells that cause joint inflammation and are typically classified as either biologic drugs, which are created by biologic processes, or non-biologic drugs, which are manufactured chemically. In general, the non-biologic DMARDs are older. Most biologic DMARDs target specific components of the immune system (e.g., signaling or cell-surface molecules). One of these non-biologic DMARDs, methotrexate, whose exact mechanism is unknown, has been used for so long in the treatment of

JIA that it is often considered part of conventional treatment, along with NSAIDs and intra-articular corticosteroids.

Although there is significant optimism that treatment with the newer biologic DMARDs may increasingly lead to long-term disease remission, there are many unanswered questions about the safety of these drugs, especially for long-term use in children. For example, the U.S. Food and Drug Administration (FDA) recently placed a box warning on the entire class of biologic DMARDs targeting tumor necrosis factor (TNF) alpha, including etanercept, infliximab, and adalimumab, due to concerns about potential increased risk of malignancy, in particular lymphoma. There are also important questions about effectiveness, including the comparative effectiveness of DMARDs versus conventional treatment and the comparative effectiveness of the various DMARDs versus one another. Furthermore, it is possible that the effectiveness of these drugs varies by category of JIA. Understanding the circumstances in which a DMARD should be used, and which DMARD(s) should be selected, is challenging because JIA is heterogeneous across the various categories. A clear synthesis of the available evidence is needed, to help clinicians provide care for children with JIA, and to identify the important gaps in the scientific literature.

Juvenile arthritis has a broad impact on a child's physical and mental health. Developing instruments that accurately assess the effect of JIA on health and well-being is critical to enable us to assess the overall impact of the disease and to quantify the efficacy of treatments. The heterogeneity of disease severity, the broad age range of affected individuals, and fluctuations in the natural history of the disease complicate the measurement of disease activity and treatment effects in children with JIA. To provide the most accurate assessment of treatment effects we depend on the performance characteristics (e.g., sensitivity, specificity, responsiveness to change) of the outcomes measures reported in the scientific literature. Multiple instruments have been developed or adapted to assess severity of disease, disability, and quality of life in JIA. Understanding the reliability, validity, and responsiveness of these instruments will facilitate interpretation of clinical trial data.

This comparative effectiveness review summarizes the evidence on the benefits and harms of DMARDs compared to conventional treatment (NSAIDs and/or intra-articular corticosteroids) with or without methotrexate, and of the various DMARDs compared to one another, in children with JIA. In addition, this review summarizes the usefulness of selected tools commonly used to measure clinical outcomes associated with JIA.

Key questions addressed are:

Key Question 1. In children[a] with JIA,[b] does treatment with DMARDs,[c] compared to conventional treatment (i.e., NSAIDs or corticosteroids) with or without methotrexate,[d] improve laboratory measures of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

[a]"Children" are defined as individuals aged 18 years or younger.
[b]"JIA" includes any category of any severity of the following:

- JIA according to the International League of Associations for Rheumatology (ILAR) criteria;
- Juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition; or
- Juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.

[c]DMARDs evaluated are: abatacept, adalimumab, anakinra, canakinumab, etanercept, infliximab, intravenous immunoglobulin (IVIG), rilonacept, rituximab, and tocilizumab (biologic DMARDs); and azathioprine, cyclosporine A, penicillamine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus (FK506), and thalidomide (non-biologic DMARDs).
[d]Conventional treatments evaluated are: betamethasone, triamcinolone acetonide, triamcinolone hexacetonide, celecoxib, etodolac, ibuprofen, indomethacin, meloxicam, naproxen, oxaprozin, and tolmetin.

Key Question 2. In children with JIA, what are the comparative effects of DMARDs[e] on laboratory markers of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

[e]This question is identical to Key Question 1, but focuses on comparisons of one DMARD versus another, rather than on comparisons of DMARDs versus conventional treatments.

Key Question 3. In children with JIA, does the rate and type of adverse events[f] differ between the various DMARDs or between DMARDs and conventional treatment with or without methotrexate?

[f]Because of the known risks associated with DMARDs, we focused primarily on serious infections and the development of cancer when assessing adverse events. Other adverse events considered included mortality, hepatitis, bone marrow suppression, nausea or vomiting, and risks to a fetus or pregnant mother.

Key Question 4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories[g] of JIA?

[g]Categories of JIA include:

- Systemic arthritis
- Oligoarthritis
- Rheumatoid-factor positive (RF+) Polyarthritis
- Rheumatoid-factor negative (RF-) polyarthritis
- Enthesitis-related arthritis
- Psoriatic arthritis
- Other (arthritis of unknown cause with symptoms lasting more than 6 weeks).

Key Question 5. What are the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures[h] for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?

[h]The outcomes measures assessed were those most commonly used in clinical trials and practice, as well as newer instruments of particular interest that were selected in consultation with the project's technical expert panel (TEP). The outcome measures assessed were:

- Measures of disease activity:
  - Active joint count (AJC)
  - Physician global assessment of disease activity (PGA)
  - Parent/patient global assessment of well-being (PGW)
- Measure of functional status/disability:
  - Childhood Health Assessment Questionnaire (CHAQ)
- Measures of health-related quality of life:
  - Child Health Questionnaire (CHQ)
  - Pediatric Quality of Life Inventory (PedsQL) 4.0
  - Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM)
- Composite measures of response to therapy and developing definitions of disease status:
  - American College of Rheumatology Pediatric Response Criteria (ACR Pediatric 30)
  - Juvenile Arthritis Disease Activity Score (JADAS)
  - A consensus-based definition of remission
  - Flare
  - Minimal disease activity (MDA)

These instruments were assessed for test-retest reliability, inter- and intra-rater reliability, internal reliability, construct validity, responsiveness (standardized response mean and responsiveness index), and feasibility metrics such as time to administer.

Conclusions

Table A provides an aggregated view of the strength of evidence and brief conclusions, based on this review, of the comparative benefits and harms of DMARDs for children with JIA.

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA

Key question	Strength of evidence	Conclusions
1. In children with JIA, does treatment with DMARDs, compared to conventional treatment:		
a. Improve laboratory measures of inflammation?	Low	Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR—erythrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This conclusion is based on 14 studies of 1,060 subjects.

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)

Key question	Strength of evidence	Conclusions
b. Improve radiological progression?	Insufficient	Insufficient data are available to evaluate the impact of DMARDs on radiological progression. Only one cohort study of 63 subjects reported data on radiological progression.
c. Improve symptoms?	Moderate	Among children who have responded to a biologic DMARD, randomized discontinuation trials show that continued treatment for from 4 months to 2 years decreases the risk of having a flare (RR 0.46, 95% CI 0.36 to 0.60). This conclusion is based on four studies of 322 subjects. Among the non-biologic DMARDs, there is some evidence that methotrexate is superior to conventional therapy and oral corticosteroids, based on two randomized trials of 215 subjects.
d. Improve health status?	Low	Changes in health status were reported in 12 studies involving 927 subjects. Health status improved inconsistently with treatment with DMARDs.
2. In children with JIA, what are the comparative effects of DMARDs on:		
a. Laboratory measures of inflammation?	Low	Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR). However, ESR is inconsistently associated with treatment. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects.
b. Radiological progression?	Insufficient	No study addressed radiologic progression.
c. Symptoms?	Low	The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in symptoms between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor-quality RCT of 94 subjects found that etanercept was similar to infliximab.

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)

Key question	Strength of evidence	Conclusions
d. Health status?	Low	The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in health status between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor quality RCT of 94 subjects found that etanercept was similar to infliximab.
3. In children with JIA, do the rate and type of adverse events differ between:		
a. The various DMARDs?	Insufficient	Three RCTs directly compared two DMARDs; two compared penicillamine to hydroxychloroquine, and one compared leflunomide to methotrexate. The rate and type of adverse events did not differ between treatment groups in these studies. High variability across studies in the ascertainment and reporting of adverse events preclude valid comparisons of the rate and type of adverse events among the various DMARDs. Recently published studies of adverse event reporting databases provide indirect evidence that suggests a possible relationship between cancer and exposure to tumor necrosis factor α blockers.
b. DMARDs and conventional treatment with or without methotrexate?	Insufficient	No RCT directly compared a DMARD to conventional treatment. Thirteen trials directly compared a DMARD to placebo. The rate and type of adverse events were generally similar between intervention and placebo groups, with the notable exceptions of infliximab plus methotrexate being associated with more serious adverse events (32% vs. 5% over differing lengths of followup), and methotrexate being associated with higher rates of laboratory abnormalities (35% vs. 13%).
4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?	Insufficient	Only one study—an RCT of methotrexate versus placebo in which each group could also receive oral corticosteroids, intra-articular corticosteroids, and NSAIDs—evaluated efficacy by JIA category. No difference was found among those with extended oligoarticular JIA (n = 43) and systemic JIA (n = 45). We did not identify any studies that provide reliable information on the comparative safety or rates or types of adverse events among the various categories of JIA.

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)

Key question	Strength of evidence	Conclusions
5. What is the validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?	Insufficient	Most of the studies examining the psychometric properties of the instruments used in JIA were fair quality cross-sectional or longitudinal non-randomized controlled trials. No one instrument or outcomes measure appeared superior in measuring disease activity or functional status. The current response criteria of the ACR Pediatric 30, a composite measure that includes articular indices, functional status, laboratory measures, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, given that the ACR Pediatric 30 is a relative measure of disease activity, the impact of JIA category on percent improvement is unclear, as certain instruments, such as the CHAQ, appear to have differential responsiveness depending on extent of disease at baseline. The ACR Pediatric 30 is also a relative measure of disease activity and not a measure of current disease state.

Abbreviations: ACR = American College of Rheumatology; CHAQ = Childhood Health Assessment Questionnaire; CI = confidence interval; DMARD(s) = disease-modifying antirheumatic drug(s); ESR = erythrocyte sedimentation rate; JIA = juvenile idiopathic arthritis; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial; RR = risk ratio.

Remaining Issues

Despite the importance of DMARDs for the treatment of childhood JIA, there is a paucity of comparative evidence for long-term benefits and harms. One particularly important challenge is the development of outcome measure tools that fully describe the impact of the condition and that are both feasible to administer and sensitive to changes in the status of the condition. Some of the measures that are commonly used (e.g., ESR) may not reflect meaningful changes in disease status. Similarly, radiographs to assess joint changes may be difficult to interpret because of the large amount of cartilage. Multi-dimensional instruments appear to better assess outcomes. Full understanding of the impact of treatment requires understanding not only relative improvement but the overall status of the condition.

Future Research

Although DMARDs have improved health outcomes for children with JIA, few data are available to evaluate the comparative effectiveness of either specific DMARDs or general classes of DMARDs (e.g., non-biologic vs. biologic, or by mechanism of action). Research on the effectiveness of treatments for JIA is challenging because it is a rare condition that includes multiple categories, which could potentially respond differentially to therapy. Furthermore, the

health impact of JIA fluctuates over time. Therefore, trials require large sample sizes with long followup periods.

Developing a summary estimate of effectiveness of the DMARDs is challenging because there is:

- *Heterogeneity in the study population*. Changes in the definition of JIA (e.g., JRA, JCA) may have led to the inclusion in studies of individuals who may respond differently to treatments. Similarly, differences by disease category (e.g., polyarticular, pauciarticular, systemic) might lead to different conclusions about the effectiveness of treatment.
- *Variation in comparators*. Over time, the standard of care for JIA has changed. For example, relatively recent studies of biologic DMARDs often allow methotrexate, a DMARD, in the comparator group, while older studies do not include methotrexate in the comparator groups. Some older studies included systemic corticosteroids as a comparator.
- *Variation in outcome measures*. Outcome measures vary across the studies and are sometimes incompletely described. Some studies report the percentage improvement from baseline without providing baseline data or an estimate of variability. Among six randomized discontinuation trials identified for this review, four reported laboratory measures of inflammation, four reported whether a flare occurred, three reported active joint count, and four reported quality of life as measured by CHAQ. Of those that reported the CHAQ score, one reported only the percentage change from baseline without the absolute value or measure of dispersion (e.g., range, standard deviation), and two gave average values without measures of dispersion.

Future trials in this domain should consider:

- *The challenge of the appropriate comparator*. Trials are needed to evaluate the effectiveness of DMARDs compared to conventional therapy as well as against other DMARDs. Defining conventional therapy is challenging because it evolves with advances in the field. Factorial designs involving multiple treatments are a potential solution. Patient-level meta-analysis, pre-planned across different trials, may also help address this issue.
- *The issue of treatment-by-category interaction*. To fully explore comparative effectiveness, larger studies will be needed. In addition, patient-level meta-analysis may help address this challenge.
- *The need for study populations who are representative of typical patients with JIA.* Subjects from the studies included in this review were identified through specialty clinics, which is appropriate for rare conditions. However, baseline characteristics varied. Studies should be designed to reflect the comparative effectiveness for typical subjects at various points along the disease spectrum (e.g., at presentation, after failing conventional treatment).
- *The variable course of JIA*. Trials that evaluate the efficacy of treatment should be sufficiently long, with frequent assessment of health status, to capture the natural variability of the disease course.
- *Reporting of adverse events*. There is a need for standardized definitions for, and systematic ascertainment and reporting of, adverse events possibly associated with therapeutic interventions in the treatment of JIA.

- *The impact of DMARDs on the specific health conditions associated with JIA.* These conditions include uveitis and macrophage activation syndrome.

Study designs other than randomized controlled trials (RCTs) will be important in understanding the role of DMARDs in JIA. Randomized discontinuation trials have helped to define the risk of flare in patients who respond to a particular DMARD. Large cohort studies will be important for evaluating the risk of adverse events associated with DMARDs. Such studies could also be important for better characterizing long-term outcomes in JIA.

Few high-quality data are available regarding the adverse events associated with DMARDs. Because JIA is a chronic illness, understanding the long-term adverse effects of these drugs is critical. One solution to evaluating risk would be to develop registries for DMARDs when used for childhood JIA. Understanding such risk will also provide information about the sequence in which these drugs should be used for difficult-to-treat JIA, or the impact of using multiple drugs. Implementing more general disease-based registries could not only help assess risk but help evaluate the comparative effectiveness of a wide array of interventions.

Our findings suggest that short-term mortality rates associated with DMARDs are very low—we identified only a single patient among several thousand treated who died shortly after receiving a DMARD. The incidence of malignancies during a short course of DMARD treatment also appears to be very low. However, the available evidence is inadequate to determine whether the rates and types of adverse events differ between the various DMARDs or between DMARDs and conventional treatment. The findings from RCTs do not reveal a clear pattern pertaining to adverse events associated with the treatment of JIA with DMARDs compared to placebo. A review of other study designs revealed marked differences in the rate and type of adverse event by DMARD, but these findings should be interpreted with caution for several reasons, including: variable definitions of adverse events across studies; non-systematic methods of ascertaining adverse events; nearly universal lack of standard reporting of serious adverse events; a predominance of case reports and uncontrolled series; small sample sizes in most series and RCTs; a limited number of studies for many individual DMARDs; and frequent use of multiple medications and other co-interventions.

Finally, our findings suggest the need for better clinical outcomes measures that are responsive to change across the full spectrum of disease severity. Consistent use of such outcomes measures would facilitate comparative effectiveness research.

The heterogeneity in disease severity and the broad impact of the disease on both physical and psychosocial aspects of children's lives make it difficult to accurately assess children using one instrument or measure. Given the complex nature of JIA, with the potential for both chronic and acute functional limitations and pain, it is difficult to find one tool or instrument that can be responsive to all the facets of disease. Efforts to develop a more standardized composite measure which could incorporate articular indices, severity, and a broader assessment of functional limitations and psychosocial impact would be useful to better differentiate levels of disease activity and overall impact of disease. The current response criteria of the ACR Pediatric 30 definition of improvement, a composite measure which includes articular indices, functional status, laboratory measures, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, the ACR Pediatric 30 is a relative

measure of disease activity and therefore does not fully describe overall disease status. A relative change in the ACR Pediatric 30 is thus difficult to interpret.

Developing an instrument or composite measure to accurately describe all the aspects of JIA, including disease activity, functional status, and quality of life would improve our understanding of the overall impact of JIA. In addition, focusing on the most responsive outcome measures to assess treatment effects would enhance our ability to detect promising new treatments.

Introduction

Background

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease in childhood, with an overall prevalence of 7 to 400 per 100,000 children.[1,2] JIA is an important cause of chronic disease in childhood, with prevalence similar to type I diabetes mellitus.[3] Several classification systems have been used over time to categorize the various categories of juvenile arthritis, including juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA), based upon clinical presentation and disease course. In 1995, the International League of Associations for Rheumatology (ILAR) proposed a new classification system, JIA, which consists of seven main categories. These categories are useful in examining potential differences in treatment response and prognosis. The main categories of JIA are:[4]

- Systemic arthritis: Initial presentation includes spiking fever, rash, and arthritis; one-quarter of children may have severe destructive disease.
- Oligoarthritis: Affects up to four joints within the first 6 months of illness; may be persistent (i.e., involving no more than four joints) or extended (i.e., involving more than four joints after the first 6 months of illness), and may be associated with uveitis.
- Polyarthritis Rheumatoid Factor-Negative: Affects five or more joints during the first 6 months of disease. May be associated with uveitis.
- Polyarticular Rheumatoid Factor-Positive: Affects five or more joints during the first 6 months of disease, and is more likely to result in destructive joint disease. May be associated with uveitis.
- Enthesitis-related arthritis: May be associated with uveitis.
- Psoriatic arthritis: May be associated with uveitis.
- Undifferentiated: Arthritis lasting more than 6 weeks that does not meet the criteria for any of the above categories, or that meets the criteria for more than one category.

It is important to note, however, that the previous definitions of JCA and JRA will be used when reviewing literature published prior to the acceptance of the JIA categorization system.

JIA can place a severe physical and psychological burden on affected children and be a major stressor to their families. As is true for all chronic conditions in childhood, treatment of JIA may be enhanced through the use of a multidisciplinary team to address these issues. There is no cure for JIA, but over the past 25 years new therapies have provided great advances in treatment and symptom control. Previous treatments with non-steroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen) and corticosteroids (systemic or intra-articular) were only partially effective in treating the symptoms of arthritis and reducing long-term complications (e.g., growth delay, erosive joint disease, persistently active disease, mortality). Treatment with the class of agents known as disease-modifying antirheumatic drugs (DMARDs) has become an increasingly important component of care because these drugs appear to lead to better disease control, with higher numbers of children achieving remission, and fewer children suffering long-term joint damage. DMARDs interfere with the making or working of immune cells that cause joint inflammation and are typically classified as either biologic drugs, which are created by biologic processes, or non-biologic drugs, which are manufactured chemically. In general, the non-biologic DMARDs are older. Most biologic DMARDs target specific components of the immune

system (e.g., signaling or cell-surface molecules). One of these non-biologic DMARDs, methotrexate, whose exact mechanism is unknown, has been used for so long in the treatment of JIA that it is often considered part of conventional treatment, along with NSAIDs and intra-articular corticosteroids.

Although there is significant optimism that treatment with the newer biologic DMARDs may increasingly lead to long-term disease remission, there are many unanswered questions about the safety of these drugs, especially for long-term use in children. For example, the U.S. Food and Drug Administration (FDA) recently placed a box warning on the entire class of biologic DMARDs targeting tumor necrosis factor (TNF) alpha, including etanercept, infliximab, and adalimumab, due to concerns about potential increased risk of malignancy, in particular lymphoma. There are also important questions about effectiveness, including the comparative effectiveness of DMARDs versus conventional treatment and the comparative effectiveness of the various DMARDs versus one another. Furthermore, it is possible that the effectiveness of these drugs varies by category of JIA. Understanding the circumstances in which a DMARD should be used, and which DMARD(s) should be selected, is challenging because JIA is heterogeneous across the various categories. A clear synthesis of the available evidence is needed to help clinicians provide care for children with JIA and to identify the important gaps in the scientific literature.

Juvenile arthritis has a broad impact on a child's physical and mental health. Developing instruments that accurately assess the effect of JIA on health and well-being is critical to enable us to asses the overall impact of the disease and to quantify the efficacy of treatments. The heterogeneity of disease severity, the broad age range of affected individuals, and fluctuations in the natural history of the disease complicate the measurement of disease activity and treatment effects in children with JIA. To provide the most accurate assessment of treatment effects we depend on the performance characteristics (e.g., sensitivity, specificity, responsiveness to change) of the outcomes measures reported in the scientific literature. Multiple instruments have been developed or adapted to assess severity of disease, disability, and quality of life in JIA. Understanding the reliability, validity, and responsiveness of these instruments will facilitate interpretation of clinical trial data.

In this comparative effectiveness review, we examine the scientific literature on DMARDs for JIA in childhood. Moreover, we review evidence regarding the usefulness of available outcomes measures for JIA that are commonly used in clinical trials and within the clinical practice setting.

Scope and Key Questions

This review summarizes the evidence on the benefits and harms of DMARDs compared to conventional treatment (NSAIDs and/or intra-articular corticosteroids) with or without methotrexate, and of the various DMARDs compared to one another, in children with JIA. In addition, this review summarizes the usefulness of selected tools commonly used to measure clinical outcomes associated with JIA.

Key questions addressed are:

Key Question 1. In children[a] with JIA,[b] does treatment with DMARDs,[c] compared to conventional treatment (i.e., NSAIDs or corticosteroids) with or without methotrexate,[d] improve laboratory measures of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

[a]"Children" are defined as individuals aged 18 years or younger.
[b]"JIA" includes any category of any severity of the following:

- JIA according to the International League of Associations for Rheumatology (ILAR) criteria;
- Juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition; or
- Juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.

[c]DMARDs evaluated are: abatacept, adalimumab, anakinra, canakinumab, etanercept, infliximab, intravenous immunoglobulin (IVIG), rilonacept, rituximab, and tocilizumab (biologic DMARDs); and azathioprine, cyclosporine A, penicillamine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus (FK506), and thalidomide (non-biologic DMARDs).
[d]Conventional treatments evaluated are: betamethasone, triamcinolone acetonide, triamcinolone hexacetonide, celecoxib, etodolac, ibuprofen, indomethacin, meloxicam, naproxen, oxaprozin, and tolmetin.

Key Question 2. In children with JIA, what are the comparative effects of DMARDs[e] on laboratory markers of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

[e]This question is identical to Key Question 1, but focuses on comparisons of one DMARD versus another, rather than on comparisons of DMARDs versus conventional treatments.

Key Question 3. In children with JIA, does the rate and type of adverse events[f] differ between the various DMARDs or between DMARDs and conventional treatment with or without methotrexate?

[f]Because of the known risks associated with DMARDs, we focused primarily on serious infections and the development of cancer when assessing adverse events. Other adverse events considered included mortality, hepatitis, bone marrow suppression, nausea or vomiting, and risks to fetus or pregnant mother.

Key Question 4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories[g] of JIA?

[g]Categories of JIA include:

- Systemic arthritis
- Oligoarthritis
- Rheumatoid-factor positive (RF+) polyarthritis
- Rheumatoid-factor negative (RF-) polyarthritis
- Enthesitis-related arthritis
- Psoriatic arthritis
- Other (arthritis of unknown cause with symptoms lasting more than 6 weeks).

Key Question 5. What are the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures[h] for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?

[h]The outcomes measures assessed were those most commonly used in clinical trials and practice, as well as newer instruments of particular interest that were selected in consultation with the project's technical expert panel (TEP). The outcome measures assessed were:

- Measures of disease activity:
  - Active joint count (AJC)
  - Physician global assessment of disease activity (PGA)
  - Parent/patient global assessment of well-being (PGW)
- Measure of functional status/disability:
  - Childhood Health Assessment Questionnaire (CHAQ)
- Measures of health-related quality of life:
  - Child Health Questionnaire (CHQ)
  - Pediatric Quality of Life Inventory (PedsQL) 4.0
  - Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM)
- Composite measures of response to therapy and developing definitions of disease status:
  - American College of Rheumatology Pediatric Response Criteria (ACR Pediatric 30)
  - Juvenile Arthritis Disease Activity Score (JADAS)
  - A consensus-based definition of remission
  - Flare
  - Minimal disease activity (MDA)

These instruments were assessed for test-retest reliability, inter- and intra-rater reliability, internal reliability, construct validity, responsiveness (standardized response mean and responsiveness index), and feasibility metrics such as time to administer.

Table 1. DMARDs evaluated

Generic name	Biologic or non-biologic?	U.S. trade name(s)	Mechanism of action	FDA-approved for JIA?*
Abatacept	Biologic	Orencia	T-cell co-stimulation modulator; soluble fusion protein	Yes
Adalimumab	Biologic	Humira	TNF inhibitor; anti-TNF monoclonal antibody	Yes
Anakinra	Biologic	Kineret	IL-1 receptor antagonist	No
Canakinumab	Biologic	Ilaris	IL-1 inhibitor; anti-IL-1beta monoclonal antibody	No
Etanercept	Biologic	Enbrel	TNF inhibitor; fusion protein TNF receptor inhibitor,	Yes
Infliximab	Biologic	Remicade	TNF inhibitor ;anti-TNF monoclonal chimeric antibody	No
IVIG	Biologic	Baygam, Carimune NF, Flebogamma 5% DIF, Gammar P, Gamunex 10%, Gammagard S/D, Gammagard Liquid 10%, Gammar P, Iveegam EN, Octagam 5%, Panglobulin, Polygam S/D, Privigen 10%, Vivaglobin	Interaction with activating Fc receptors	No

Table 1. DMARDs evaluated (continued)

Generic name	Biologic or non-biologic?	U.S. trade name(s)	Mechanism of action	FDA-approved for JIA?*
Rilonacept	Biologic	Arcalyst	IL-1 inhibitory; soluble fusion protein)	No
Rituximab	Biologic	Rituxan	Binds to CD20 antigen	No
Tocilizumab	Biologic	Actemra	IL-6 receptor antagonist	No
Azathioprine	Non-biologic	Azasan; Imuran	Purine synthesis inhibitor	No
Cyclosporine A	Non-biologic	Neoral, Gengraf	Calcineurin inhibitor	No
Penicillamine	Non-biologic	Depen; Cuprimine	Unknown (may lower IgM rheumatoid factor, depresses T-cell activity)	No
Hydroxy-chloroquine	Non-biologic	Plaquenil	Not well understood, may reduce T-lymphocyte transformation and chemotaxis	No
Leflunomide	Non-biologic	Arava	Isoxazole immunomodulatory agent	No
Methotrexate	Non-biologic	Methotrexate LPF	Unknown (anti-metabolite, inhibits dihydrofolic acid reductase)	Yes
Mycophenolate mofetil	Non-biologic	CellCept	Guanosine synthesis inhibitor	No
Sulfasalazine	Non-biologic	Azulfidine Sulfazine	Unknown	Yes
Tacrolimus (FK506)	Non-biologic	Prograf	Calcineurin inhibitor	No
Thalidomide	Non-biologic	Thalomid	Unknown	No

*Labeling refers to any pediatric approval.
Abbreviations: CD = cluster of differentiation; Fc = fragment crystallizable; FDA = U.S. Food and Drug Administration; IgM = immunoglobulin M; IL = interleukin; IVIG = intravenous immunoglobulin; JIA = juvenile idiopathic arthritis; T–cell/–lymphocyte = thymus cell/lymphocyte; TNF = tumor necrosis factor

Table 2. Conventional treatments evaluated

Generic name	Drug type	U.S. trade name(s)	FDA-approved for JIA?*
Betamethasone	Intra-articular corticosteroid	Celestone	Yes
Triamcinolone acetonide	Intra-articular corticosteroid	Kenalog	Yes
Triamcinolone hexacetonide	Intra-articular corticosteroid	Aristospan	No
Celecoxib	NSAID	Celebrex	Yes
Etodolac	NSAID	Lodine	No
Ibuprofen	NSAID	Motrin, Advil	Yes
Indomethacin	NSAID	Indocin, Indocin SR	No
Meloxicam	NSAID	Mobic	Yes
Naproxen	NSAID	Naprosyn, Aleve	Yes
Oxaprozin	NSAID	Daypro	Yes
Tolmetin	NSAID	Tolectin	Yes

*Labeling refers to any pediatric approval
Abbreviations: FDA = U.S. Food and Drug Administration; JIA = juvenile idiopathic arthritis; NSAID = non-steroidal anti-inflammatory drug

Methods

Topic Refinement

The topic for this report was nominated in a public process. With input from a group of key informants, the topic was refined to assure its relevance to stakeholders, after which the proposed analytic framework and key questions were posted to a public website for comment. The EPC subsequently revised the analytic framework and key questions based on the comments received.

Search Strategy

We conducted a comprehensive search of the scientific literature to identify randomized controlled trials (RCTs), non-randomized comparative studies, case series, and case reports relevant to the key questions. Searches of electronic databases used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE®, adapted as needed for other sources. For Key Questions 1-4 we combined search terms for JIA with terms for the interventions of interest; for Key Question 5 we supplemented this basic search with general terms for clinical outcomes measures and specific terms for the measures of interest. Detailed search strategies are provided in Appendix A. We also reviewed selected gray literature identified by the SRC, abstracts presented at relevant meetings (the 2008 and 2009 meetings of the American College of Rheumatology and the 2008 and 2009 meetings of the Pediatric Academic Societies), and the reference lists of relevant review articles and included studies for all key questions.

To identify literature describing the comparative benefits and harms of DMARDs (Key Questions 1-4) and the accuracy of clinical outcome measures (Key Question 5) we searched:

- MEDLINE® via PubMed (1966 to December 23, 2010);
- EMBASE® (1947 to December 23, 2010);
- Gray literature identified by the SRC;
- Conference abstracts (as described above);
- Reference lists of review articles and included primary studies.

Our searches identified a total of 4815 citations. We imported all citations into an electronic database (EndNote® version X13).

Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, and outcome measures specified in the key questions. The abstract screening criteria we applied are listed in Appendix B. We then applied a second, more stringent set of criteria for inclusion and exclusion at the full-text stage (Appendix B). In general, we included peer-reviewed, English-language reports of studies that had a sample population of individuals 18 years or younger with JIA according to the current ACR definition. For Key Questions 1, 2, and 4, the study duration had to be at least 3 months. To be included for Key Questions 1-4, studies had to include at least one of the DMARDs included in our list. In addition, Key Questions 1 and 2 each required comparators. For Key Question 1, the comparator was conventional treatment, and for Key Question 2, the comparator was another DMARD. Case reports could be included for Key Question 3. For Key Question 5, any treatment intervention or

comparator (including none) and any study duration were acceptable. We restricted Key Question 5 to studies of specified clinical outcome measures for childhood JIA.

The remainder of this section describes in greater detail the criteria we used to screen the available literature.

Population and Condition of Interest

This review focused on individuals aged 18 years or younger with:

- Juvenile idiopathic arthritis (JIA) according to the International League of Associations for Rheumatology (ILAR) criteria; or
- Juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition; or
- Juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.

Any diagnostic category of any severity was acceptable. In many cases, insufficient information was reported to verify the diagnosis; therefore, we accepted diagnoses as reported by the study authors. We included studies with patients of mixed ages only if results were reported separately for the relevant subgroups.

Interventions and Comparators of Interest

For Key Questions 1, 2, and 4, we included DMARDs as listed in Table 1 as the interventions of interest. The comparator was conventional treatment (Table 2), defined as NSAIDs or intra-articular corticosteroids with or without methotrexate. Many studies evaluated DMARDs plus conventional treatment versus conventional treatment alone. We considered methotrexate to be a component of the test intervention if the comparator group did not receive methotrexate. We considered methotrexate to be a component of the comparator if individuals in both the treatment and comparison groups could receive methotrexate. Key Questions 3 and 5 did not require a comparator.

Outcomes of Interest

We considered a wide range of outcomes pertaining to the benefits and harms of DMARDs (Key Questions 1-4) and the utility of clinical outcome measures (Key Question 5). These outcomes included:

For Key Questions 1-4:

- Efficacy outcomes: Improvement in intermediate or long-term outcomes. Intermediate outcomes included laboratory measures of inflammation, active joint count, number of joints with limited range of motion, radiographic evidence of the progression of disease, and global assessment of current status. Long-term outcomes included pain control, clinical remission, quality of life, growth, development, joint function, functional ability, and mortality.
- Adverse events: These are specific to the interventions being examined. Because of the known risks associated with DMARDs, we focused primarily on serious infections and the development of cancer when assessing adverse events. Other categories we examined included mortality, hepatitis, bone marrow suppression, nausea or vomiting, and risks to fetus or pregnant mother.

For Key Question 5:

- Outcomes of interest: Inter- and intra-rater reliability, test-retest reliability, responsiveness (standardized response mean and responsiveness index), time to administer, and construct validity.
- Instruments evaluated: Based on studies identified in our search for articles relevant to Key Questions 1-4, and in consultation with the project's technical expert panel (TEP), we selected for detailed review the instruments most commonly used in clinical trials and newer instruments of growing importance. These included: measures of disease activity (active joint count, physician global assessment of disease activity, parent/patient global assessment of well-being), a measure of functional status/disability (Childhood Health Assessment Questionnaire), measures of health-related quality of life (Child Health Questionnaire, Pediatric Quality of Life Inventory 4.0, Pediatric Quality of Life Inventory Rheumatology Module), and composite measures of disease status or response to therapy (American College of Rheumatology Response Criteria, remission, flare, minimal disease activity). We chose to focus on studies in which the instrument's psychometric characteristics were examined specifically for children with JIA. Therefore, we excluded initial psychometric evaluations of general health-related quality-of-life instruments conducted in children without JIA and studies of disease-specific instruments in which children with JIA were only a small proportion of the overall sample.

Timing

We included comparative studies that evaluated the efficacy or effectiveness of treatment if the intervention period lasted at least 3 months (Key Questions 1, 2, or 4). We included all reports of adverse events, regardless of the duration of treatment (Key Question 3). We also included all studies of clinical outcomes measures (Key Question 5), regardless of followup duration.

Setting

We did not restrict the setting of the included studies.

Types of Studies

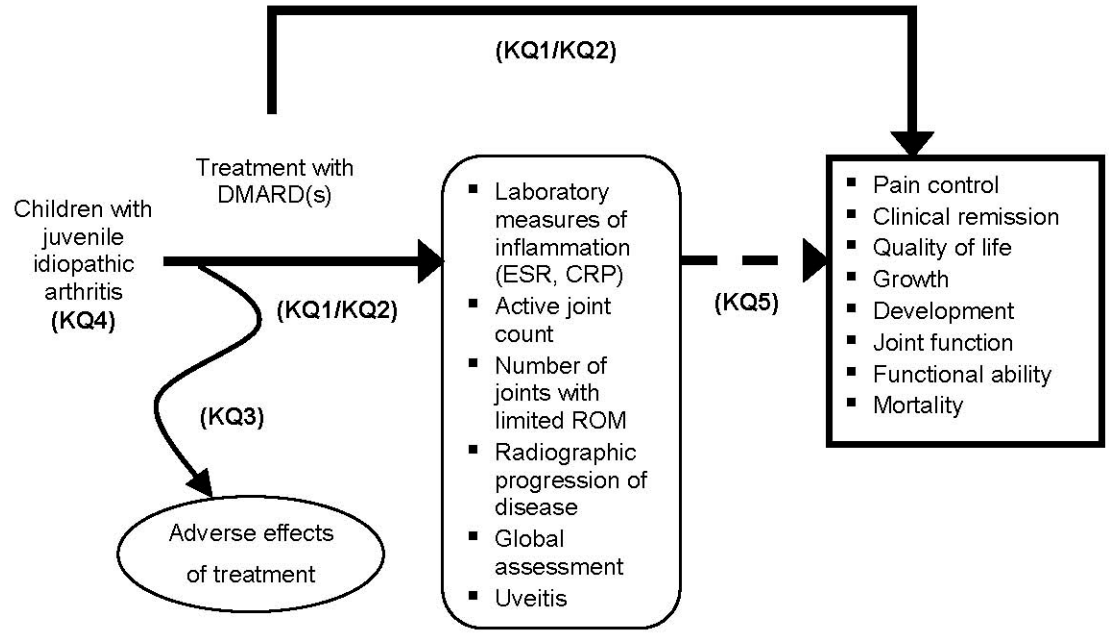
To evaluate the efficacy or effectiveness of treatment and adverse events (Key Questions 1 to 4), we included prospective comparative clinical studies of any design, including randomized controlled trials (RCTs), non-randomized controlled clinical trials, and cohort studies. To evaluate adverse events (Key Question 3), we also included case series and case reports. To evaluate clinical outcomes measures (Key Question 5), we considered prospective clinical studies and cross-sectional studies.

Analytic Framework

Figure 1 depicts the key questions within the context of the population, interventions, comparators of interest, outcomes, timing, and settings (PICOTS). In general, the figure illustrates how treatment of JIA in children with DMARDs versus conventional treatment (intra-articular corticosteroids and NSAIDs with or without methotrexate) may result in intermediate

outcomes, such as changes in laboratory measures of inflammation, changes in the active joint count, or radiographic progression of disease, and/or long-term outcomes, such as clinical remission, changes in quality of life, changes in growth, and changes in development. Also, adverse events may occur at any point after the treatment is received.

Figure 1. Analytic framework



Data Extraction

We developed separate data abstraction form/evidence table templates for abstracting data from included studies that addressed treatment effects (benefits and adverse effects) and the performance of clinical outcome instruments (Appendix C). Abstractors worked in pairs: the first abstracted the data, and the second over-read the article and the accompanying abstraction to check for accuracy and completeness. Completed evidence tables are provided in Appendix D.

For studies reporting efficacy outcomes, we extracted the following data from clinical trials and cohort studies: geographical location; study dates; funding source; interventions (including dose, duration, dose titration protocol [if any], and cointerventions [if any]); study design; population characteristics (including age, sex, race/ethnicity, type of JIA, baseline severity, and comorbidities); recruitment setting; inclusion and exclusion criteria; numbers screened, eligible, enrolled, and lost to followup; and results for each outcome.

For adverse events, we also abstracted data from case series and case reports. We developed an Excel spreadsheet to abstract the following data from both the peer-reviewed, published literature, as well as the gray literature, including published abstracts and letters to the editor: DMARD interventions, study design, total sample size, intervention sample size, gender, and the nature of the adverse event. There was wide variability across studies in how adverse events were defined, ascertained, and reported, and different terms were used to report similar events (e.g., "rash," "skin changes," "dermatitis," or "dermatologic event"). To facilitate comparisons across studies and interventions for the purpose of this report, we developed a classification

system that included 29 categories (including death), plus an "other" category. Patients who experienced multiple different adverse events thus contributed data points to the respective adverse event categories. We did not abstract multiple symptoms for a given patient when these symptoms were all attributed by the authors to a given diagnosis (e.g., a patient diagnosed with pneumonia and reporting symptoms of cough, fever, chest pain, and dyspnea contributed only to the "respiratory" adverse event category). We included a given diagnosis only once (e.g., we classified "pneumonia" as a respiratory adverse event rather than "infection"). A single investigator abstracted, categorized, and summarized the adverse events data for this report. Results are given in Appendix E.

Quality Assessment

For Key Questions 1, 2, and 4, we used the criteria to assess the quality of individual controlled trials and prospective cohort studies described in AHRQ's Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[5]

Individual studies were graded as "good," "fair," or "poor" in quality according to the following definitions:

> A "good" study has the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
>
> A "fair" study is susceptible to some bias, but probably not sufficient to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *possibly* valid, while others are *probably* valid.
>
> A "poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

If a study was rated as fair or poor, assessors were instructed to note important limitations on internal validity related to the following variables:

1. Initial assembly of comparable groups.
2. Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
3. Important differential loss to followup or overall high loss to followup.
4. Measurements: Equal, reliable, and valid (includes masking of outcome assessment).
5. Clear definition of interventions.
6. All important outcomes considered.
7. Analysis: Adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.

Assessment of each study's quality was made by a single rater and then evaluated by a second rater. Disagreements were resolved by consensus. Final quality assessments for individual studies are included in the evidence tables (Appendix D).

Quality was not rated for the case reports and case series included for Key Question 3. No established quality measurement evaluation systems have been developed for studies evaluating the reliability and validity of clinical outcome measures (Key Question 5). We therefore adapted pertinent criteria from the QUADAS tool used to assess the quality of diagnostic tests studies.[6] We considered the selection of study participants, independent and blind comparison of the study instrument to other outcome measures, and the appropriateness of the analytic approach.

Rating the Body of Evidence

We assessed the strength of the body of evidence for each key question using the a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[7] Unlike GRADE, the EPC GRADE method does not make specific clinical recommendations, uses "low" to encompass the original GRADE categories of "low" and "very low," and uses "insufficient" when an estimate of effect cannot be generated.[5] In rating the strength of evidence, we considered the number of studies, the size of the studies, strength of study design, and the quality of individual studies. In addition, as part of the GRADE framework, we assessed the consistency across studies of the same design, consistency across different study designs, the magnitude of effect, and applicability. Finally, if applicable, we considered the likelihood of publication bias and (especially for observational studies) the potential influence of plausible confounders. We commented specifically when it was difficult or impossible to assess certain of these dimensions. The overall strength of a given body of evidence was rated qualitatively using the following four-level scale:

> High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
>
> Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
>
> Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
>
> Insufficient—Insufficient evidence to make a decision or assign high, moderate, or low grade.

Assessing Applicability

We followed the recommendations in AHRQ's *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*[5] by abstracting data on the population studied, the intervention and comparator, the outcomes measured and timing of assessments. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, symptom severity and categories of JIA for the included sample, DMARD dose and comparators, and clinical relevance and timing of the outcome measures. Using notations on

applicability from the evidence tables along with our summary tables, we summarized issues of applicability qualitatively.

Data Synthesis

We planned to perform meta-analysis if there were sufficient studies that were conceptually homogeneous and reported the needed data to compute a summary estimate. In deciding whether to conduct meta-analyses, we considered primarily the basic study design (e.g., RCT), the intervention, and the comparator. Because of the small number of included studies and heterogeneity in comparisons, meta-analysis was conducted for only one comparison; all other literature was synthesized qualitatively. Meta-analysis was performed using Review Manager, version 5.0.24.[8] The pooled effects estimate for the binary outcome was expressed as a risk ratio (RR) with 95 percent confidence interval (CI). We tested the difference in estimates of treatment effect between the treatment and control groups using a 2-sided z test with statistical significance considered at a P value of less than 0.05. We examined heterogeneity by using the Cochran Q and the I^2 test.[9,10] We predefined heterogeneity as low, moderate, and high, with I^2 statistics greater than 25 percent, 50 percent, and 75 percent, respectively.[9] Meta-analysis with a fixed-effect model was utilized because the observed heterogeneity was low.[10] For Key Question 3, we used results from clinical trials and cohort studies to describe rates of adverse effects. We used case reports and case series to describe potential adverse events that have not been reported in clinical trials.

Peer Review Process

Peer review was conducted to provide independent evaluation of the systematic review methods and content. External stakeholders nominated to review this report included clinicians and representatives of professional societies, as well as members of the TEP. AHRQ concurred with these nominees to conduct peer review based on an assessment of their independence and expertise. The review was also available for public comment by other stakeholders and experts.

Results

Literature Search and Screening

Searches of all sources identified a total of 4815 potentially relevant citations. Table 3 details the number of citations identified from each source.

Table 3. Sources of citations

Source	Number of citations
MEDLINE®	1746
EMBASE®	2720
Gray literature identified by the SRC	314
Conference abstracts	11
References of review articles and primary studies	11
Other (recommendations from staff at AHRQ or TEP or from project investigators)	13
Total:	**4815**

Figure 2 describes the flow of literature through the screening process. Of the 4815 citations identified by our searches, 3998 were excluded at the abstract screening stage. Of the 817 articles that passed the initial abstract screening, 313 were gray literature articles that were excluded from further review. The remaining 504 articles went on to full-text screening. Of these, 306 were excluded, leaving a total of 198 included articles. Appendix F provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. Literature flow diagram

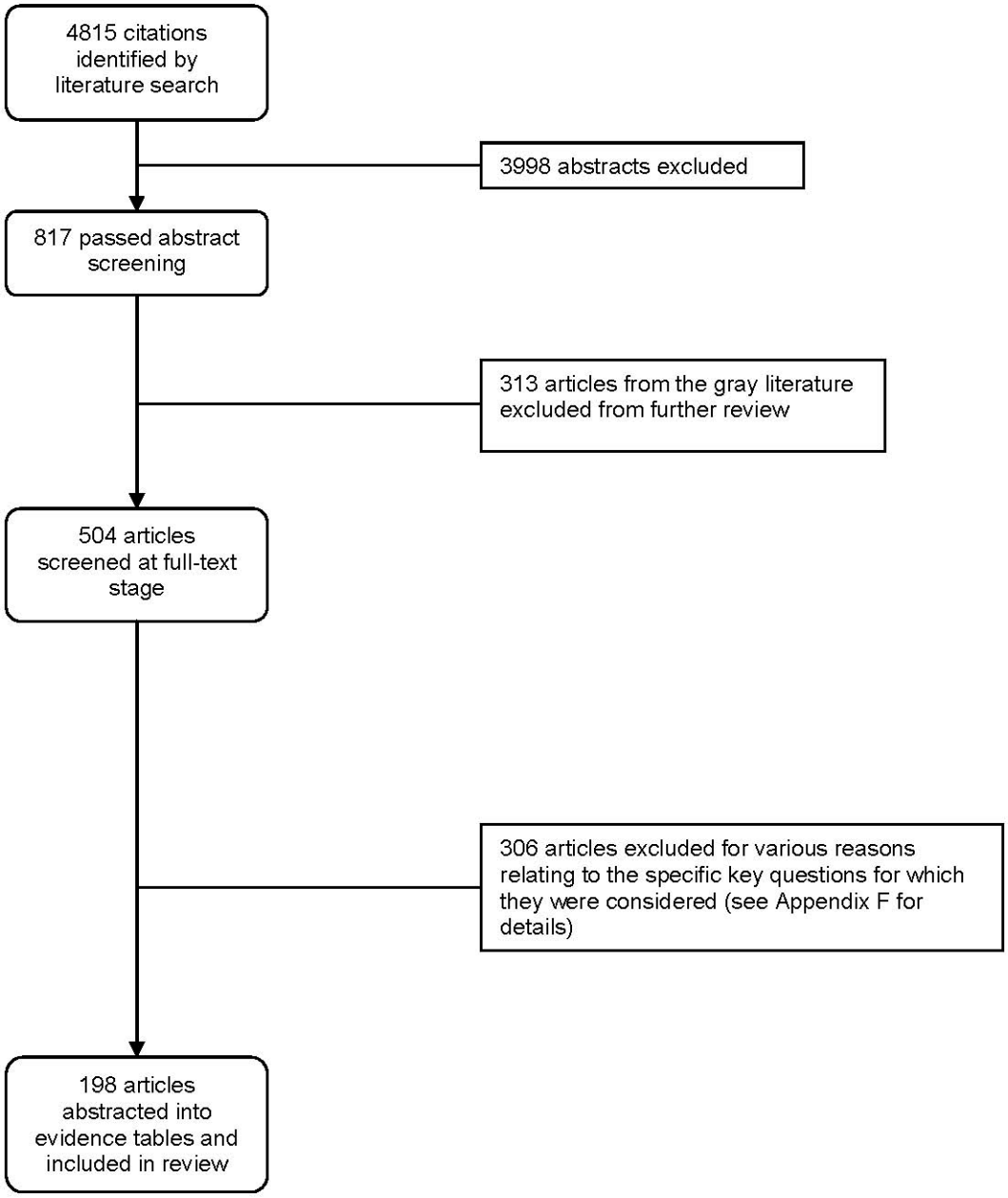
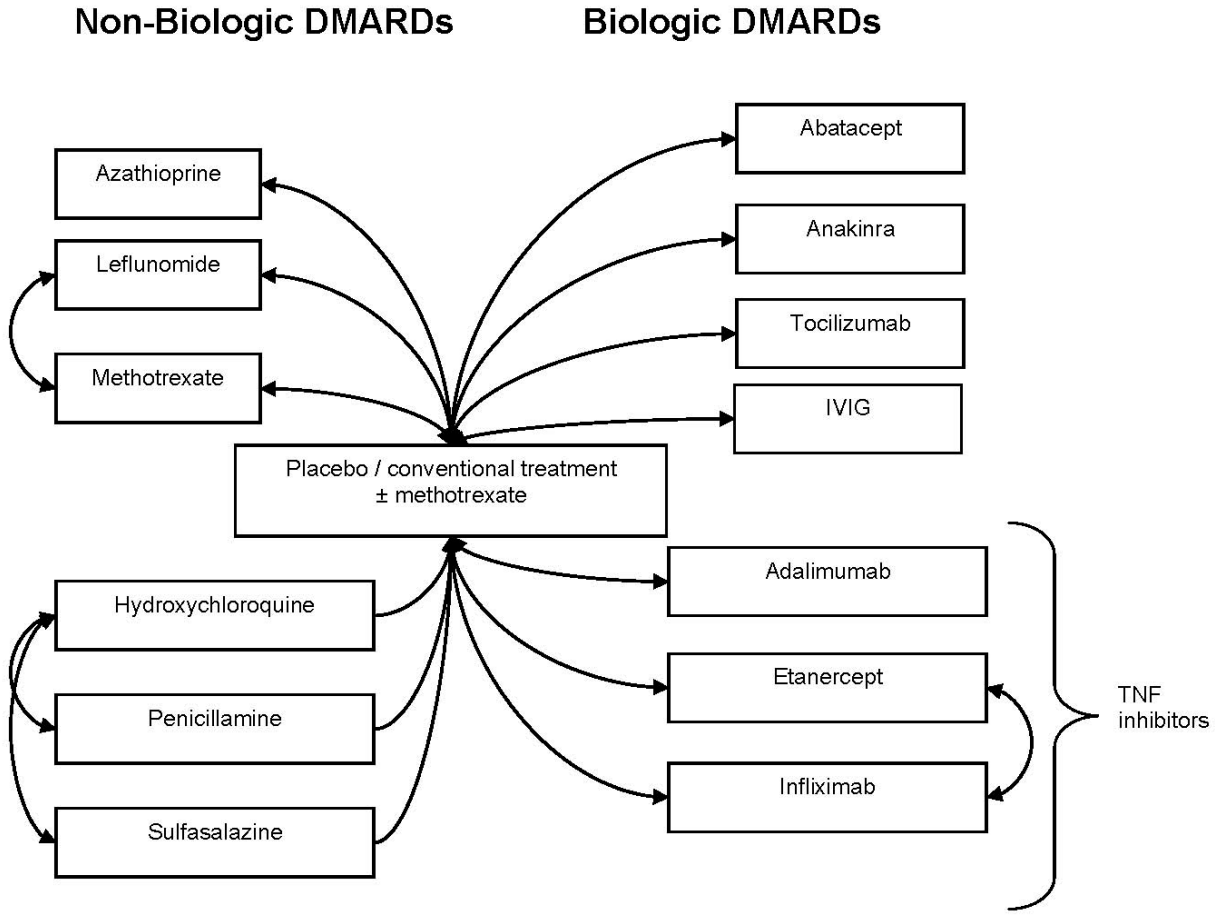


Figure 3 summarizes the treatment comparisons evaluated in the included efficacy studies (Key Questions 1, 2, and 4). Six non-biologic DMARDs and seven biologic DMARDs have been compared to conventional treatment with or without methotrexate. Two different sets of non-biologic DMARDs have been directly compared (leflunomide vs. methotrexate and hydroxychloroquine vs. penicillamine), and two biologic DMARDs have been directly compared (etanercept vs. infliximab). Three of the biologic DMARDs that have been compared to conventional treatment were in the same class (TNF inhibitors: adalimumab, etanercept, and infliximab). However, study heterogeneity precluded meta-analysis of this combined class versus

conventional treatment. Details on the number of studies describing each treatment comparison are provided under the relevant Key Question, below.

Figure 3. Treatment comparisons evaluated in efficacy studies



Key Question 1. In children with JIA, does treatment with DMARDs, compared to conventional treatment, improve laboratory measures of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

Key Points

- Among the non-biologic DMARDs, there is some evidence that methotrexate is superior to conventional therapy and oral corticosteroids.
- Among children who have responded to a biologic DMARD, randomized discontinuation trials suggest that continued treatment for 4 months to 2 years decreases the risk of having a flare. Although these studies evaluated DMARDs with different mechanisms of action (abatacept, adalimumab, anakinra, etanercept, intravenous immunoglobulin [IVIG], tocilizumab) and used varying comparators, followup periods, and descriptions of flare, the finding of a reduced risk of flare was precise and consistent.

- Conventional treatment has changed over time (e.g., use of oral corticosteroids in older studies of non-biologic DMARDs versus more frequent use of methotrexate in more recent studies of biologic DMARDs). Comparing the effectiveness of biologic and non-biologic DMARDs is challenging because of variations in comparators and how these comparators are described.
- There is significant variation in outcome measures and how these outcome measures are reported.

Detailed Analysis

Literature Identified

We identified of 20 publications describing 18 unique studies and involving 1532 patients that compared DMARDs to conventional treatments with or without methotrexate. Among these were 10 studies that evaluated seven biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, IVIG, and tocilizumab; see Table 4) and eight studies that evaluated five non-biologic DMARDs (azathioprine, penicillamine, hydroxychloroquine, methotrexate, and sulfasalazine; see Table 5).

There were 10 RCTs, of which four (described in five papers) were of good quality,[11-15] four were of fair quality,[16-19] and two were of poor quality.[20,21] Key problems in the fair- and poor-quality studies included unclear methods of allocating to therapy, questionable blinding, and incomplete followup. There were two open-label comparison studies of poor quality.[22,23] Six studies were randomized discontinuation studies, of which three (described in four papers) were of good quality,[24-27] two were of fair quality,[28,29] and one was of poor quality.[30]

A detailed summary of these studies, by DMARD evaluated, is provided below.

There were no good-quality RCTs comparing biologic DMARDs to conventional therapy. There were two good-quality RCTs comparing methotrexate, a non-biologic DMARD, to conventional therapy.[13,14] However, in both studies, each group could also receive oral corticosteroids, which are not currently considered conventional therapy. A single good-quality trial of sulfasalazine showed better short-term (24-week) outcomes than treatment with NSAIDs.[15]

Table 4. Studies comparing biologic DMARDs versus conventional treatments with or without methotrexate

Study	DMARD(s)	Comparator(s)	Other arthritis drugs	Study design	Study quality	Study population (n)	Followup duration	Key questions addressed
Ruperto et al., 2008[24]	Abatacept	Placebo	Methotrexate, oral corticosteroids, NSAIDs, analgesics	Randomized discontinuation trial with open label followup	Good	JIA: - Persistent oligoarthritis (5) - Extended oligoarthritis (43) - Polyarthritis (205) - Systemic (60)	6 months (RCT) with 5-yr followup	1, 3
Lovell et al., 2008[25]	Adalimumab	Placebo	Methotrexate, NSAIDs, oral corticosteroids	Randomized discontinuation trial with open label followup	Good	JRA - Polyarticular (171)	32 weeks (RCT) up to 56 week followup	1, 3
Ilowite et al., 2009[30]	Anakinra	Placebo	Methotrexate, NSAIDs, oral corticosteroids	Randomized discontinuation trial with open label followup	Poor	JIA: - Polyarticular (33) - Pauciarticular (6) - Systemic (11)	16 week (RCT) and 12 month followup	1, 3, 4
Lovell et al., 2000[26]	Etanercept	Placebo	NSAIDs, oral corticosteroids, pain medication except for 12 hours before joint assessment	Randomized discontinuation trial	Good	JRA: - Polyarticular (62) - Pauciarticular (6) - Systemic (34)	4 month (RCT)	1, 3, 4
Smith et al., 2005[16]	Etanercept	Placebo	Methotrexate, prednisone	RCT	Fair	JRA with uveitis (12)	12 months	1, 3
Ruperto et al., 2007[17]	Infliximab or infliximab with methotrexate	Placebo and methotrexate	NSAIDs, opioids, oral corticosteroids	RCT with active treatment extension	Fair	JRA - Polyarticular onset (74) - Pauciarticular onset (28) - Systemic onset (19)	52 weeks	1, 3

Table 4. Studies comparing biologic DMARDs versus conventional treatments with or without methotrexate (continued)

Study	DMARD(s)	Comparator(s)	Other arthritis drugs	Study design	Study quality	Study population (n)	Followup duration	Key questions addressed
Giannini et al., 1996[28]	IVIG	Placebo	NSAIDs, methotrexate, sulfasalazine, hydroxy-chloroquine	Randomized discontinuation trial with open label followup	Fair	JRA - Polyarticular (19)	4 months (RCT)	1, 3
Oppermann et al., 1994[22]	IVIG	Methyl-prednisolone	NSAIDs, methotrexate, oral corticosteroids	Open-label comparison	Poor	JCA (20)	Unclear; 6-8 months?	1
Silverman et al., 1994[20]	IVIG	Placebo	NSAIDs, up to 2 SAARDs (not listed)	RCT	Poor	JRA - Systemic (31)	6 months	1, 3
Yokota et al., 2008[29]	Tocilizumab	Placebo	Oral corticosteroids	Randomized discontinuation trial with open label followup	Fair	JIA (43)	12 week RCT, 48 week followup	1, 3

Abbreviations: DMARD(s) = disease-modifying antirheumatic drug(s); JCA = juvenile chronic arthritis; JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; NSAID(s) = non-steroidal anti-inflammatory drug(s); RCT = randomized controlled trial; SAARD(s) = slow-acting antirheumatic drug(s)

Table 5. Studies comparing non-biologic DMARDs versus conventional treatments with or without methotrexate

Study	DMARD(s)	Comparator(s)	Other arthritis drugs	Study design	Study quality	Study population (n)	Followup duration	Key questions addressed
Kvien et al., 1986[18]	Azathioprine	Placebo	NSAIDs, prednisolone	RCT	Poor	JRA: - Polyarticular-onset (16) - Pauciarticular onset (9) - Systemic onset (7)	16 weeks	1, 3
Prieur et al., 1985[19]	Penicillamine	Placebo	Pyridoxine hydrochloride	RCT	Fair	JCA: - Polyarticular onset (35) - Pauciarticular onset (14) - Systemic onset (25)	6 months	1, 3
Brewer et al., 1986[11] and Van Kerckhove et al., 1988[12]	Penicillamine or hydroxy-chloroquine	Placebo	NSAIDs, acetaminophen, codeine	RCT	Good	JRA: - Polyarticular (142) - Pauciarticular (11) - Systemic (9)	12 months	1, 2, 3
Kvien et al., 1985[21]	Penicillamine or hydroxy-chloroquine	Gold	Acetaminophen, NSAIDs	Open-label RCT	Poor	JRA: -Polyarticular (49) -Pauciarticular (23)	50 weeks	
Riddle et al., 2006[23]	Methotrexate	NSAIDs, methylpredni-solone	Not reported	Open-label comparison	Poor	JIA (63)	4 months	1, 3
Giannini et al., 1992[13]	Methotrexate	Placebo	NSAIDs, prednisolone	RCT	Good	JIA (127)	6 months	1, 3, 4
Woo et al., 2000[14]	Methotrexate	Placebo	Prednisolone, intra-articular corticosteroids, NSAIDs	RCT with crossover	Good	JIA - Extended oligoarticular (43) - Systemic (45)	12 months	1, 3, 4
van Rossum et al., 1998[15]	Sulfasalazine	Placebo	NSAIDs	RCT	Good	JCA: - Polyarticular (32) - Oligoarticular (37)	24 weeks	1, 3

Abbreviations: DMARD(s) = disease-modifying antirheumatic drug(s); JCA = juvenile chronic arthritis; JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; NSAID(s) = non-steroidal anti-inflammatory drug(s); RCT = randomized controlled trial

Biologic DMARDs Versus Conventional Treatment With or Without Methotrexate

Abatacept

One good-quality randomized discontinuation study evaluated abatacept.[24] During the 6-month double-blind period of this study, there was statistically significant improvement compared to placebo in the active joint count (4.4 vs. 6; $p = 0.02$), CHAQ score (0.8 vs. 0.7; $p = 0.04$), physician global assessment (14.7 vs. 12.5; $p < 0.01$), and ACR Pediatric 90 (40 percent vs. 16 percent; $p < 0.01$). There was no statistically significant improvement in parent/patient global assessment (17.9 vs. 23.9; $p = 0.70$) or erythrocyte sedimentation rate (ESR; 25.1 vs. 30.7; $p = 0.96$).

Adalimumab

We found one good-quality randomized discontinuation trial that compared adalimumab to conventional therapy.[25] The results were stratified by use of methotrexate. At the end of the 48-week double-blind phase, the proportion of patients who had a flare of disease in the adalimumab without methotrexate group was lower than in the conventional treatment group without methotrexate (43 percent vs. 71 percent; $p = 0.03$), and lower than in those groups that did receive methotrexate (37 percent vs. 65 percent; $p = 0.02$). The proportion who achieved ACR Pediatric 50 score in the adalimumab without methotrexate group was higher than in the conventional treatment without methotrexate group (53 percent vs. 32 percent; $p = 0.01$), and higher than in those groups that received methotrexate (63 percent vs. 38 percent; $p = 0.03$). Although the proportion who achieved ACR Pediatric 90 score was higher in the adalimumab without methotrexate group than in the conventional treatment without methotrexate group (30 percent vs. 18 percent), the difference was not statistically significant ($p = 0.28$). Similarly, the difference in the proportion who achieved the ACR Pediatric 90 among those who also received methotrexate was higher in the adalimumab group than in the conventional treatment group, but did not achieve statistical significance (42 percent vs. 27 percent; $p = 0.17$).

Anakinra

One randomized discontinuation trial compared anakinra to conventional therapy.[30] This study was rated as poor in quality because it did not have sufficient statistical power to evaluate efficacy, there was insufficient reporting of randomization and concealment. The main goal of the study was to evaluate safety. By week 28 of blinded treatment, 16 percent who received anakinra and 40 percent who received placebo had had a flare ($p = 0.11$). There was improvement in the CHAQ score in the anakinra group compared to placebo (-0.25 vs. 0.13; no p-value reported). Similarly, there was improvement in the ESR among those who were treated with anakinra (-2.21 vs. 13.73; no p-value reported).

Etanercept

Two studies evaluated etanercept versus placebo. One good-quality randomized discontinuation trial evaluated children with a polyarticular course of JRA.[26] In the double-blind component, fewer patients who received etanercept had a flare (28 percent vs. 81 percent; $p = 0.003$). There was also an improvement in the CHAQ score (-0.8 vs. -0.1). Overall, there was a 54 percent median improvement among those who received etanercept compared to no median change in the placebo group. There was an overall improvement in the number of active joints (7

vs. 13; no p-value reported); physician global assessment (2 vs. 5; no p-value reported); parent global assessment (3 vs. 5; no p-value reported); ESR (18 vs. 30; no p-value reported); and the proportion who achieved ACR Pediatric 50 (72 percent vs. 23 percent; no p-value reported).

The other study of etanercept was a fair-quality RCT that evaluated efficacy for the treatment of uveitis.[16] This study had a small sample size. During the study, 6 of 12 in the test treatment arm and 2 of 5 in the conventional treatment arm improved. This was described by study investigators as no apparent difference.

Infliximab

One fair-quality RCT compared infliximab to conventional treatment.[17] This study inconsistently and incompletely reported outcomes. The study did not find statistically significant differences between infliximab and conventional treatment in the ACR Pediatric 50 at 14 weeks (50 percent vs. 33.9 percent, respectively; $p = 0.13$) or the rate of clinical remission at 52 weeks (44.1 percent vs. 43.1 percent, respectively).

IVIG

Three studies compared IVIG to conventional treatment. One small (19 total in the double-blind phase), fair-quality, randomized discontinuation trial[28] found a 3 percent decrease in the active joint count among those who were treated compared to a 30 percent increase in the placebo group. Physician global assessment improved for 3 percent of patients in the treatment group and worsened for 91 percent in the placebo group. This study used a main outcome measure that has not been validated and provided no statistical significance testing; there was also a potential conflict of interest with the study sponsor.

Another study[22] compared IVIG to methylprednisolone. This study was considered to be of poor quality because it was open-label and non-randomized, analyses were not adjusted for baseline differences, and the sample was not adequately described. Investigators found no statistically significant difference between the IVIG and methylprednisolone groups for ESR (59 at baseline and 21 at 6 months vs. 61 at baseline and 24 at 6 months, respectively).

A small RCT[20] found that IVIG compared to conventional therapy was associated with a non-statistically significant improvement in the median change in active joint count (-2 vs. -1) and in physician global assessment of improvement (50 percent improvement vs. 27 percent improvement; $p > 0.3$). This study was considered to be of poor quality because of the small sample size and high dropout rate.

Tocilizumab

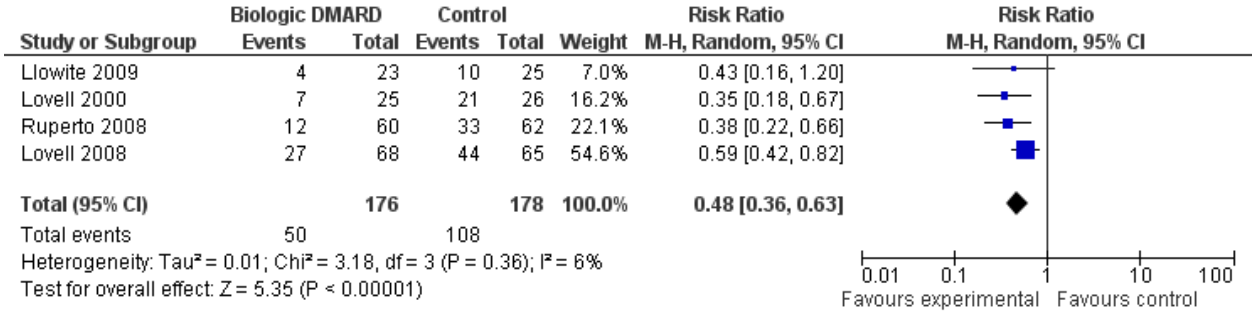
One fair-quality randomized discontinuation trial evaluated tocilizumab.[29] The screening and randomization procedures were not described. No p-values were reported for the outcomes of interest in this review. From the RCT component, the active joint count in the tocilizumab group decreased from 3.5 to 0. Similarly, in the conventional treatment group it decreased from 4 to 0. There was improvement in the CHAQ score for each group (-0.5 vs. -0.25). Both physician global assessment (51.0 to 5.5 vs. 51 to 14) and parent global assessment (51.0 to 4.5 vs. 55 to 39) improved. The ESR decreased for both the tocilizumab and conventional treatment group (35 to 0.1 vs. 38 to 15). The ACR Pediatric scores were reported graphically. The ACR Pediatric 70 increased in the tocilizumab group from approximately 70 percent to approximately 80 percent, but decreased in the conventional treatment group from approximately 80 percent to approximately 30 percent.

Meta-Analysis of Randomized Discontinuation Trials

Randomized discontinuation trials include only patients who initially responded to a treatment and primarily assess the risk of worsening when treatment is withdrawn. These studies evaluate sustainability of treatment effects and not the potential treatment effect among those who have not yet begun treatment. The randomized discontinuation trials identified by our search evaluated only biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, IVIG, tocilizumab).

Four of the trials reported flare of arthritis,[24-26,30] allowing us to calculate a summary measure of the risk of flare over the 4-month to 2-year durations of the studies. Other outcomes were too heterogeneous or were reported too incompletely to calculate a summary estimate. Although there were differences in the interventions, comparators, and duration of followup among the four studies, we found very little statistical heterogeneity. Figure 4 summarizes the risk ratio (RR) for flare (with 95 percent confidence interval [CI]) based on a random-effects model. Overall, the RR for having a flare among those who continued compared to those who discontinued was 0.48 (95 percent CI 0.36 to 0.63) over 4 months to 2 years. Although there is heterogeneity in study design, the RR for having a flare was similar across all studies ($\chi^2 = 3.18$, df = 3, p = 0.36; $I^2 = 6$ percent). This suggests that among those who respond to a biologic DMARD, there is a significant risk of flare after discontinuation. There was insufficient evidence regarding the efficacy of the biologic DMARDs from the other studies that compared these treatments to conventional therapy with or without methotrexate.

Figure 4. Comparison of symptomatic flares in children with JIA randomized to continuing a biologic DMARD versus placebo.
Flares are listed as "Events" in the figure.



Non-Biologic DMARDs Versus Conventional Treatment With or Without Methotrexate

Azathioprine

One poor-quality RCT evaluated azathioprine.[18] Allocation was not specified; there were baseline differences between those who received and did not receive azathioprine; it was unclear if outcomes were assessed blinded to the intervention status of subjects; and the outcomes were not well described. At 16 weeks of treatment, this study found non-statistically significant improvements with azathioprine in the number of active joints (-7 vs. -1; p = 0.45), physician global assessment (-5 vs. -2; p = 0.12), and the proportion with 50 percent improvement in ESR (4/13 subjects vs. 2/11 subjects; p = 0.36).

Hydroxychloroquine

Two RCTs evaluated hydroxychloroquine. One (described in two publications[11,12]) found no significant difference in the change in mean active joint count compared to placebo after 12 months (6.7 [95 percent CI -9.4 to -4] vs. -5.4 [-8 to -2.8]). The physician global assessment appeared slightly better for hydroxychloroquine than for placebo (70 percent better, 26 percent same, 2 percent worse compared to 53 percent better, 41 percent same, 6 percent worse; no p-value reported). There was no difference in the mean ESR decrease at 12 months (10 each).

The other study was an open-label RCT that compared hydroxychloroquine to gold.[21] This study was considered to be of poor quality because allocation concealment was not specified, there were important baseline differences between the treatment groups, it was unclear if outcomes were assessed blinded to the intervention, and the outcomes were not well described. At 50 weeks, there were no statistically significant differences in the active joint count (−4 vs. −5), median change in the physician global assessment (-8 vs. -9), or change in the ESR (−12 vs. −11). Similarly, the physician overall assessment of at least 50 percent improvement was not statistically significantly different between the hydroxychloroquine group and the gold group (12 of 17 improved vs. 10 of 15 improved, respectively).

Methotrexate

Three studies compared methotrexate to conventional treatment without methotrexate. One good-quality RCT compared low-dose methotrexate, very low-dose methotrexate, and placebo in a 6-month trial.[13] The mean active joint count decreased with low-dose methotrexate (-7.5), very low-dose methotrexate (-5.2), and placebo (-5.2; $p > 0.3$ overall). Physician global assessment improved with low-dose methotrexate compared to placebo ($p = 0.02$), but there was no statistically significant difference between the low-dose and very low-dose methotrexate groups for this outcome ($p = 0.06$). Based on a composite index with at least 25 percent improvement in articular score and improvement according to physicians and parents, 63 percent of those in the low-dose methotrexate group improved, compare to 32 percent in the very low-dose methotrexate group, and 36 percent in the placebo group ($p = 0.013$).

Another good-quality study[14] compared methotrexate to placebo among children with extended oligoarticular JIA or systemic JIA in a double-blind RCT with crossover. Among those with oligoarticular JIA, there was statistically significant improvement in physician global assessment ($p < 0.001$) and ESR ($p < 0.001$) with methotrexate. The change in the number of joints with synovitis (-3) did not achieve statistical significance ($p < 0.1$). Similarly, among those with systemic JIA, there was improvement in physician global assessment ($p < 0.001$), but not in ESR ($p = 0.06$) or in the number of joints with synovitis ($p = 0.06$) in patients taking methotrexate.

A poor-quality, non-randomized study compared methotrexate to NSAIDs and to methylprednisolone.[23] In this study, the active joint count improved more in the methylprednisolone group than in either the methotrexate or NSAID groups (-7.1 vs. -4 vs. -0.8, respectively; $p = 0.008$). This study, however, had confounding by indication; the analysis did not adjust for potential confounders; outcomes were not assessed blinded to the treatment condition; and patients were not blinded to their treatment assignments.

Penicillamine

Four publications describing three distinct studies evaluated penicillamine. One good-quality RCT[11,12]) found no statistically significant effect on the mean active joint count with

penicillamine compared to placebo after 12 months (-3 [95 percent CI -4.8 to -1.1] vs. -5.4 [-8 to -2.8]); results were similar for physician global assessment (56 percent better, 28 percent same, 16 percent worse vs. 53 percent better, 41 percent same, 6 percent worse) and mean decrease in ESR (9.4 vs. 10).

A fair-quality RCT[19] found no statistically significant effect on ESR in a 6-month study in patients treated with penicillamine compared to conventional treatment (-18 vs. -8). However, this study did find a statistically significant decrease in the number of painful joints in patients taking penicillamine (-3 vs. -1.6; $p < 0.04$). This study was of fair quality because the patients in the placebo group may have had worse disease.

A poor-quality, open-label RCT[21] found no statistically significant effect for penicillamine compared to gold at 50 weeks in the active joint count (-2.5 vs. -5), median change in the physician global assessment (-7.5 vs. -9), change in ESR (-8 vs. -11), or the proportion of patients who had at least a 50 percent improvement based on physician assessment (8/12 vs. 10/15).

Sulfasalazine

One good RCT evaluated sulfasalazine versus placebo.[15] In this study, it was unclear which time points were compared. However, there was statistically significant improvement with sulfasalazine in active joint count (-5.54 vs. -0.78; $p = 0.005$), physician global assessment (-1.95 vs. -0.99; $p = 0.0002$), patient/parent global assessment (-0.98 vs. -0.44; $p = 0.01$), and decrease in ESR (-0.74 vs. -0.04; $p < 0.001$). The number of improved joints by x-ray findings was not statistically significantly different (0.71 vs. 0.53).

Key Question 2. In children with JIA, what are the comparative effects of DMARDs on laboratory markers of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

Key Point

- There are few direct comparisons of DMARDs in children with JIA, and insufficient evidence to determine if any specific drug or drug class has greater beneficial effects.

Detailed Analysis

Literature Identified

We identified six reports describing five unique studies and involving 520 patients that directly compared various DMARDs with one another (Table 6). Among these studies were one that compared two biologic DMARDs (etanercept and infliximab) and four that compared various non-biologic DMARDs (penicillamine, hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine). A detailed summary of these studies, by treatment comparison, is provided below. Of the five studies, one was an open-label, non-randomized comparison, and the rest were RCTs. However, only two of the studies were considered to be of good quality (one comparing penicillamine to hydroxychloroquine and another comparing leflunomide to methotrexate in a non-inferiority design study); the rest were poor in quality.

Table 6. Studies comparing various DMARDs with one another

Study	DMARD(s)	Other arthritis drugs	Study design	Study quality	Study population (n)	Followup duration	Key questions addressed
Lahdenne et al., 2003[31]	Etanercept vs. infliximab (biologics)	Methotrexate, prednisolone, cyclosporine A, sulfasalazine, intra-articular corticosteroids, NSAIDs	Open-label comparison	Poor	JIA - Polyarticular (24)	12 months	2, 3
Kvien et al., 1985[21]	Penicillamine vs. hydroxy-chloroquine	NSAIDs, prednisone	Open-label RCT	Poor	JRA: - Pauciarticular onset (41) - Polyarticular onset (31)	50 weeks	2, 3
Brewer et al., 1986[11] and Van Kerckhove et al., 1988[12]	Penicillamine vs. hydroxy-chloroquine	NSAIDs, acetaminophen, codeine, antibiotics	RCT	Good	JRA: - Polyarticular (142) - Pauciarticular (11) - Systemic (9)	12 months	1, 2, 3
Hoza et al., 1991[32]	Hydroxy-chloroquine vs. sulfasalazine	NSAIDs, prednisone	RCT	Poor	JCA: Oligoartuclar onset (13) - Polyarticular onset (23) - Systemic onset (3)	6 months	2, 3
Silverman et al., 2005[33]	Leflunomide vs. methotrexate	NSAIDs, prednisone, intra-articular corticosteroids	RCT with optional extension	Good	JRA - Polyarticular (94)	16 weeks (RCT) then 32 weeks	2, 3

Abbreviations: DMARD(s) = disease-modifying antirheumatic drug(s); JCA = juvenile chronic arthritis; JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial

Comparisons of Biologic DMARDs

Etanercept vs. Infliximab

One poor-quality, non-randomized, open-label study compared etanercept to infliximab.[31] This study was considered to be of poor quality because drug switching made it hard to interpret findings, few data were provided about the subjects, and assessment was not blinded to therapy. In addition, a total of 6 of the 24 subjects did not complete the study. Among the 10 receiving etanercept, one was withdrawn for non-compliance. Among the 14 receiving infliximab, 4 withdrew because of adverse events and one withdrew because of failure to reach the ACR Pediatric 50. After 12 months of treatment, the change in active joint count was similar between etanercept (-9.5 [95 percent CI -19 to -3]) and infliximab (-11.5 [95 percent CI -17 to -7.5]). Results were also similar in the two treatment groups for changes in the CHAQ score (-0.81 vs. −0.31; p = 0.12), physician global assessment (-29 vs. -35; p = 0.65), patient/parent global assessment (-24.5 vs. -27.5; p = 0.81), ACR Pediatric 75 (67 percent each), ACR Pediatric 50 (78 percent vs. 89 percent; p-value not reported, but calculated as 0.53) and ESR (28.5 vs. -25; p = 0.37).

Comparisons of Non-Biologic DMARDs

Penicillamine vs. Hydroxychloroquine

Two publications[11,12] described a good-quality RCT that compared penicillamine and hydroxychloroquine to placebo (results described above, under Key Question 1) and to one another. At 12 months, neither active drug was superior to the other based on active joint count, ESR, or physician global assessment.

One poor-quality, open-label RCT[21] compared hydroxychloroquine and penicillamine to gold (results described above, under Key Question 1) and to one another. At 50 weeks, there were no significant differences between the two DMARDs in active joint count, physician global assessment, or ESR.

Sulfasalazine vs. Hydroxychloroquine

One poor-quality RCT compared sulfasalazine to hydroxychloroquine.[32] This study was considered to be of poor quality because there was an inadequate description of the subjects, it was unclear if the study was blinded, and many of the outcomes were not validated. After 6 months, the average number of affected joints decreased by 1.5 in the sulfasalazine group and by 0.6 in the hydroxychloroquine group (no p-value reported). During this time, the ESR decreased in both the sulfasalazine group (52.7 to 36.3; no p-value reported) and hydroxychloroquine group (41.2 to 28.9; no p-value reported). Physician global assessment (9 better, 9 worse, 3 no effect for sulfasalazine vs. 8 better, 3 worse, 7 no effect for hydroxychloroquine; no p-value reported) and patient global assessment (10 better, 7 worse, 3 no effect for sulfasalazine vs. 7 better 5 worse 3 no effect for hydroxychloroquine; no p-value reported) were similar in the two groups.

Leflunomide vs. Methotrexate

One good-quality RCT compared leflunomide to conventional treatment with methotrexate.[33] This 16-week study with a 32-week blinded extension found improvements in both groups. The active joint count decreased for the leflunomide and conventional treatment groups (-8.1 vs.

−8.9; p = not significant). Similarly, in both groups there were improvements in the CHAQ score (−0.44 vs. -0.39; p = not significant), physician global assessment (-31.5 vs. -32.1; p = not significant), parent global assessment (-15.9 vs. -22; p = not significant), and ESR (-6.5 vs. 7.2; p = not significant). As the trial proceeded, the methotrexate group appeared to have a greater improvement in the proportion of patients who had an ACR Pediatric 30, Pediatric 50, or Pediatric 70 response. For example, 70 percent of the leflunomide group and 83 percent of the methotrexate group achieved an ACR Pediatric 70 response at 48 vs. 16 weeks. The improvement was not statistically significant for either the leflunomide (p = 0.01) or methotrexate (p = 0.06) groups. No statistical comparison was made between the two groups.

Key Question 3. In children with JIA, does the rate and type of adverse events differ between the various DMARDs or between DMARDs and conventional treatment with or without methotrexate?

Key Points

- There are few direct comparisons of DMARDs with one another in children with JIA, and insufficient evidence to determine if there are differential rates of adverse events between specific drugs or drug classes.
- Reported rates of adverse events are similar between DMARDs and placebo in nearly all published RCTs.
- Adverse event rates may be underestimated by clinical trials that excluded patients who did not tolerate an intervention during a run-in phase.
- Our review identified 11 incident cases of cancer among several thousand children treated with one or more DMARDs.
- Two recently published studies identified 66 cases of malignancy worldwide in children with JIA exposed to a tumor necrosis factor α blocker.
- The available data on harm must be interpreted with caution because data on adverse events have not been systematically collected or reported across studies.

Detailed Analysis

Literature Identified

Of the 15 eligible RCTs identified by our search strategy, 13 included a placebo comparison and reported adverse events. Eight of these were traditional RCTs and five were randomized discontinuation trials. Because one of these studies included three study arms, a total of 14 DMARDs or DMARD combinations were directly compared to placebo. Anakinra, abatacept, etanercept, infliximab, tocilizumab, azathioprine, hydroxychloroquine, and sulfasalazine were each represented by a single study; etanercept, IVIG, and penicillamine were each represented by two studies; and methotrexate was compared to placebo in one study and was used in combination with infliximab in another study. A total of 914 unique patients were represented in the 13 placebo-controlled trials.

Our wider review of the adverse events literature identified a total of 151 publications that reported adverse events possibly associated with a DMARD among patients with JIA (Appendix E). Of these 151 publications, 19 (13 percent) were RCTs; the remainder were open-label

extension phases of previously published RCTs, prospective or retrospective series, or case reports. Four thousand and three hundred and forty-four (4344) patients were represented in these reports, with 2286 patients (53 percent) participating in an RCT. There was insufficient information in these publications to determine whether data from some patients were included in more than one published report. Furthermore, some series included some patients who were either adults or who did not have JIA.

An additional two publications[34,35] identified 66 (possibly not unique) cases of malignancies diagnosed in children undergoing treatment for JIA with a DMARD; we discuss these two studies separately because they did not include information about the population of patients from which these cases were identified.

Reporting standards for adverse events varied greatly across studies. For the purpose of this report, we consolidated the many different descriptions of reported adverse events into 24 broad categories, which we in turn categorized as involving a primary organ system, being an isolated symptom, or as "other." We did not include minor or transient events (e.g., rash) that were identified by the authors of the published reports as possibly associated with infusion of the drug.

Placebo-Controlled RCTs of Biologic DMARDs

Safety data from the 13 placebo-controlled trials are summarized in Table 7 (Parts 1-3) and described in greater detail for the specific DMARDs evaluated in the sections that follow.

Table 7. Adverse events reported in RCTs

Table 7, Part 1. Dropouts and adverse events related to organ systems

DMARD	Study	Intervention	Sample size	Dropouts due to AEs	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
Biologic agents										
Abatacept	Ruperto et al., 2008[24]	Drug	62	-	-	-	-	-	-	-
		Placebo	60	-	-	-	-	-	-	-
Anakinra	Ilowite et al., 2009[30]	Drug	25	-	6	2	-	8	6	-
		Placebo	25	-	1	10	-	7	4	-
Etanercept	Lovell et al., 2000[26]	Drug	25	0	1	1				
		Placebo	26	0	-	-	-	-	-	-
	Smith et al., 2005[16]	Drug	7	-	-	-	-	-	-	-
		Placebo	5	-	-	-	-	-	-	-
Infliximab + MTX	Ruperto et al., 2007[17]	Drug + MTX	60	2	-	-	-	-	-	-
		Placebo + MTX	62	1	-	-	-	-	-	-
IVIG	Giannini et al., 1996[28]	Drug	10	0	-	-	-	-	-	-
		Placebo	9	0	-	-	-	-	-	-
	Silverman et al., 1994[20]	Drug	14	-	-	-	-	-	-	0
		Placebo	17	-	-	1	-	-	-	-
Tocilizumab	Yokota et al., 2008[29]	Drug	20	1	1	-	-	2	-	-
		Placebo	23	1	1	-	-	4	-	-

Table 7, Part 1. Dropouts and adverse events related to organ systems (continued)

DMARD	Study	Intervention	Sample size	Dropouts due to AEs	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
Non-biologic agents										
Azathioprine	Kvien et al., 1986[18]	Drug	17	3	-	1	2	-	-	-
		Placebo	15	0	-	-	-	-	-	-
Hydroxychloroquine	Brewer et al., 1986[11]	Drug	57	3	-	2	7	-	-	-
		Placebo	51	3	-	-	4	-	-	-
Methotrexate	Giannini et al., 1992[13]	Drug	86	3	10	0	0	-	-	-
		Placebo	41	0	5	-	-	-	-	-
Penicillamine	Brewer et al., 1986[11]	Drug	54	2	-	4	2	-	-	1
		Placebo	51	2	-	-	4	-	-	-
	Prieur et al., 1985[19]	Drug	38	-	6	3	-	-	-	-
		Placebo	36	-	4	1	-	-	-	-
Sulfasalazine	van Rossum et al., 1998[15]	Drug	35	10	24	9	-	-	9	-
		Placebo	34	0	18	3	-	-	5	-

Table 7, Part 2. Specific symptoms

DMARD	Study	Intervention	Sample size	Fever	Nausea/vomiting	Pain	Alopecia/Hirsutism	Bleeding	Infection
Biologic agents									
Abatacept	Ruperto et al., 2008[24]	Drug	62	-	-	-	-	-	-
		Placebo	60	-	-	-	-	1	1
Anakinra	Ilowite et al., 2009[30]	Drug	25	3	-	0	-	-	-
		Placebo	25	2	-	2	-	-	-
Etanercept	Lovell et al., 2000[26]	Drug	25	-	-	-	-	-	-
		Placebo	26	-	-	-	-	-	-
	Smith et al., 2005[16]	Drug	7	-	-	-	-	-	5
		Placebo	5	-	-	-	-	-	3
Infliximab + MTX	Ruperto et al., 2007[17]	Drug + MTX	60	-	-	-	-	-	41
		Placebo + MTX	62	-	-	-	-	-	28
IVIG	Giannini et al., 1996[28]	Drug	10	-	-	-	-	-	-
		Placebo	9	-	-	-	-	-	-
	Silverman et al., 1994[20]	Drug	14	-	-	-	-	-	-
		Placebo	17	-	-	-	-	-	-
Tocilizumab	Yokota et al., 2008[29]	Drug	20	-	-	-	-	-	1
		Placebo	23	-	-	-	-	-	1

Table 7, Part 2. Specific symptoms (continued)

DMARD	Study	Intervention	Sample size	Fever	Nausea/vomiting	Pain	Alopecia/Hirsutism	Bleeding	Infection
Non-biologic agents									
Azathioprine	Kvien et al., 1986[18]	Drug	17	1	1	1	1	1	3
		Placebo	15	-	-	2	1	0	-
Hydroxychloroquine	Brewer et al., 1986[11]	Drug	57	-	-	-	-	-	-
		Placebo	51	-	-	-	-	-	-
Methotrexate	Giannini et al., 1992[13]	Drug	86	-	-	6	-	-	-
		Placebo	41	-	-	0	-	-	-
Penicillamine	Brewer et al., 1986[11]	Drug	54	-	-	-	-	-	-
		Placebo	51	-	-	-	-	-	1
	Prieur et al., 1985[19]	Drug	38	-	-	-	-	-	2
		Placebo	36	-	-	-	-	-	-
Sulfasalazine	van Rossum et al., 1998[15]	Drug	35	-	-	-	-	-	-
		Placebo	34	-	-	-	-	-	-

Table 7, Part 3. Other

DMARD	Study	Intervention	Sample size	Anemia	Other hematologic abnormality	Macrophage activation syndrome	Other laboratory abnormality	Elevated liver enzymes	Other	Serious AEs	Death
Biologic agents											
Abatacept	Ruperto et al., 2008[24]	Drug	62	-	-	-	-	-	-	0	-
		Placebo	60	-	-	-	-	-	-	2	-
Anakinra	Ilowite et al., 2009[30]	Drug	25	-	-	-	-	-	7	-	-
		Placebo	25	-	-	-	-	-	9	-	-
Etanercept	Lovell et al., 2000[26]	Drug	25	-	-	-	-	-	-	-	-
		Placebo	26	-	-	-	-	-	1	-	-
	Smith et al., 2005[16]	Drug	7	-	-	-	-	-	-	-	-
		Placebo	5	-	-	-	-	-	-	-	-
Infliximab + MTX	Ruperto et al., 2007[17]	Drug + MTX	60	-	-	-	-	-	-	19	-
		Placebo + MTX	62	-	-	-	-	-	-	3	1
IVIG	Giannini et al., 1996[28]	Drug	10	-	-	-	-	-	-	-	-
		Placebo	9	-	-	-	-	-	-	-	-
	Silverman et al., 1994[20]	Drug	14	-	-	1	-	1	-	-	-
		Placebo	17	-	-	-	-	-	-	-	-
Tocilizumab	Yokota et al., 2008[29]	Drug	20	-	-	-	-	-	-	-	0
		Placebo	23	-	-	-	-	-	-	-	0

Table 7, Part 3. Other (continued)

DMARD	Study	Intervention	Sample size	Anemia	Other hematologic abnormality	Macrophage activation syndrome	Other laboratory abnormality	Elevated liver enzymes	Other	Serious AEs	Death
Non-biologic agents											
Azathioprine	Kvien et al., 1986[18]	Drug	17	-	2	-	-	-	1	-	-
		Placebo	15	-	-	-	-	-	0	-	-
Hydroxychloroquine	Brewer et al., 1986[11]	Drug	57	6	4	-	8	-	-	-	-
		Placebo	51	2	2	-	5	-	-	-	-
Methotrexate	Giannini et al., 1992[13]	Drug	86	-	-	-	30	0	3	-	-
		Placebo	41	-	-	-	5	-	0	-	-
Penicillamine	Brewer et al., 1986[11]	Drug	54	2	4	-	9	-	-	-	-
		Placebo	51	2	2	-	5	-	-	-	-
	Prieur et al., 1985[19]	Drug	38	-	1	-	-	-	1	-	-
		Placebo	36	-	-	-	-	-	0	-	-
Sulfasalazine	van Rossum et al., 1998[15]	Drug	35	-	2	-	4	2	-	1	-
		Placebo	34	-	0	-	0	0	-	0	-

Abbreviations to Table 7, Parts 1-3: AEs = adverse events; DMARD = disease-modifying antirheumatic drug; IVIG = intravenous immunoglobulin; MTX = methotrexate; RCTs = randomized controlled trials

Abatacept

One good-quality study[24] randomized 62 patients to abatacept in a 6-month RCT that was preceded by an open-label run-in phase. No adverse events associated with abatacept or placebo were reported.

Anakinra

One study rated as being of fair quality for the purposes of evaluating safety randomized 25 patients to anakinra in a 16-week RCT that was preceded by an open-label run-in phase.[30] Among the patients in the anakinra arm, 6 (24 percent) had gastrointestinal events, 2 (8 percent) had dermatologic events, 8 (32 percent) had respiratory events, 6 (24 percent) had neurologic events, 3 (12 percent) had fever, 2 (6 percent) reported pain, and 7 (28 percent) had other adverse events. None of the adverse events was considered by the authors to be serious. These rates were similar to those observed in the placebo arm, with the exception of the 10 patients (40 percent) who reported dermatologic events.

Etanercept

Two studies compared etanercept to placebo. One[26] was a good-quality study that evaluated only children with polyarticular JRA. Of the 25 patients randomized to the etanercept arm after an open-label run-in phase, gastrointestinal and dermatologic events were each reported in one patient (four percent). There were no dropouts due to adverse events. The second study[16] was a fair-quality RCT that evaluated the safety and efficacy of etanercept for the treatment of uveitis. Unspecified infections were reported in 5 of the 7 patients (71 percent) in the etanercept arm, and in 3 of the 5 patients (60 percent) in the placebo arm

Infliximab

Infliximab plus methotrexate was compared to placebo plus methotrexate in one fair-quality RCT.[17] This study inconsistently and incompletely reported outcomes, and there was insufficient information to compare adverse event rates in the two study arms over all time periods. Infection was reported in 41 of the 60 patients (68 percent) who received infliximab 3 mg/kg plus methotrexate during the 14 weeks of the RCT phase and the subsequent 38 weeks of the open-label continuation phase, compared to 28 of 62 patients (45 percent) in the placebo plus methotrexate arm during the 14-week RCT phase. Nineteen serious adverse events were reported among the 60 patients (32 percent) in the infliximab plus methotrexate arm over 52 weeks, compared to 3 of 62 patients (5 percent) in the placebo plus methotrexate group over 14 weeks. The nature of the serious adverse events was not reported. Two patients (three percent) in the infliximab plus methotrexate arm and one patient (two percent) in the placebo plus methotrexate arm dropped out because of adverse events.

IVIG

Two studies compared IVIG to placebo. One small, fair-quality study[28] reported no adverse events during the course of the 4-month RCT phase preceded by a 3- to 6-month run-phase among the 10 patients randomized to IVIG or the 9 patients randomized to placebo. Another study,[20] rated poor in quality, reported macrophage activation syndrome in 1 patient (7 percent) and elevated liver enzymes in another (7 percent) among the 14 patients randomized to IVIG, and no similar adverse events among the patients in the placebo arm.

Tocilizumab

One fair-quality study compared tocilizumab to placebo during a 12-week double-blind RCT phase preceded by a 6-week run-in phase.[29] One patient in each group (5 percent) dropped out because of adverse events. Of the 20 patients in the tocilizumab arm, 1 (5 percent) reported a gastrointestinal event, 2 (10 percent) reported a respiratory event, and 1 (5 percent) reported a mononucleosis infection. Similar rates of adverse events were reported by patients in the placebo arm.

Placebo-Controlled RCTs of Non-Biologic DMARDs

Azathioprine

One fair-quality study compared azathioprine to placebo in a 16-week RCT.[18] Among the 17 patients randomized to azathioprine, 3 (18 percent) dropped out because of adverse events, 3 (18 percent) had an infection, 2 (12 percent) had renal or urologic events, and 2 (12 percent) had a hematologic abnormality. The adverse event rate for dermatologic events, fever, nausea/vomiting, pain, alopecia, or bleeding was 6 percent among patients in the azathioprine arm. Among the 15 patients randomized to placebo, none dropped out because of adverse events, 2 (13 percent) reported pain, and 1 (7 percent) reported alopecia.

Hydroxychloroquine

One fair-quality RCT compared both hydroxychloroquine and penicillamine to placebo over the course of 12 months.[11] Of the 57 patients in the hydroxychloroquine arm, 3 (5 percent) dropped out due to adverse events, 2 (4 percent) had a dermatologic event, 7 (12 percent) had a renal or urologic event, 6 (11 percent) had anemia, 4 (7 percent) had a hematologic abnormality,

and 8 (14 percent) had other laboratory abnormalities. Adverse event rates were similar among patients in the placebo arm.

Methotrexate

A single good-quality study compared methotrexate to placebo in a double-blind RCT of 6 months' duration.[13] Forty-six patients were randomized to low-dose (10 mg/m^2/week) methotrexate, 40 were randomized to very low-dose (5 mg/m^2/week) methotrexate, and 41 were randomized to placebo. Of the 86 patients in a methotrexate arm, 3 (3 percent) dropped out due to adverse events, 10 (12 percent) reported a gastrointestinal event, 6 (7 percent) reported pain, and 30 (35 percent) had a laboratory abnormality (compared to 13 percent in the placebo arm). None of the patients in the placebo arm dropped out because of adverse events.

Penicillamine

One fair-quality RCT compared both penicillamine and hydroxychloroquine to placebo over the course of 12 months.[11] Of the 51 patients in the penicillamine arm, 2 (4 percent) dropped out do to adverse events, 4 (8 percent) had a dermatologic event, 1 (2 percent) had an ophthalmologic event, 2 (4 percent) had anemia, 4 (8 percent) had a hematologic abnormality, and 9 (17 percent) had other laboratory abnormalities. In another study, a good-quality RCT of 6 months' duration,[19] 38 patients were randomized to the penicillamine arm. Among those patients, 6 (16 percent) reported a gastrointestinal event, 3 (8 percent) reported a dermatologic event, 2 (5 percent) had an infection, and 1 (3 percent) had a hematologic abnormality. Adverse event rates were similar among the patients in the placebo arms in both studies.

Sulfasalazine

A single good-quality RCT of 6 months' duration compared sulfasalazine to placebo.[15] Among the 35 patients randomized to sulfasalazine, 10 (29 percent) dropped out due to adverse events (compared to none in the placebo arm), 24 (69 percent) reported a gastrointestinal event, 9 (26 percent) reported a dermatologic event, 9 (26 percent) reported a neurologic event, 2 (6 percent) had hematologic abnormalities, 2 (6 percent) had elevated liver enzymes, and 4 (11 percent) had other laboratory abnormalities. All of the adverse event rates were higher in the sulfasalazine group than in the placebo group.

Other Studies

The data from our wider review of the literature reporting adverse events among patients with JIA undergoing treatment with a DMARD are summarized in Appendix E. Patients treated with one or more DMARDs in the placebo-controlled RCTs described in the preceding two sections are included in Appendix E; patients in non-DMARD comparison arms of those RCTs are not included. The "other" category of adverse events includes a wide variety of events that were infrequently reported, such as asthenia, malaise, hostility, or taste disturbance.

A single death possibly associated with DMARD use was reported in a girl on immunosuppressive therapy with cyclosporine A and methotrexate who died of Legionella pneumonia at the age of 53 months.[36] Autopsy revealed stage IV lymphoma that was not previously diagnosed.

An additional 10 cases of cancer, seven of them lymphomas, were identified: two cases of thyroid carcinoma (one with etanercept,[37] the other with etanercept plus methotrexate[38]); a case of yolk sac carcinoma with etanercept plus methotrexate;[38] two cases of lymphoma with

etanercept plus methotrexate;[38,39] two cases of lymphoma in patients who had received infliximab, etanercept, and methotrexate;[39] and three cases of lymphoma with methotrexate alone.[40-42] Apart from than the 11 cases of cancer among the several thousand patients represented by the publications we reviewed, there was no clear evidence of a high incidence or prevalence of any given serious adverse event associated with DMARDs.

Two studies reported cases of malignancies possibly associated with tumor necrosis factor α blockers in children with JIA. Diak et al.[34] searched the U.S. Food and Drug Administration Adverse Event Reporting System through April 2008 to identify reported malignancy among persons aged 22 years or younger who had received treatment with infliximab, etanercept, or adalimumab. The authors identified 48 cases, half of which were lymphomas. The majority of reported cases (88 percent) involved the concomitant use of other immunosuppressants. McCroskery et al.[35] searched the etanercept clinical trials database and global safety databases to identify 15 confirmed and 3 potential malignancies in children with JIA who had been treated with etanercept. Seven of the confirmed cases were lymphomas. Neither study reported the size of the population of children from which these cases were identified, thereby precluding accurate estimation of event rates.

Key Question 4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?

Key Point

- Insufficient data are available to evaluate the efficacy, effectiveness, safety, or adverse effects of treatment with DMARDs by category of JIA.

Detailed Analysis

Literature Identified

The studies considered for this question were those identified for Key Questions 1 and 2, which also included the placebo-controlled trials considered for Key Question 3.

Efficacy and Effectiveness

Only one study compared the efficacy of the DMARD studied (methotrexate) across different diagnostic categories of JIA.[14] There was no statistically significant difference in the efficacy of methotrexate for oligoarticular JIA versus systemic JIA.

Safety and Adverse Events

The only study we identified that explicitly compared the efficacy of treatment by diagnostic category[14] did not report data on safety data or adverse events. We did not identify any studies that provided reliable information on the comparative safety or rates or types of adverse events among the various categories of JIA.

Key Question 5. What are the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?

Key Points

- The CHAQ was the most extensively evaluated instrument of the priority measures we considered. While it demonstrated high reproducibility and internal consistency, it had only moderate correlations with indices of disease activity and quality of life, and poor to moderate responsiveness. The CHAQ is sensitive to the degree of disability at baseline, with higher responsiveness for those with initially worse functional impairment.
- In general, reliability was moderate to high for measures of physical function for all measures examined, but poor to moderate for psychosocial domains. Similar findings were noted for measures of validity and responsiveness, where measures of psychosocial function and quality of life showed less correlation with disease activity indices and less responsiveness compared to the physical aspects of JIA. These findings are important to consider when discussing risk and benefits of altering treatments, as patients may have different tradeoffs based on the psychosocial aspects of disease.
- No one instrument or outcome measure appears superior in describing the various aspects of JIA with adequate reliability, validity, and responsiveness.
- Definitions to describe various disease states including improvement, remission, and flare have been developed, but further studies are needed to better define their psychometric properties.

Detailed Analysis

Measures Evaluated

As described in the Methods section, based on our initial review of the literature identified, and in collaboration with the project's technical expert panel (TEP), we selected seven measures for detailed evaluation for Key Question 5. This section provides basic descriptions of these seven measures. While several other outcome instruments have been developed for JIA, including the Juvenile Arthritis Functional Assessment Scale and Report and the Juvenile Arthritis Functionality Scale, their psychometric properties were not independently examined, as they were not selected as priority measures by the TEP.

Measures of Disease Activity

- **Active joint count (AJC):** Standard full joint count assesses 71 possible joints for active disease, defined as joints with swelling or pain/tenderness on range of motion. Limited range of motion may also be assessed, but this is listed as a separate measure from active joint count. This requires a full musculoskeletal exam by a health professional.
- **Physician global assessment of disease activity (PGA):** Typically assessed by asking the physician to rate the child's overall disease activity on a visual analog scale (VAS), with higher scores indicating greater disease activity. Most commonly assessed utilizing a 100 mm VAS; representative anchors are "remission" and "very severe." The same scale is used for all categories of JIA.
- **Parent/patient global assessment of well-being (PGW):** Assessed by a VAS, most commonly by asking the parent/caretaker to assess how their child is doing after considering all the ways that arthritis affects their child's life. Representative anchors are "very well" and "very poorly." While the PGA assesses only disease activity, the PGW is an assessment of overall well-being.

Measures of Functional Status/Disability

- **Childhood Health Assessment Questionnaire (CHAQ):** The CHAQ was adapted from the Stanford Health Assessment Questionnaire (HAQ), a validated measure used in adult populations to describe disability quantitatively. The CHAQ focuses on disability and discomfort caused by JIA, which have previously been identified as the major indicators of disease impact. The CHAQ consists of a disability index (CHAQ-DI; 30 items, 8 domains), and two visual analogue scales, one for pain/discomfort (100 mm VAS), and the second for overall well-being (100 mm VAS). The disability index is scored based on the amount of difficulty the child has in completing various tasks. To allow for variation based on the child's age and development, rather than disease status, a "not applicable" category also exists. The instrument is usually completed by parents, although there is a child's form for children over 8 years of age. The CHAQ is scored from 0 to 3, with higher scores indicating greater disability. The CHAQ is widely used and has been validated in multiple languages. A ceiling effect has been noted with the CHAQ, with poor discriminate ability for children with mild functional impairments. Furthermore, it does not distinguish nor correct for impairments due to old damage versus active disease.

Measures of Health-Related Quality of Life

- **Child Health Questionnaire (CHQ):** The CHQ is a general quality-of-life questionnaire which has been in used in children with JIA. It is a self-administered questionnaire with both a parent form, which is available in two lengths (50 or 28 items) and a child form with 87 items (for children aged > 10 years). Most studies in JIA utilize the 50-item questionnaire for parents. The CHQ addresses multiple domains, including physical functioning, bodily pain or discomfort, general health, range in health, limitations in schoolwork and activities with friends, mental health, behavior, self-esteem, family cohesion, limitations in family activities, and emotional or time impact on parent. Scores range from 0 to 100, with higher scores indicating better well-being. Scores are calculated using equations provided in the CHQ manual. The CHQ is reported as a physical score (CHQ PhS) and a psychosocial score (CHQ PsS), as well as a combined score.
- **Pediatric Quality of Life Inventory (PedsQL) 4.0:** The PedsQL is a self-administered questionnaire consisting of generic core questions and disease-specific questions. It applies to children ages 2 to 18 years and includes both a child and parent component. The generic core has 23 items assessing 4 domains: physical, emotional, social, and school functioning.
- **Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM):** The PedsQL-RM consists of 22 items addressing 5 domains: pain and hurt, daily activities, treatment, worry, and communication. The total score is on a 0 to 100 scale, with higher scores indicating better quality of life. The total score is calculated from the physical score and a psychosocial score (average of emotional, social, and school functioning scores).

The above-listed measures are further described and compared in Table 8.

Definitions of Treatment Response now Under Development

In addition to the measures prioritized for detailed evaluation, we identified four developing definitions of treatment response: ACR Pediatric response criteria, a consensus-based definition of remission,[43,44] flare,[45] and minimal disease activity. These definitions are multi-dimensional, often using data from the measures we evaluated in detail.

Table 8. Outcomes measures assessed

Measure/ instrument	Number of items	Domains description	Response categories	Scoring range	Mode of administration	Feasibility	Comments
Measures of disease activity							
Active joint count	Full 71 joints exam	Active arthritis	Active, inactive	0 to 71*	Health professional	Joint count summed	Reduced joint count measures exist
Physician global assessment	1 item	Active disease	Most commonly 100 mm VAS	0 to 100*	Health professional	Measure distance from 0 anchor	
Parent/patient global assessment	1 item	VAS or categorical, overall well-being	Most commonly 100 mm VAS	0 to 100*	Self-administered	Value of VAS, no calculation	Assesses disease activity, functional status, and quality of life
Measures of functional status							
CHAQ	CHAQ-DI: 30 items VAS: - Pain - Overall well-being	Physical function (covering 8 domains) Pain Overall well-being	0 to 3, and NA 0 = no difficulty 3 = inability to perform	Physical function: 0 to 3* VAS: 0-100 mm*	Self-administered, parent or patient	5 minutes to complete Score: highest score in each domain = score for domain; 2 minutes to score	Adapted from Stanford Health Assessment questionnaire
Measures of health-related quality of life							
CHQ	Parent form: 50 or 28 items Child form: 87 items	Physical health Pain Mental health School Social Family	0 to 100 0 = poor well-being 100 = excellent well being	0 to 100^#	Self-administered Children self-administer after age 10 years	Apply scoring formula as per manual	
PedsQL 4.0	23 items	Physical Emotional Social School functioning	5-point Likert scale (never to always)	0 to 100^	Self-administered	Together (generic and rheumatology module) takes 10-15 minutes	
PedsQL-RM	22 items	Pain and hurt Daily activities Treatment Worry Communication	5-point Likert scale (never to always)	0 to 100^	Self-administered		

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; CHAQ-DI = Childhood Health Assessment Questionnaire Disability Index; CHQ = Child Health Questionnaire; NA = not applicable; PedsQL = Pediatric Quality of Life Inventory; PedsQL-RM = Pediatric Quality of Life Inventory-Rheumatology Module; VAS = visual analog scale

*Higher score equals higher disease activity/functional impairment.

^Higher score indicates better quality of life.

#Mean score in United States: 50, SD 10.

Literature Identified

We identified of 35 publications describing 34 unique studies and involving 14,831 patients that investigated the psychometrics of the selected outcomes measures or developing definitions of treatment response (see Table 9). Among these were 14 studies that evaluated reliability, 21 studies that evaluated validity, and 9 that evaluated responsiveness for the selected outcomes measures. Overall, there were 3 RCTs, 11 longitudinal non-randomized trials, 16 cross-sectional studies, 3 studies with both a longitudinal arm and cross-sectional component, and 1 study (of a developing definition of treatment response) that involved a consensus-forming process. Of our selected outcomes measures, the CHAQ was most extensively studied, with 23 studies. The overall quality of the studies was fair, with few studies commenting on blinding, and only one[46] reporting sample size calculations.

Table 9. Studies of psychometric properties of common JIA outcomes measures and developing definitions of treatment response

Study	Instruments	Psychometrics	N	Study design (followup)	Study population
Outcomes measures of interest					
Bekkering et al., 2007[47]	CHAQ	Reliability Validity	28	Cross-sectional	JIA
Brown et al., 2005[46]	CHAQ	Reliability Responsiveness	92	Longitudinal (6 wk, 6 mo)	JIA
Brunner et al., 2005[48]	CHAQ	Validity	77	Cross-sectional	JRA
Brunner et al., 2005[49]	CHAQ	Responsiveness	92	Longitudinal (3.5 mo)	JRA
Dempster et al., 2001[50]	CHAQ	Reliability Responsiveness	131	Cross-sectional	JRA (spondyloarthropathy)
Geerdink et al., 2009[51]	CHAQ	Validity Feasibility	51	Cross-sectional	JIA
Len et al., 1994[52]	CHAQ	Reliability Validity Feasibility	53	Cross-sectional	JRA
Palmisani et al., 2006[53]	CHAQ	Validity	223	Cross-sectional	JIA
Pouchot et al., 2002[54]	CHAQ	Reliability Validity	306	Cross-sectional	JIA
Pouchot et al., 2004[55]	CHAQ	Validity	306	Cross-sectional	JIA
Saad-Magalhaes et al., 2010[56]	CHAQ	Validity Responsiveness	3193	Mixed cross-sectional and longitudinal (6 mo)	JIA
Singh et al., 1994[57]	CHAQ	Reliability Validity	72	Cross-sectional	JRA
Stephens et al., 2007[58]	CHAQ	Reliability	74	RCT	JIA
Takken et al., 2006[59]	CHAQ	Reliability Validity	76	Mixed cross-sectional and longitudinal	JIA
Tennant et al., 2001[60]	CHAQ	Reliability Validity	53	Cross-sectional	JIA
van der Net et al., 1996[61]	CHAQ	Validity Feasibility	23	Cross-sectional	JCA (polyarthritis)
Cespedes-Cruz et al., 2008[62]	CHQ	Validity	521	RCT (6 mo)	JIA (polyarthritis)
Oliveira et al., 2007[63]	CHQ	Validity	3324	Cross-sectional	JIA
Selvaag et al., 2003[64]	CHQ	Reliability Validity Responsiveness	116	Longitudinal (10 mo)	JRA
Sawyer et al., 2005[65]	PedsQL	Reliability Validity	54	Longitudinal (12 mo)	JIA

Table 9. Studies of psychometric properties of common JIA outcomes measures and developing definitions of treatment response (continued)

Study	Instruments	Psychometrics	N	Study design (followup)	Study population
Bazso et al., 2009[66]	CHAQ , joint count	Validity	434, 3324, 595	Mixed cross-sectional and longitudinal (6 mo)	JIA
Bekkering et al., 2001[67]	CHAQ, joint count	Validity	21	Cross-sectional	JIA (systemic onset JIA)
Magni-Manzoni et al., 2005[68]	CHAQ, joint count, PGA, PGW	Responsiveness	115	Longitudinal	JIA
Ruperto et al., 1999[69]	CHAQ, joint count, PGA, PGW	Responsiveness	26	Longitudinal (3 mo)	JCA (oligoarthritis)
Moretti et al., 2005[70]	CHAQ, joint count, PGA, PGW, CHQ	Responsiveness	44	Longitudinal (6 mo)	JIA (oligoarthritis)
Filocamo et al., 2007[71]	CHAQ, PGW, PGA, CHQ	Validity Responsiveness Feasibility	211 [114 longitudinal]	Longitudinal (6 mo)	JIA
Brunner et al., 2004[72]	CHAQ, PedsQL, PGW	Reliability	119	Longitudinal (3.5 mo)	86% JRA
Consolaro et al., 2007[73]	PGA, PGW	Reliability	537	Cross-sectional	JIA
FIlocamo,et al., 2010[74]	PGA, PGW	Validity	397	Cross-sectional	JIA
Sztajnbok et al., 2007[75]	PGA, PGW	Reliability Validity	197	Cross-sectional	JIA
Developing definitions of treatment response					
Lurati et al., 2006[76]	ACR Pediatric 30, ACR Pediatric 20	Validity	75	Longitudinal	JIA
Giannani et al., 1997[77]	Definition of improvement	Validity	77	Consensus-forming process	JRA
Ruperto et al., 1998[78]	Definition of improvement	Validity	111	Longitudinal (6 mo)	JCA (polyarthritis)
Brunner et al., 2002[45] and Lovell et al., 2000[26]	Definition of flare	Validity	25	Randomized discontinuation trial	JRA (polyarthritis)

Abbreviations: ACR Pediatric = American College of Rheumatology Response Criteria; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; JCA = juvenile chronic arthritis; JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; mo = month(s); PedsQL = Pediatric Quality of Life Inventory; PGA = physician global assessment of disease activity; PGW = Parent/patient global assessment of well-being; RCT = randomized controlled trial; wk = week(s)

Reliability

Reliability addresses the consistency of the instrument in measuring the construct of interest. We examined three areas of reliability: reproducibility, inter-rater reliability, and internal consistency. Instruments with greater reproducibility and inter-rater reliability may be more feasible to use in clinical trials and require smaller sample sizes to detect clinically important differences between treatment groups. We identified 10 studies examining various aspects of reliability for the CHAQ;[46,47,50,52,54,57-60,72] two studies each for the PGA, PGW[73,75] and PedsQL;[65,72] and one for the CHQ.[64]

Reproducibility, also called test-retest reliability, measures the extent to which an instrument scores the same value on repeat administration, assuming the patient's status is unchanged. This was assessed for the CHAQ in five studies, all of which demonstrated high correlation between administrations (correlation coefficient range 0.79 to 0.96).[47,52,54,57,58] The reliability of the PedsQL and CHQ are less well established in JIA populations. We did not identify any studies reporting reproducibility or internal consistency data in JIA populations for the joint counts, PGA, PGW, CHQ, or PedsQL.

Inter-rater reliability was most commonly explored to determine the correlation between parent and patient scores. Inter-rater reliability was measured for the CHAQ, CHQ, and PedsQL, all of which demonstrated a moderate to strong correlation between parent and child when assessing functional status or disability (CHAQ: 0.54 to 0.84;[46,50,57,72] CHQ PhS: 0.69 to 0.87;[64] PedsQL: 0.46 to 0.8, and PedsQL-RM: 0.3 to 0.90.[65,72] The correlation between parent and child was lower for psychosocial domains in two studies, including the PedsQL-RM worry domain (correlation coefficient 0.3)[65] and the CHQ PsS (correlation coefficient range, 0.38-0.53).[64]

Inter-rater reliability of the global assessment measures (PGA and PGW) was examined through comparisons of the physician and parent assessments, rather than parent/patient. The PGA and PGW were compared in two studies[73,75] and were found to have high rates of discordance. The first study focused on discordance between parent- and physician-reported global assessment of 0 (no disease activity/good overall well-being), while the second study examined discordance overall in the rating between parents and physicians across the spectrum of disease activity (as defined by a difference of greater than 1 cm on the VAS). Both studies demonstrated discordance in 60 percent of participants.

Internal consistency, assessed most commonly using Cronbach's alpha, refers to the extent to which all items measure the same construct. Internal consistency was evaluated in four studies for the CHAQ, with all showing high internal consistency (Cronbach's alpha 0.88 to 0.94 for all domains except the domain for "arising" [0.69]).[54,57,59,60] In addition, shorter versions of the CHAQ-DI were found to have high internal consistency, with Cronbach's alpha of 0.93 for both the 29-item and 18-item instruments.[59]

Validity

Validity refers to how well an instrument measures what it claims to measure. For some outcomes, such as joint inflammation, a reference standard is available (e.g., synovial biopsy) but may not be feasible or acceptable to patients. However, for many of the constructs assessed by the clinical outcome instruments we evaluated, there is no reference standard. Therefore, we evaluated construct validity based on how well the measures correlated with other indicators of disease, such as global assessments, articular counts, and scores from other validated instruments. We focused on studies in which the psychometric dimensions of the instrument

were specifically evaluated for children with JIA. Validation studies looking at the performance of an instrument among rheumatology patients in general, but not specifically in JIA patients, are not included in this review.

Of the 21 articles that met our inclusion criteria, 17 explored validation of the CHAQ[47,48,51-57,59-61,63,66,67,71,75] four validation of the CHQ,[62-64,71] and two validation of the PGA and PGW.[74,75] In addition, one study focused on the correlation of the PedsQL and PedsQL-RM with pain assessments.[65]

Results are summarized in Table 10. The CHAQ was most strongly correlated with the PGW, with a median correlation of 0.54 (0.44 to 0.7, 6 studies).[48,53,54,56,71,75] Of the articular measures of disease, both the AJC and the joints with limited range of motion (LROM) demonstrated moderate correlations with the CHAQ, with a median correlation of 0.45 (0.14 to 0.67, 9 studies[48,53-57,60,71,75]) and 0.49 (0.3 to0.76, 7 studies[47,48,53,55,63,66,71]), respectively. There was considerable variability in these correlations, with the most significant variations among children categorized by disease duration. For children early in the course of disease, the CHAQ correlated less well with AJC than for children later in the course of disease (0.14 and 0.61, respectively). Those with late disease had a strong correlation with LROM (0.76), but lower correlations with PGA (0.51).[53] Modified forms of the CHAQ, including reduced-item and digital versions, have been validated as well, although the correlation with measures of articular measures is slightly less than for the original CHAQ (values of 0.34 to 0.59).[47,51,59]

While there were no strong correlations between indicators of disease activity and the CHAQ, there were moderately strong correlations with other measures of functional status, including Steinbrocker functional class (Kendall Tau b 0.77).[57] There were also moderate correlations with measures of quality of life, including the PedsQL (-0.62) and the PedsQL-RM (-0.63).[48] Of interest, while there were moderate correlations between the CHAQ and the physical scale of the CHQ (PhS) (-0.58), there was poor correlation with the psychosocial scale of the CHQ (PsS) (-0.25).[64]

Studies of the CHQ reported on the physical scale and psychosocial scales separately. The two studies reporting on validity of the CHQ found consistently higher correlations between the physical component on all measures, from physician and parent/patient global assessments to articular indices and functional status.[63,64] While the CHQ was found to differentiate healthy children from those with JIA, we did not find any results indicating discriminate validity to accurately classify children with JIA by the extent of their disease.[62]

The PedsQL and PedsQL-RM have been studied in the general pediatric rheumatology populations, but the only study focusing on JIA evaluated correlations of both instruments with pain assessments. Child-reported pain assessments correlated with all subscales of the PedsQL and PedsQL-RM, and parent pain assessments correlated with three of four subscales for both instruments.[65]

Table 10. Validity—correlations of instruments with measures of diseases and other instruments

Instrument	PGA median (range)	PGW median (range)	AJC median (range)	LROM median (range)	Swollen joint count median (range)	Other instruments
CHAQ[47,48,51-57,59-61,63,66,67,71,75]	0.45 (0.2 to 0.67) 9 studies	0.54 (0.44 to 0.70) 6 studies	0.45 (0.14 to 0.67) 9 studies	0.47 (0.33 to 0.76) 6 studies	0.40 (0.22 to 0.65) 4 studies	PedsQL: -0.62 PedsQL-RM: -0.63 CHQ PhS: -0. 63 and 0.58 (2 studies) CHQ PsS: -0.25 (one study) Steinbrocker functional class: 0.77 Disease Activity Index: 0.60 ACR Functional Class: 0.64 Digital CHAQ: 0.97
CHQ[63,64,71]	CHQ PhS: -0.54 (-0.52 to -0.56) 2 studies CHQ PsS: -0.048 1 study	CHQ PhS: -0.64 (-0.63 to -0.65) 2 studies CHQ PsS: -0.315 1 study	CHQ PhS: -0.39 (-0.36 to -0.42) 2 studies CHQ PsS: -0.024 1 study			CHAQ: CHQ PhS: -0.54 (-0.50 to -0.57) 2 studies CHQ PsS: -0.25 (-0.22 to -0.28) 2 studies
PGA[74,75]	-	0.54	0.62 (0.47 to 0.77) 2 studies	0.49 (0.4 to 0.58) 2 studies	0.64 (0.51 to 0.76) 2 studies	CHAQ: 0.39 CHQ PhS: -0.53 CHQ PsS: -0.13
PGW[74,75]	0.54	-	0.45 (0.40 to 0.49) 2 studies	0.43 (0.38 to 0.48) 2 studies	(0.42 to 0.43) 2 studies	CHAQ: 0.53 CHQ PhS: -0.7 CHQ Pss: -0.29

Abbreviations: ACR = American College of Rheumatology; AJC = active joint count; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CHQ PhS= Child Health Questionnaire physical score; CHQ PsS = Child Health Questionnaire psychosocial score; LROM = limited range of motion; PedsQL = Pediatric Quality of Life Inventory; PedsQL-RM = Pediatric Quality of Life Inventory Rheumatology Module; PGA = physician global assessment of disease activity; PGW = Parent/patient global assessment of well-being

Responsiveness

Responsiveness is determined by two properties: reproducibility and the ability to register changes in scores when a patient's symptom status shows clinically important improvement or deterioration. Although there is no universally recommended measure of responsiveness, most indices rely on calculation of an effect size. The effect size is a unit-free index that uses the mean change score in the numerator and a measure of variability in the denominator. The standardized response mean (SRM)[79] and the responsiveness index[80,81] are particularly useful approaches to calculating effect sizes for this application because they incorporate information about the response variance into the denominator. According to Cohen and colleagues,[82] an effect size of 0.2 to 0.3 is considered a small effect, around 0.5 (0.4 to 0.7) a medium effect, and 0.8 or above a large effect. Deyo and others argue that the issue is not just sensitivity to change, but the ability to discriminate between those who improve and those who do not.[80,83] Receiver operating characteristic (ROC) curves are proposed as an approach for describing how well various changes in scale scores can distinguish between improved and unimproved patients. This approach requires a valid reference standard to make these clinical classifications.

Responsiveness was assessed in nine studies (Table 11). The responsiveness of the CHAQ was assessed in six studies.[46,56,68-71] The results of the six studies were quite variable, with effect sizes ranging from 0 to 0.5. The two studies evaluating responsiveness in oligoarticular populations found the CHAQ was less responsive in patients with oligoarticular disease compared to polyarticular disease, with SRM of 0 to 0.25 for oligoarticular and 0.48 to 0.6 for polyarticular populations.[46,56,68-70] This difference in responsiveness by disease category was seen even when the same definition of improvement was used.[56,69]

Three studies reported on the responsiveness of the global assessment measures and joint count indices. The most responsive measure was the PGA, with a large effect size, 1.59 (95 percent CI 1.0 to 2.32).[68-70] However, in two of these studies, the patients' initial designation as improved or not improved was based on the physician's assessment, either as a categorical assessment on a 5-point scale for the first study,[70] or by a definition of flare based on the addition or escalation of therapy in the second.[68] Swollen joint count and active joint count were also found to have moderate to high responsiveness (effect sizes 1.3 and 0.7, respectively) and may be appropriate alternative measures.[69]

The responsiveness of the CHQ was formally evaluated in two studies, both of which demonstrated poor overall responsiveness, with an SRM of 0.23 and an effect size of 0.18 to 0.23.[64,70] However, in the study that reported responsiveness separately based on disease state, the responsiveness was high in those designated as improved, at 0.96., indicating that the CHQ is sensitive to improvement, but the SRM was lower (-0.60) in those with worsening disease. [64]

The minimum clinically important difference (MCID) was evaluated for the CHAQ in two studies. The MCID helps clinicians interpret study results by estimating the amount of change on an instrument that is associated with a clinically meaningful change in the patient's status. The first study explored the question of minimal clinically important change using a theoretical scenario, and found a mean MCID for improvement of -0.13 in the CHAQ, and 0.75 for worsening.[50] The second study evaluated MCID in a JIA population and found that results differed by which external standard of disease was used, patient, parent, or physician assessment of disease. The mean MCID for improvement was -0.188 to 0 compared to child ratings, and 0 for parent and physician ratings.[49] The authors concluded that changes in a patient's condition

did not correlate well with the CHAQ, and therefore that the CHAQ is unlikely to be to a useful tool when making short-term medical decisions.

The ability of the various outcome measures to differentiate those who improved from those who did not was assessed using ROC curves. In general, ROC curves of 0.5 indicate the measure is no better than chance in discriminating between those who improved compared to those who worsened, while values closer to 1 indicate better discrimination. One study reported on ROC curves for our instruments of interest. The most discriminate measure of the instruments we examined was the physician global assessment, with a ROC curve of 0.86 (95 percent CI 0.72 to 0.95), compared to the parent global assessment value of 0.63 (0.46 to 0.78) and the CHAQ value of 0.56 (0.41 to 0.71).[70]

Table 11. Responsiveness

Instrument	Standardized response means	Effect sizes	ROC curves
CHAQ[46,56,68-71]	Median (range): Responders: 0.60 (0.39 to 0.8) Non-responders: 0.08 (0.01 to 0.15)	Median (range): 0.24 (0 to 0.5)	Value (95% CI): 0.56 (0.41 to 0.71)
Physician and Parent/patient global assessments[68-70]	Median (range): PGA: 0.9 (0.82 to 2.07) PGW: 0.5 (0.3 to 0.8) Mean change: PGA: 5.4 (2.6) PGW: 1.5 (2.0)	Median (range): PGA: 1.46 (1.0 to 2.32) PGW: 0.5(0.33 to 0.97)	Value (95% CI): PGA: 0.86 (0.72 to 0.95) PGW: 0.63 (0.46 to 0.78)
Joint counts[69]	Number swollen joints: 0.7 Active joints: 1.3	Number swollen joints: 1.3 Active joints: 0.7	
CHQ[64,70]	CHQ PhS: 0.19 CHQ PsS: 0.28 CHQ overall: 0.23	CHQ PhS: 0.18 CHQ PsS: 0.23	CHQ PhS: 0.67(0.5 to 0.81) CHQ PsS: 0.71 (0.54 to 0.85)

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; CHQ PhS= Child Health Questionnaire physical score; CHQ PsS = Child Health Questionnaire psychosocial score; CI = confidence interval; PGA = physician global assessment of disease activity; PGW = Parent/patient global assessment of well-being; ROC = receiver operating characteristic

Composite Definitions of Disease Status or Response to Therapy

Because JIA is a complex disorder, several composite definitions have been developed to categorize disease status or response to therapy. We describe these briefly below

American College of Rheumatology Pediatric Response Criteria (ACR Pediatric 30)

The ACR Pediatric 30 response criteria is based on a core set of six variables: (1) physician global assessment of disease activity; (2) parent/patient global assessment of overall well-being; (3) measure of functional ability (CHAQ or JAFAS); (4) number of joints with active arthritis; (5) number of joints with limited range of motion; and (6) ESR.[76-78] This measure is scored on a relative scale, based on percent improvement or worsening, and was developed to assess response to therapy in clinical trials. The initial response criteria were developed using a combination of statistical and consensus formation techniques.[77] For each of the 240 definitions of improvement considered, the sensitivity and specificity were calculated using the physicians' consensus rating of improvement as the reference standard. Nine of the definitions with a sensitivity and specificity greater than 80 percent were retained, including the ACR Pediatric 30,

which was rated highest based on sensitivity, specificity, measures of agreement, and face validity. The ACR Pediatric 30 is defined as 30 percent or more improvement in three of the six variables, with no more than one variable worsening by more than 30 percent. Similar definitions exist for ACR Pediatric 20, 50, 70, and 90, with the exception of requiring greater percentages of improvement, with no more than one variable worsening by 30 percent or more. These scores provide a relative measure of response, but not current disease state.

Juvenile Arthritis Disease Activity Score (JADAS)

The JADAS is a recently developed composite instrument designed to better characterize disease activity in JIA patients. It consists of four measures: (1) physician global assessment of disease activity (10 cm VAS); (2) parent/patient global assessment of overall well-being (10 cm VAS); (3) number of joints with active arthritis; and (4) ESR. While these measures are also included in the ACR Pediatric 30, 50 and 70 core set, the JADAS excludes the measures for "functional assessment" and "number of joints with limited range of motion," as they were considered to reflect disease damage rather than just disease activity. Furthermore, the JADAS aims to quantify the absolute level of disease activity, rather than relative improvement, as measured by the ACR Pediatric response criteria. While initial validation studies have been performed,[84] it is unclear how fully this outcome measure will be adopted in future studies, though its ability to characterize a patient's absolute response to therapy, as well as to describe differences in disease activity between groups of patients, is promising.

Remission

A consensus-based definition of "remission" identifies three categories: inactive disease, remission on medications, and remission off medications.[43,44] A Delphi serial questionnaire consensus-formation approach was used to draft the criteria. The criteria for inactive disease include no active arthritis; no fever, rash, splenomegaly, serositis, or generalized lymphadenopathy attributable to JIA; a normal ESR or C-reactive protein; and the best possible score on the physician global assessment of disease activity. In addition, the definition of inactive disease requires there to be no active uveitis. Children with 6 continuous months of inactive disease, as defined above, on medication meet the definition for clinical remission on medication, while 12 months of inactive disease off antirheumatic medications defines clinical remission off medication.[43,44] While these definitions have been applied retrospectively to JIA populations, further validations studies are underway.

Flare

A preliminary definition of flare was derived from a cohort of patients with polyarticular JIA using the six core response variables as defined in the ACR Pediatric.[26,45] The authors defined the standard of flare as treatment with placebo and then examined various definitions of flare based on receiver-operator characteristics. All 25 in the etanercept arm were presumed not to flare; therefore, the specificity of the flare definition equals the number without relapse by the candidate definition divided by the total in the etanercept group. Based on this methodology, a flare was defined as a 40 percent worsening in two of six core set items without improvement in more than one core set variable by 30 percent. This study was based on 51 children, and further validation studies are needed.

Minimal Disease Activity

The authors who defined minimal disease activity (MDA) developed the definition in acknowledgement that many children with JIA do not achieve full remission with current treatments, and that a more reasonable goal for treatment might be minimally active disease.[85] They therefore reviewed patient visits where changes in therapy were initiated verse visits where no change was made or medication was discontinued. They examined measures of disease activity at those visits and established cutoff values that best identified states of MDA. Their results defined MDA as a physician global assessment of < 2.5 cm and swollen joint count of 0 for oligoarticular disease; and a physician global assessment of < 3.4 cm, parent global assessment < 2.1 cm, and a swollen joint count of < 1 for polyarticular disease.[86] Validation studies are needed.

Summary and Discussion

A succinct summary of the results of this review of the comparative benefits and harms of DMARDs for children with JIA is presented in the tables that follow. First, we provide an aggregated view of the strength of evidence and brief conclusions (Table 12). Next, we describe the nature and quality of the evidence for Key Questions 1, 2, and 4 in a format recommended by the GRADE committee (Tables 13-16).[7] We then provide a tabular summary of the evidence for Key Question 5 (Table 17). Finally, we comment on the applicability of our findings.

Table 12. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA

Key question	Strength of evidence	Conclusions
1. In children with JIA, does treatment with DMARDs, compared to conventional treatment:		
a. Improve laboratory measures of inflammation?	Low	Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR). However, ESR is inconsistently associated with treatment. This conclusion is based on 14 studies of 1060 subjects.
b. Improve radiological progression?	Insufficient	Insufficient data are available to evaluate the impact of DMARDs on radiological progression. Only one cohort study of 63 subjects reported data on radiological progression.
c. Improve symptoms?	Moderate	Among children who have responded to a biologic DMARD, randomized discontinuation trials show that continued treatment for from 4 months to 2 years decrease the risk of having a flare (RR 0.46, 95% CI 0.36 to 0.60). This conclusion is based on four studies of 322 subjects. Among the non-biologic DMARDs, there is some evidence that methotrexate is superior to conventional therapy and oral corticosteroids, based on two randomized trials of 215 subjects.
d. Improve health status?	Low	Changes in health status were reported in 12 studies involving 927 subjects. Health status improved inconsistently with treatment with DMARDs.

Table 12. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)

Key question	Strength of evidence	Conclusions
2. In children with JIA, what are the comparative effects of DMARDs on:		
a. Laboratory measures of inflammation?	Low	Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR). However, ESR is inconsistently associated with treatment. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects.
b. Radiological progression?	Insufficient	No study addressed radiologic progression.
c. Symptoms?	Low	The non-biologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in symptoms between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor-quality RCT of 94 subjects found that etanercept was similar to infliximab.
d. Health status?	Low	The non-biologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in health status between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor quality RCT of 94 subjects found that etanercept was similar to infliximab.

Table 12. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)

Key question	Strength of evidence	Conclusions
3. In children with JIA, does the rate and type of adverse events differ between:		
a. The various DMARDs?	Insufficient	Three RCTs directly compared two DMARDs; two compared penicillamine to hydroxychloroquine, and one compared leflunomide to methotrexate. The rate and type of adverse events did not differ between treatment groups in these studies. High variability across studies in the ascertainment and reporting of adverse events preclude valid comparisons of the rate and type of adverse events among the various DMARDs. Recently published studies of adverse event reporting databases provide indirect evidence that suggests a possible relationship between cancer and exposure to tumor necrosis factor α blockers.
b. DMARDs and conventional treatment with or without methotrexate?	Insufficient	No RCT directly compared a DMARD to conventional treatment. Thirteen trials directly compared a DMARD to placebo. The rate and type of adverse events were generally similar between intervention and placebo groups, with the notable exceptions of infliximab plus methotrexate being associated with more serious adverse events (32% vs. 5% over differing lengths of followup), and methotrexate being associated with higher rates of laboratory abnormalities (35% vs. 13%).
4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?	Insufficient	Only one study – an RCT of methotrexate versus placebo in which each group could also receive oral corticosteroids, intra-articular corticosteroids, and NSAIDs – evaluated efficacy by JIA category. No difference was found among those with extended oligoarticular JIA (n = 43) and systemic JIA (n = 45). We did not identify any studies that provide reliable information on the comparative safety or rates or types of adverse events among the various categories of JIA.

Table 12. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)

Key question	Strength of evidence	Conclusions
5. What are the validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?	Insufficient	Most of the studies examining the psychometric properties of the instruments used in JIA were fair-quality cross-sectional or longitudinal non-randomized controlled trials. No one instrument or outcomes measure appeared superior in measuring disease activity or functional status. The current response criteria of the ACR Pediatric 30, a composite measure that includes articular indices, functional status, laboratory measure, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, given that the ACR Pediatric 30 is a relative measure of disease activity, the impact of JIA category on percent improvement is unclear, as certain instruments, such as the CHAQ, appear to have differential responsiveness depending on extent of disease at baseline. The ACR Pediatric 30 is also a relative measure of disease activity and not a measure of current disease state.

Abbreviations: ACR = American College of Rheumatology; CHAQ = Childhood Health Assessment Questionnaire; CI = confidence interval; DMARD(s) = disease-modifying antirheumatic drug(s); ESR = erythrocyte sedimentation rate; JIA = juvenile idiopathic arthritis; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial; RR = risk ratio

GRADE summary tables were developed to describe the strength of evidence. For Key Question 1, separate GRADE summary tables are presented for the biologic and non-biologic DMARDs. We identified six randomized discontinuation trials that were conducted for the biologic DMARDs. Unlike RCTs or prospective cohort trials, randomized discontinuation trials evaluate the risk of worsening disease among those who initially responded to therapy. Because of this fundamental difference, we present a separate GRADE strength of evidence rating for the randomized discontinuation studies for each outcome. GRADE summary tables do not apply to Key Question 3 or Key Question 5. Findings from Key Question 3 are summarized in Tables 7 (Parts 1-3), under Results, and in Appendix E. Findings from Key Question 5 are summarized by outcome measure in Table 16.

Table 13. GRADE summary table for key question 1—biologic DMARDs

	Domains pertaining to strength of evidence					
Number of studies; subjects	**Design**	**Risk of bias/study quality**	**Consistency**	**Directness**	**Precision**	**Strength of evidence**
Laboratory measures of inflammation						Low
1; 31	RCT	Poor (high dropout rate)	NA	Direct	Imprecise	-
4; 322	Randomized discontinuation trials	Poor to Good	Inconsistent	Direct	Precise	
1; 20	Cohort	Poor (open-label)	NA	Direct	Imprecise	-
Radiologic progression						Insufficient
0; 0	RCT	-	-	-	-	-
0; 0	Randomized discontinuation trials	-	-	-	-	-
0;0	Cohort	--	--	--	--	-
Symptoms						Moderate
3; 165	RCT	Fair (one study had high dropout rate)	Consistent	Direct	Imprecise	-
6; 341	Randomized discontinuation trials	Good	Consistent	Direct	Precise	
0; 0	Cohort	-	-	-	-	-
Health status						Low
1; 31	RCT	Poor (high dropout rate)	NA	Direct	Imprecise	-
4; 272	Randomized discontinuation trials	Good	Inconsistent	Direct	Imprecise	
0; 0	Cohort	-	-	-	-	-

Abbreviations: DMARDs = disease-modifying antirheumatic drugs; NA = not applicable; RCT = randomized controlled trial

Table 14. GRADE summary table for key question 1—non-biologic DMARDs

	Domains pertaining to strength of evidence					
Number of studies; subjects	**Design**	**Risk of bias/study quality**	**Consistency**	**Directness**	**Precision**	**Strength of evidence**
Laboratory measures of inflammation						Low
7; 624	RCT	Fair (open-label or unblinded)	Inconsistent	Direct	Imprecise	-
1; 63	Cohort	Poor (open-label)	NA	Direct	Imprecise	-
Radiologic progression						Low
1; 69	RCT	Good	NA	Direct	Imprecise	-
0; 0	Cohort	-	-	-	-	-
Symptoms						Moderate (MTX) Low (other non-biologic)
7; 624	RCT	Fair (open-label or unblinded)	Consistent	Direct	Imprecise	-
1; 63	Cohort	Poor (open-label)	NA	Indirect	Imprecise	-
Health status						Moderate (MTX) Low (other non-biologic)
7; 624	RCT	Fair (open-label or unblinded)	Consistent	Direct	Imprecise	-
1; 63	Cohort	Poor (open-label)	NA	Indirect	Imprecise	-

Abbreviations: DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; NA = not applicable; RCT = randomized controlled trial

Table 15. GRADE summary table for key question 2

	Domains pertaining to strength of evidence					
Number of studies; subjects	**Design**	**Risk of bias/study quality**	**Consistency**	**Directness**	**Precision**	**Strength of evidence**
Laboratory measures of inflammation						Low
4; 448	RCT	Fair (some studies with incomplete blinding)	Inconsistent	Direct	Imprecise	-
1; 72	Cohort	Poor (insufficient data)	NA	Direct	Imprecise	-
Radiologic progression						Insufficient
0; 0	RCT	-	-	-	-	-
0; 0	Cohort	-	-	-	-	-
Symptoms						Low
4; 448	RCT	Fair (some studies with incomplete blinding)	Inconsistent	Direct	Imprecise	-
1; 72	Cohort	Poor (insufficient data)	NA	Direct	Imprecise	-
Health status						Low
4; 448	RCT	Fair (some studies with incomplete blinding)	Inconsistent	Direct	Imprecise	-
1; 72	Cohort	Poor (insufficient data)	NA	Direct	Imprecise	-

Abbreviations: NA = not applicable; RCT = randomized controlled trial

Table 16. GRADE summary table for key question 4

	Domains pertaining to strength of evidence					
Number of studies; subjects	**Design**	**Risk of bias/study quality**	**Consistency**	**Directness**	**Precision**	**Strength of evidence**
Laboratory measures of inflammation						Insufficient
1; 88	RCT	Good	NA	Direct	Imprecise	-
0; 0	Cohort	-	-	-	-	-
Radiologic progression						Insufficient
0; 0	RCT	-	-	-	-	-
0; 0	Cohort	-	-	-	-	-
Symptoms						Insufficient
1; 88	RCT	Good	NA	Direct	Imprecise	-
0; 0	Cohort	-	-	-	-	-
Health status						Insufficient
1; 88	RCT	Good	NA	Direct	Imprecise	-
0; 0	Cohort	-	-	-	-	-

Abbreviations: NA = not applicable; RCT = randomized controlled trial

Table 17. Evidence summary table for key question 5

Number of studies; subjects	Evidence summary
Active joint count	
12; 8064	Shows high responsiveness and moderate correlation with other measures of disease activity and functional status, but poor correlation with psychosocial aspects of quality of life. Lack of inter-rater reliability data.
Physician global assessment of disease activity	
12; 8668	Moderate correlations with measures of disease activity, the CHAQ, and quality-of-life measures. Responsiveness difficult to measure, as often compared to other physician measures of disease activity. No data on inter-rater reliability between providers.
Parent/patient global assessment of well-being	
8; 8182	Moderate correlations with other measures of disease activity, the CHAQ, and physical aspects of the quality of life measures, but poor correlation with psychosocial aspects of the CHQ. Moderate responsiveness and discriminate abilities.
CHAQ	
23; 13,374	Most commonly reported outcome measure with strong reliability, including moderate to strong inter-rater reliability between parent and child. Moderate correlations with other measures of disease activity, but poor responsiveness, which varies depending on how extensive the arthritis is at baseline (ceiling effect).
CHQ	
5; 4687	Limited data for JIA population. Moderate to strong parent to child inter-rater reliability for physical components, but lower for psychosocial aspects. Similarly, moderate correlations with measures disease activity, and the CHAQ for the physical component of the CHQ, but poor for the psychosocial domains. Poor responsiveness.
PedsQL/PedsQL-RM	
2; 173	Insufficient data in JIA populations to evaluate fully. Moderate to strong parent to child inter-rater reliability for physical components, but lower for psychosocial aspects.

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; JIA = juvenile idiopathic arthritis; PedsQL = Pediatric Quality of Life Inventory; PedsQL-RM = Pediatric Quality of Life Inventory-Rheumatology Module

Applicability was assessed for Key Question 1 only. Insufficient evidence was available to rate applicability for Key Questions 2 and 3, and Key Question 4 and 5 were not amenable to assessment of applicability. For Key Question 1, we assessed applicability as follows:

- Population: There was variation across studies in the definition of JIA and both duration and severity of illness, likely reflecting the range of patients seen in usual practice. However, six of the studies of the biologic DMARDs were randomized discontinuation studies, which include patients who have responded to the intervention.
- Intensity or quality of treatment: With the exception of methotrexate, the non-biologic DMARDs are less often used than the newer biologic DMARDs. The intensity of treatment in the studies of the biologic DMARDs is consistent with current recommendations.
- Choice of, and dosing of, the comparator: Methotrexate, a non-biologic DMARD, is a standard treatment for JIA. Six of the studies of the biologic DMARDs included methotrexate as a comparator; none of the studies of the non-biologic DMARDs included methotrexate as a comparator. The reasons for use or dose escalation of the comparator drugs were usually not described.
- Outcomes: The most commonly reported outcome measures were laboratory indicators of inflammation (e.g., ESR) or the ACR Pediatric 30. The ACR Pediatric 30 blends several relevant outcomes (e.g., active joint count, functional status, pain), but is not normally used in daily clinical practice. As described for Key Question 5, new instruments to better assess response to therapy and changes in health-related quality of life are in development.
- Timing of followup: Five of the studies of biologic DMARDs and five of the studies of non-biologic DMARDs actively followed subjects for more than 6 months. This would allow sufficient time to detect clinically important benefits and may be long enough to identify important harms.

Future Research

Efficacy of DMARDs

Although DMARDs have improved health outcomes for children with JIA, few data are available to evaluate the comparative effectiveness of either specific DMARDs or general classes of DMARDs (e.g., non-biologic vs. biologic, or by mechanism of action). Not surprisingly, methotrexate, the oldest of the DMARDs used for children with JIA, is the most studied DMARD. Because it is frequently used, methotrexate is often considered to be a component of conventional treatment both in clinical care and in research studies. Good-quality studies support the efficacy of methotrexate. The paucity of evidence precludes head-to-head comparisons of the newer DMARDs against each other, with or without methotrexate.

Research on the effectiveness of treatments for JIA is challenging because it is a rare condition that includes multiple categories, which could potentially respond differentially to therapy. Furthermore, the health impact of JIA fluctuates over time. Therefore, trials require large sample sizes with long follow-up periods.

Developing a summary estimate of effectiveness of the DMARDs is challenging because there is:

- Heterogeneity in the study population. Changes in the definition of JIA (e.g., JRA, JCA) may have led to the inclusion in studies of individuals who may respond differently to treatments. Similarly, differences by disease category (e.g., polyarticular, pauciarticular, systemic) might lead to different conclusions about the effectiveness of treatment. This may be particular relevant when examining response rates for systemic JIA given its similarities to auto-inflammatory diseases.
- Variation in comparators. Over time, the standard of care for JIA has changed. For example, relatively recent studies of biologic DMARDs often allow methotrexate, a DMARD, in the comparator group, while older studies do not include methotrexate in the comparator groups. Some older studies included systemic corticosteroids as a comparator.
- Outcome measures vary across the studies and are sometimes incompletely described. For example, some studies report the percentage improvement from baseline without providing baseline data or an estimate of variability. Among the six randomized discontinuation trials, for example, four reported laboratory measures of inflammation,[24,26,29,30] four reported whether a flare occurred,[24-26,30] three reported active joint count,[24,28,29] and four reported quality of life as measured by CHAQ.[24,26,29,30] Of those that reported the CHAQ score, one[26] reported only the percentage change from baseline without the absolute value or measure of dispersion (e.g., range, standard deviation), and two[29,30] gave average values without measures of dispersion.

Future trials in this domain should consider:

- The challenge of the appropriate comparator. Trials are needed to evaluate the effectiveness of DMARDs compared to conventional therapy as well as against other DMARDs. Defining conventional therapy is challenging because it evolves with advances in the field. Factorial designs involving multiple treatments are a potential

solution. Patient-level meta-analysis, pre-planned across different trials, may also help address this issue.

- The issue of treatment-by-category interaction. To fully explore comparative effectiveness, larger studies will be needed. In addition, patient-level meta-analysis may help address this challenge.
- The need for study populations who are representative of typical patients with JIA. Subjects from the studies included in this review were identified through specialty clinics, which is appropriate for rare conditions. However, baseline characteristics varied. Studies should be designed to reflect the comparative effectiveness for typical subjects at various points along the disease spectrum (e.g., at presentation, after failing conventional treatment). Furthermore, most evidence regarding treatment impact is from patients with poly-articular forms of JIA with fewer data on persistent oligoarthritis, a common type of JIA.
- The variable course of JIA. Trials that evaluate the efficacy of treatment should be sufficiently long with frequent assessment of health status to capture the natural variability of the disease course.
- The need for standardized outcome measures. In addition to providing a better understanding of the impact of the trial, standardized outcome measures would facilitate high-quality meta-analysis.
- The need for standardized definitions for, and systematic ascertainment and reporting of, adverse events possibly associated with therapeutic interventions in the treatment of JIA.
- The impact of DMARDs on the specific health conditions associated with JIA, including uveitis and macrophage activation syndrome.

Study designs other than RCTs will be important in understanding the role of DMARDs in JIA. Randomized discontinuation trials have helped to define the risk of flare in patients who respond to a particular DMARD. Large cohort studies will be important for evaluating the risk of adverse events associated with DMARDs. Such studies could also be important for better characterizing long-term outcomes in JIA. Disease registries could be an important strategy for developing such cohort studies. In addition, such registries could provide indirect evidence about the benefits of treatment.

Safety of DMARDs

Few high-quality data are available regarding the adverse events associated with DMARDs. Because JIA is a chronic illness, understanding the long-term effects of these drugs is critical. One solution to evaluating risk would be to develop registries for DMARDs when used for childhood JIA. Understanding such risk will also provide information about the sequence in which these drugs should be used for difficult-to-treat JIA, or the impact of using multiple drugs.

Our findings suggest that short-term mortality rates associated with DMARDs are very low (we identified only a single patient among several thousand treated who died shortly after receiving a DMARD). The incidence of malignancies during a short course of DMARD treatment also appears to be very low. Simard et al.[87] have demonstrated that the incidence of malignancies among children with JIA appears to be higher, in general, over the past 20 years, than in the two decades prior to the advent and utilization of biologic DMARDs. These data are, however, confounded by numerous factors, most notably the frequent concurrent use of immunosuppressants in children undergoing treatment for JIA.

The available evidence is inadequate to determine whether the rates and types of adverse events differ between the various DMARDs or between DMARDs and conventional treatment. The findings from RCTs do not reveal a clear pattern pertaining to adverse events associated with the treatment of JIA with DMARDs compared to placebo. Our wider review of the adverse events literature revealed marked differences in the rate and type of adverse event by DMARD, but these findings should be interpreted with caution for several reasons, including: variable definitions of adverse events across studies; non-systematic methods of ascertaining adverse events; nearly universal lack of standard reporting of serious adverse events; a predominance of case reports and uncontrolled series; small sample sizes in most series and RCTs; a limited number of studies for many individual DMARDs; and frequent use of multiple medications and other co-interventions.

Impact of DMARDs on Health Outcomes

Our findings suggest the need for better clinical outcomes measures that are responsive to change across the full spectrum of disease severity. Consistent use of such outcomes measures would facilitate comparative effectiveness research.

The heterogeneity in disease severity and the broad impact of the disease on both physical and psychosocial aspects of children's lives make it difficult to accurately assess children using one instrument or measure. Given the complex nature of JIA, with the potential for both chronic and acute functional limitations and pain, it is difficult to find one tool or instrument that can be responsive to all the facets of disease. Efforts to develop a more standardized composite measure which could incorporate articular indices, severity, and a broader assessment of functional limitations and psychosocial impact would be useful to better differentiate levels of disease activity and overall impact of disease. The current response criteria of the ACR Pediatric 30 definition of improvement, a composite measure which includes articular indices, functional status, laboratory measure, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, given that the ACR Pediatric 30 is a relative measure of disease activity, the impact of JIA category on percent improvement is unclear, as certain instruments, such as the CHAQ, appear to have differential responsiveness by extent of disease at baseline. The ACR Pediatric 30 is also a relative measure and not a measure of current disease state.

The outcomes measured and reported should be tailored to the questions a study is investigating. If the question is whether a new therapy reduces active arthritis, utilizing outcome measures that focus on factors felt to reflect active disease, such as the JADAS, rather than overall disease status (active disease, disease damage, functional status, and quality of life) may prove particularly useful in more accurately addressing articular response to treatment. In addition, focusing on the most responsive outcome measures to assess treatment effects would enhance our ability to detect promising new treatments. Reporting functional status and quality of life are also important, especially given that many of our current treatments are delivered by infusion or injection and have varying side effects that can negatively impact one's quality of life. However, by reporting articular measures separately from functional status and quality of life measures, one may actually improve our understanding of the overall impact of JIA, including the influence of active arthritis, articular damage, and various treatment regimens.

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Abbreviations

ACR	American College of Rheumatology
ACR Pediatric	American College of Rheumatology Pediatric Response Criteria
AHRQ	Agency for Healthcare Research and Quality
AJC	Active joint count
CD	Cluster of differentiation
CHAQ	Childhood Health Assessment Questionnaire
CHAQ-DI	Childhood Health Assessment Questionnaire Disability Index
CHQ	Child Health Questionnaire
CHQ PhS	Child Health Questionnaire physical score
CHQ PsS	Child Health Questionnaire psychosocial score
CI	Confidence interval
DMARD(s)	Disease-modifying antirheumatic drug(s)
EPC	Evidence-based Practice Center
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
Fc	Fragment crystallizable
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAQ	Stanford Health Assessment Questionnaire
IgM	Immunoglobulin M
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IVIG	Intravenous immunoglobulin
JCA	Juvenile chronic arthritis
JADAS	Juvenile Arthritis Disease Activity Score (JADAS)
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LROM	Limited range of motion
MDA	Minimal disease activity
MeSH	Medical Subject Headings
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
PedsQL	Pediatric Quality of Life Inventory
PedsQL-RM	Pediatric Quality of Life Inventory Rheumatology Module
PGA	Physician global assessment of disease activity
PGW	Parent/patient global assessment of well-being
PICOTS	Population, interventions, comparators of interest, outcomes, timing, settings
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
RR	Risk ratio
SAARD(s)	Slow-acting antirheumatic drug(s)
SRC	Scientific Resource Center
T-cell/-lymphocyte	Thymus cell/lymphocyte
TEP	Technical expert panel
TNF	Tumor necrosis factor

Appendix A. Exact Search Strings

Search Strategies Used to Search MEDLINE® via PubMed®—Last Search Date December 23, 2010

Key Questions 1, 2, 3, and 4

(("arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]) AND ((("abatacept"[Substance Name] OR "abatacept"[All Fields]) OR ("abatacept"[Substance Name] OR "abatacept"[All Fields] OR "orencia"[All Fields]) OR ("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields]) OR ("interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "kineret"[All Fields]) OR ("azathioprine"[MeSH Terms] OR "azathioprine"[All Fields]) OR ("azathioprine"[MeSH Terms] OR "azathioprine"[All Fields] OR "imuran"[All Fields]) OR ("canakinumab"[Substance Name] OR "canakinumab"[All Fields]) OR ilaris[All Fields] OR ("cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporine a"[All Fields]) OR ("cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "neoral"[All Fields]) OR gengraf[All Fields] OR ("penicillamine"[MeSH Terms] OR "penicillamine"[All Fields] OR "d penicillamine"[All Fields]) OR Depen[All Fields] OR ("penicillamine"[MeSH Terms] OR "penicillamine"[All Fields] OR "cuprimine"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]) OR ("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields]) OR ("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields] OR "plaquenil"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields] OR "remicade"[All Fields]) OR ("leflunomide"[Substance Name] OR "leflunomide"[All Fields]) OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "ivig"[All Fields]) OR carimune[All Fields] OR flebogamma[All Fields] OR ("Gamunex"[Substance Name] OR "Gamunex"[All Fields] OR "gamunex"[All Fields]) OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "gammagard"[All Fields]) OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "iveegam"[All Fields]) OR ("Octagam"[Substance Name] OR "Octagam"[All Fields] OR "octagam"[All Fields]) OR panglobulin[All Fields] OR polygam[All Fields] OR ("Privigen"[Substance Name] OR "Privigen"[All Fields] OR "privigen"[All Fields]) OR ("leflunomide"[Substance Name] OR "leflunomide"[All Fields] OR "arava"[All Fields]) OR ("methotrexate"[MeSH Terms] OR "methotrexate"[All Fields]) OR ("mycophenolate mofetil"[Substance Name] OR "mycophenolate mofetil"[All Fields]) OR ("mycophenolate mofetil"[Substance Name] OR

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Key Question 5

(("ACR30"[All Fields] OR (American[All Fields] AND College[All Fields] AND ("rheumatology"[MeSH Terms] OR "rheumatology"[All Fields]) AND 30[All Fields]) OR (American[All Fields] AND College[All Fields] AND ("rheumatology"[MeSH Terms] OR "rheumatology"[All Fields]) AND Pediatric[All Fields]) OR (ACR[All Fields] AND Pediatric[All Fields])) OR ((("arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang])) AND (("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) OR ("health status"[MeSH Terms] OR ("health"[All Fields] AND "status"[All Fields]) OR "health status"[All Fields]) OR ("outcome assessment (health care)"[MeSH Terms] OR ("outcome"[All Fields] AND "assessment"[All Fields] AND "(health"[All Fields] AND "care)"[All Fields]) OR "outcome assessment (health care)"[All Fields] OR ("outcome"[All Fields] AND "assessment"[All Fields]) OR "outcome assessment"[All Fields]) OR "disability evaluation"[MeSH Terms] OR "severity of illness index"[MeSH Terms] OR "endpoint determination/methods"[Mesh Terms])) AND (reliability[All Fields] OR ("reproducibility of results"[MeSH Terms] OR ("reproducibility"[All Fields] AND "results"[All Fields]) OR "reproducibility of results"[All Fields]) OR concordance[All Fields] OR ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields]) OR ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "specificity"[All Fields]) OR ("roc curve"[MeSH Terms] OR ("roc"[All Fields] AND "curve"[All Fields]) OR "roc curve"[All Fields] OR ("receiver"[All Fields] AND "operating"[All Fields] AND "characteristic"[All Fields]) OR "receiver operating characteristic"[All Fields]) OR (response[All Fields] AND ("Change"[Journal] OR "change"[All Fields])) OR (sensitive[All Fields] AND ("Change"[Journal] OR "change"[All Fields])) OR (("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields]) AND ("Change"[Journal] OR "change"[All Fields])) OR responsiveness[All Fields] OR ("psychometrics"[MeSH Terms] OR "psychometrics"[All Fields]) OR validity[All Fields] OR "Validation Studies as Topic"[Mesh] AND ("humans"[MeSH Terms] AND English[lang])) AND ("humans"[MeSH Terms] AND English[lang])

Search Strategies Used to Search EMBASE®—Last Search Date December 23, 2010

Key Questions 1, 2, 3, and 4

'mycophenolate mofetil'/exp OR 'mycophenolate mofetil' OR 'abatacept'/exp OR 'abatacept'/de OR 'orencia'/exp OR 'orencia'/de OR 'adalimumab'/exp OR 'adalimumab'/de OR 'anakinra'/exp OR 'anakinra'/de OR 'kineret'/exp OR 'kineret'/de OR 'azathioprine'/exp OR 'azathioprine'/de OR azasan OR 'imuran'/exp OR 'imuran'/de OR 'canakinumab'/exp OR 'canakinumab'/de OR 'ilaris'/exp OR 'ilaris'/de OR 'cyclosporine'/exp OR 'cyclosporine'/de OR 'neoral'/exp OR 'neoral'/de OR 'gengraf'/exp OR 'gengraf'/de OR 'd penicillamine'/exp OR 'd penicillamine'/de

OR 'depen'/exp OR 'depen'/de OR 'cuprimine'/exp OR 'cuprimine'/de OR 'etanercept'/exp OR 'etanercept'/de OR 'enbrel'/exp OR 'enbrel'/de OR 'hydroxychloroquine'/exp OR 'hydroxychloroquine'/de OR 'plaquenil'/exp OR 'plaquenil'/de OR 'infliximab'/exp OR 'infliximab'/de OR 'remicade'/exp OR 'remicade'/de OR 'leflunomide'/exp OR 'leflunomide'/de OR ivig OR carimune OR 'flebogamma'/exp OR 'flebogamma'/de OR 'gamunex'/exp OR 'gamunex'/de OR 'gammagard'/exp OR 'gammagard'/de OR 'iveegam'/exp OR 'iveegam'/de OR 'octagam'/exp OR 'octagam'/de OR 'panglobulin'/exp OR 'panglobulin'/de OR 'polygam'/exp OR 'polygam'/de OR 'privigen'/exp OR 'privigen'/de OR 'arava'/exp OR 'arava'/de OR 'methotrexate'/exp OR 'methotrexate'/de OR 'mycophenolate'/exp OR 'cellcept'/exp OR 'cellcept'/de OR 'rilonacept'/exp OR 'rilonacept'/de OR 'arcalyst'/exp OR 'arcalyst'/de OR 'rituximab'/exp OR 'rituximab'/de OR 'rituxan'/exp OR 'rituxan'/de OR 'sulfasalazine'/exp OR 'sulfasalazine'/de OR 'azulfidine'/exp OR 'azulfidine'/de OR 'tacrolimus'/exp OR 'tacrolimus'/de OR 'fk506'/exp OR 'fk506'/de OR 'prograf'/exp OR 'prograf'/de OR 'thalidomide'/exp OR 'thalidomide'/de OR 'thalomid'/exp OR 'thalomid'/de OR 'sulfazine'/exp OR 'sulfazine'/de OR 'tocilizumab'/exp OR 'tocilizumab'/de OR 'actemra'/exp OR 'actemra'/de OR dmards OR 'disease modifying antirheumatic drug'/exp AND ('juvenile rheumatoid arthritis'/exp OR 'juvenile rheumatoid arthritis') AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)

Key Question 5

'juvenile rheumatoid arthritis'/exp OR 'juvenile rheumatoid arthritis' AND ('reliability'/exp OR reliability OR 'reproducibility'/exp OR reproducibility OR 'sensitivity and specificity'/exp OR 'sensitivity and specificity' OR 'psychometry'/exp OR psychometry OR 'health status'/exp OR 'health status' OR 'quality of life'/exp OR 'quality of life' OR 'outcome assessment'/exp OR 'outcome assessment' OR 'validity'/exp OR validity OR 'validation study'/exp OR 'validation study' OR 'bioassay'/exp OR bioassay OR 'disability'/exp OR disability OR 'disease severity'/exp OR 'disease severity' OR 'receiver operating characteristic'/exp OR 'receiver operating characteristic' OR 'psychometrics'/exp OR psychometrics OR response OR responsiveness OR acr30 OR (american AND ('college'/exp OR college) AND ('rheumatology'/exp OR rheumatology) AND 30) OR 'endpoint determination'/exp OR 'endpoint determination' OR concordance OR sensitivity OR specificity OR (acr AND ('pediatrics'/exp OR pediatrics))) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)

Appendix B. Screening Criteria

JIA—Abstract Screening Instructions

An abstract will be **included** if all of the following criteria apply for **RCTs**:

- The sample population has JIA according to the current ACR definition (KQ1-KQ5).
- Random allocation to the intervention or placebo/control groups (KQ1-KQ3).
- One or more DMARDs are evaluated (KQ1-KQ4).
- Outcome is change in one of the pre-specified intermediate or final outcomes and is assessed using an acceptable standard (KQ1, KQ2).
- Study duration is at least 3 months (KQ1-KQ4).
- Population may be from primary or specialty care settings (KQ1-KQ5).
- Sample consists of children 18 years or younger. If the study includes adults, at least 80% of the sample will be children or the outcomes must be reported separately for the child subgroup (KQ1-KQ5).
- Original data.

An abstract will be **excluded** if any of the following criteria apply for **RCTs:**

- Non-English language publication (KQ1-KQ5)

An abstract will be **included** if all of the following criteria apply for **Observational Studies**:

- The sample population has JIA according to the current ACR definition (KQ1-KQ5).
- One or more DMARDs are evaluated (KQ1-KQ4).
- Outcome is change in one of the pre-specified intermediate or long-term outcomes and is assessed using an acceptable standard (KQ1, KQ2).
- Study duration is at least 3 months (KQ1-KQ4).
- Population may be from primary or specialty care settings (KQ1-KQ5).
- Sample consists of children 18 years or younger. If the study includes adults, at least 80% of the sample will be children or the outcomes must be reported separately for the child subgroup (KQ1-KQ5)
- Outcomes are determined prospectively and are assessed using an acceptable standard (KQ1-KQ4).
- For studies of effectiveness, there must be a treatment comparator (KQ1-KQ4).
- Case-control studies, case series, and case reports are acceptable to assess for adverse events of DMARD treatment (KQ3).
- Cross-sectional studies are acceptable to evaluate clinical outcome measure tools (KQ5).

An abstract will be **excluded** if any of the following criteria apply for **Observational Studies:**

- Non-English language publication (KQ1-KQ5).
- Cross-sectional studies for the evaluation of the impact of treatment (KQ1-KQ4).

An abstract will be identified as a **review** if it is a relevant review article, meta-analysis, methods article, or cost-effectiveness analysis.

For each abstract, please mark either **"EX"** for **Exclude**, **"IN"** for **Include** or **"R"** for **Review**.

JIA—Full-Text Screening Instructions/Exclusion Reasons

Key Questions 1-4

Key Questions 1-4 are as follows:

Key Question 1. In children with juvenile idiopathic arthritis (JIA), does treatment with disease-modifying anti-rheumatic drugs (DMARDs), compared to conventional treatment (defined as non-steroidal anti-inflammatory drugs [NSAIDs] or intra-articular corticosteroids, with or without methotrexate), improve laboratory measures of inflammation or radiological progression, symptoms (e.g., pain, symptom scores) or health status (e.g., functional ability, mortality)?

Key Question 2. In children with JIA, what are the comparative effects of various DMARDs on laboratory markers of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

Key Question 3. In children with JIA, does the rate and type of adverse events differ between the various DMARDs or between DMARDs and conventional treatment?

Key Question 4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?

General/Introductory Notes

- Key Question (KQ) 4 will draw on the entire body of evidence included for KQs 1-3; therefore, it does not have a separate set of inclusion/exclusion criteria.
- A wider range of study designs are acceptable for KQ 3 than for KQs 1-2, including case reports, non-comparative prospective studies, and retrospective studies. However, study duration must be ≥ 3 months (as for KQs 1-2).
- KQ 5 is very different from KQs 1-4 and has some distinctly different inclusion/exclusion criteria. A separate cheat sheet has been prepared for it.
- For all KQs, the study population may be drawn from primary or specialty care settings.
- For all KQs, the language of publication must be English.

(1) Publication Not Peer-Reviewed

For KQs 1–2

- Publication must be peer-reviewed (excludes editorials, letters to the editor, etc.).

For KQ 3

- Case reports published in non-peer-reviewed form (e.g., as letters) in academic journals are acceptable.
- Other types of studies must be peer-reviewed.

(2) Population not JIA/JRA/JCA

For All KQs

- The sample population must have juvenile idiopathic arthritis (JIA) according to the International League of Associations for Rheumatology (ILAR) criteria, or juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition, or juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.
- Any subtype of JIA/JRA/JCA of any severity is acceptable.

Notes/Further Guidance

Criteria for Classification of JIA (ILAR = International League of Associations of for Rheumatology) From 1998

Note: All categories require age of onset prior to 16 yrs

JIA category	Definition	Exclusions
Systemic arthritis	Arthritis and fever plus one or more: 1. rash, 2. lymph node enlargement, 3. hepato or splenomegaly, 4. serositis	
Oligoarthritis	Arthritis of 1-4 joints in the first 6 mo,	Family history of psoriasis or HLA-B27 assoc. disease, RF+, HLA-B27+ males > 8 years, systemic arthritis
Persistent	< 5 joints during course,	
Extended	> 4 joints after 6 mo	
RF- polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF-	RF+, systemic arthritis
RF+ polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF +	RF-, systemic arthritis
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least 2 of: (a) dactylitis, (b) nail abnormalities, (c) family history of psoriasis	RF+, systemic arthritis
Enthesitis related arthritis	Arthritis and enthesitis OR arthritis or enthesitis with at least 2 of: (a) sacroiliac tenderness and/or spinal pain, (b) HLA-B27, (c) family history of HLA-B27associated disease	Family history of psoriasis, systemic arthritis
Other arthritis	Children with JIA who do not fulfill criteria for any category or fulfill criteria for >1 category	

(Reference: Evaluation of the ILAR criteria for juvenile idiopathic arthritis. Krumrey-Langkammerer M, Häfner R.J Rheumatol. 2001 Nov;28(11):2544-7.)

Criteria for Classification of JRA (ACR = American College of Rheumatology) From 1976

Age of onset prior to 16 yrs

Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints:
a. Limitation of range of motion
b. Tenderness or pain on range of motion
c. Increased heat

Duration of disease 6 weeks or longer

Onset type defined by type of disease in first 6 months:
a. Polyarticular: ≥ 5 inflamed joints
b. Oligoarticular (aka: pauciarticular): < 5 joints
c. Systemic onset: arthritis with characteristic fever

Exclusion of other forms of juvenile arthritis (psoriatic, spondyloarthopathy = juvenile ankylosing spondylitis, inflammatory bowel disease associated arthritis)

Criteria for Classification of JCA (EULAR = European League Against Rheumatism) From 1977

Age of onset prior to 16 yrs

Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints):
a. Limitation of range of motion
b. Tenderness or pain on range of motion
c. Increased heat

Duration of disease 3 months or longer

Onset type defined by characteristics at presentation:
a. Polyarticular: ≥ 5 inflamed joints, Rheumatoid factor negative
b. Pauciarticular: < 5 joints
c. Systemic onset: arthritis with characteristic fever
d. Juvenile rheumatoid arthritis: ≥ 5 joints, rheumatoid factor positive
e. Juvenile ankylosing spondylitis
f. Juvenile psoriatic arthritis

(3) Population Not < 18 years

For <u>All</u> KQs

- Study sample must consist of children 18 years or younger. If the study includes adults, at least 80% of the sample must be children, or outcomes must be reported separately for the 18 years or younger subgroup.

(4) No Acceptable DMARD Intervention

For KQs 1-4

- Study must include one of the DMARDs on our list (see table next page) either:
  - Alone;
  - In combination with another DMARD on our list; or
  - In combination with conventional treatment.

Included DMARDs (Table 2 from project protocol). List of DMARDs, their mechanism of action, FDA approval status for JIA, and examples of significant warnings from the drug product label.

Generic Name	US Trade Name	Mechanism of Action	FDA-approved for JIA	Warnings—Increased Risk
Abatacept	Orencia	Anti-CD28, T-cell costimulator antibodies; biologic	Yes	Infections
Adalimumab	Humira	TNF inhibitor; biologic	Yes	Infections; cancer
Anakinra	Kineret	IL-1 receptor antagonist; biologic	No	Infections
Canakinumab	Ilaris	IL-1 blocker; biologic	No	Vertigo
Etanercept	Enbrel	TNF inhibitor; biologic	Yes	Infections; cancer
Infliximab	Remicade	TNF inhibitor; biologic	No	Infections; cancer
IVIG	Baygam, Carimune NF, Flebogamma 5% DIF, Gammar P, Gamunex 10%, Gammagard S/D, Gammagard Liquid 10%, Gammar P, Iveegam EN, Octagam 5%, Panglobulin, Polygam S/D, Privigen 10% Vivaglobin	Interaction with activating Fc receptors; biologic	No	Hepatitis; acute renal failure; venous thrombosis; aseptic meningitis
Rilonacept	Arcalyst	IL-1 blocker; biologic	No	Infection
Rituximab	Rituxan	Binds to CD20 antigen; biologic	No	Progressive multifocal leukoencephalopathy; severe skin reactions; infusion reactions
Tocilizumab	Actemra	IL-6 receptor antagonist; biologic	No	Infections; elevated lipid levels
Azathioprine	Azasan; Imuran	Purine Synthesis Inhibitor; non-biologic	No	Cancer; bone marrow suppression
Cyclosporine A	Neoral Gengraf	Inhibits calcineurin; non-biologic	No	Infections; nephrotoxicity; hepatotoxicity
D-Penicillamine	Depen; Cuprimine	Unknown (May lower IgM rheumatoid factor, depresses T-cell activity); non-biologic	No	Allergic reactions; Goodpasture's syndrome; hematologic toxicities; hepatotoxicity; myasthenia gravis
Hydroxy-chloroquine	Plaquenil	Not well understood, may reduce T-lymphocyte transformation and chemotaxis; non-biologic	No	Kidney damage; retinopathy
Leflunomide	Arava	Isoxazole immunomodulatory agent; non-biologic	No	Hepatotoxicity

Generic Name	US Trade Name	Mechanism of Action	FDA-approved for JIA	Warnings—Increased Risk
Methotrexate	Methotrexate LPF	Unknown (anti-metabolite, inhibits dihydrofolic acid reductase); non-biologic	Yes	Hepatotoxicity; cancer
Mycophenolate mofetil	CellCept	Guanosine synthesis inhibitor; non-biologic	No	Cancer; bone marrow suppression
Sulfasalazine	Azulfidine Sulfazine	Unknown; non-biologic	Yes	Bone marrow suppression; hepatotoxicity; Stevens Johnson Syndrome
Tacrolimus (FK506)	Prograf	Reduces T-cell and IL-2 activity; non-biologic	No	Cancer; infection
Thalidomide	Thalomid	Unknown; non-biologic	No	Birth defects; neuropathy

(5) No Acceptable Comparator

For KQ 1, Acceptable Comparators Are

- Conventional treatment, defined as "NSAIDs or intra-articular corticosteroids, with or without methotrexate" (see table below for acceptable NSAIDs and corticosteroids)

For KQ 2, Acceptable Comparators Are

- Any other DMARD on our list (see table above) either:
  - Alone;
  - In combination with another DMARD on our list; or
  - In combination with conventional treatment (defined as above).

For KQ 3, Acceptable Comparators Are

- None or any

Included NSAIDs and intra-articular corticosteroids (Table 1 from project protocol). List of intra-articular corticosteroids and NSAIDs FDA approval status for JIA, and examples of significant warnings from the drug product label.

Generic Name	US Trade Name	Drug Type	FDA-Approved for JIA	Warnings—Increased Risk
Betamethasone	Celestone	Intra-articular corticosteroid	Yes	Subcutaneous atrophy ; Cushing syndrome
Triamcinolone Acetonide	Kenolog	Intra-articular corticosteroid	Yes	Subcutaneous atrophy; Cushing syndrome
Triamcinolone Hexacetonide	Aristospan	Intra-articular corticosteroid	No	Subcutaneous atrophy; Cushing syndrome
Celecoxib	Celebrex	NSAID	Yes	Hepatotoxicity; nephrotoxicity; gastritis

Generic Name	US Trade Name	Drug Type	FDA-Approved for JIA	Warnings—Increased Risk
Etodolac	Lodine	NSAID	No	Cardiovascular thrombotic events; gastritis
Ibuprofen	Motrin Advil	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity
Indomethacin	Indocin Indocin SR	NSAID	Yes	Headaches: gastritis; hepatotoxicity; nephrotoxicity
Meloxicam	Mobic	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity
Naproxen	Naprosyn Aleve	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity
Oxaprozin	Daypro	NSAID	Yes	Cardiovascular thrombotic events; gastritis
Tolmetin	Tolectin	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity

(6) Study Not Prospective

Relevant Only to KQs 1–2

- Any prospective comparative study is acceptable. Studies evaluating a prospective treatment group vs. a historical control group are also acceptable.

For KQ 3

- Studies are not required to be prospective. For KQ3, any study design is acceptable (comparative or non-comparative, prospective or retrospective, any size [including case studies with n = 1]).

(7) No Outcome of Interest

For KQs 1-2

- Study must include at least one of the following intermediate or long-term outcomes:
  - Intermediate outcomes include:
    - Laboratory measures of inflammation
    - Active joint count
    - Number of joints with limited range of motion
    - Radiographic evidence of progression of disease
    - Global assessment of current status
  - Long-term outcomes include:
    - Pain control
    - Clinical remission
    - Quality of life
    - Growth

- Development
- Joint function
- Functional Ability
- Mortality

For KQ 3

- Study must report adverse events
- We are especially (but not exclusively) interested in:
  - Mortality
  - Malignancy
  - Serious infection
  - Hepatitis
  - Bone marrow suppression
  - Nausea or vomiting
  - Risks to fetus or pregnant mother

(8) Outcomes Not Measured Using an Objective Standard

Relevant Only to KQs 1-2

- Outcomes must be measured using an objective standard

(9) Study Duration < 3 Months

Relevant Only to KQs 1-2

- Study duration must be ≥ 3 months.

For KQ 3

- Any study duration is acceptable.

JIA—Full-Text Screening Instructions/Exclusion Reasons

Key Question 5

Key Question 5. What is the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?

General/Introductory Notes

- For this and all other Key Questions (KQs), the study population may be drawn from primary or specialty care settings.
- For this and all other KQs, the language of publication must be English.
- For KQ 5 specifically:
  - Any treatment intervention/comparator is acceptable (including none).

- Any study design is acceptable (including RCTs, non-randomized controlled trials, and observational studies [controlled or uncontrolled, cross-sectional or longitudinal]).
- Any study duration is acceptable (study does not need to be ≥ 3 months).

(1) Publication Not Peer-Reviewed

- Publication must be peer-reviewed (excludes editorials, letters to the editor, etc.).

(2) Population Not JIA/JRA/JCA

For All KQs

- The sample population must have juvenile idiopathic arthritis (JIA) according to the International League of Associations for Rheumatology (ILAR) criteria, or juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition, or juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.
- Any subtype of JIA/JRA/JCA of any severity is acceptable.

Notes/Further Guidance

Criteria for Classification of JIA (ILAR = International League of Associations of for Rheumatology) from 1998

Note: All categories require age of onset prior to 16 yrs

JIA category	Definition	Exclusions
Systemic arthritis	Arthritis and fever plus one or more: 1. rash, 2. lymph node enlargement, 3. hepato or splenomegaly, 4. serositis	
Oligoarthritis	Arthritis of 1-4 joints in the first 6 mo,	Family history of psoriasis or HLA-B27 assoc. disease, RF+, HLA-B27+ males > 8 years, systemic arthritis
Persistent	< 5 joints during course,	
Extended	> 4 joints after 6 mo	
RF- polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF-	RF+, systemic arthritis
RF+ polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF +	RF-, systemic arthritis
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least 2 of: (a) dactylitis, (b) nail abnormalities, (c) family history of psoriasis	RF+, systemic arthritis
Enthesitis related arthritis	Arthritis and enthesitis OR arthritis or enthesitis with at least 2 of: (a) sacroiliac tenderness and/or spinal pain, (b) HLA-B27, (c) family history of HLA-B27associated disease	Family history of psoriasis, systemic arthritis

JIA category	Definition	Exclusions
Other arthritis	Children with JIA who do not fulfill criteria for any category or fulfill criteria for >1 category	

(Reference: Evaluation of the ILAR criteria for juvenile idiopathic arthritis. Krumrey-Langkammerer M, Häfner R.J Rheumatol. 2001 Nov;28(11):2544-7.)

Criteria for Classification of JRA (ACR = American College of Rheumatology) from 1976

Age of onset prior to 16 yrs

Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints:

a. Limitation of range of motion
b. Tenderness or pain on range of motion
c. Increased heat

Duration of disease 6 weeks or longer

Onset type defined by type of disease in first 6 months:

a. Polyarticular: ≥ 5 inflamed joints
b. Oligoarticular (aka: pauciarticular): < 5 joints
c. Systemic onset: arthritis with characteristic fever

Exclusion of other forms of juvenile arthritis (psoriatic, spondyloarthopathy = juvenile ankylosing spondylitis, inflammatory bowel disease associated arthritis)

Criteria for Classification of JCA (EULAR = European League Against Rheumatism) from 1977

Age of onset prior to 16 yrs

Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints):

a. Limitation of range of motion
b. Tenderness or pain on range of motion
c. Increased heat

Duration of disease 3 months or longer

Onset type defined by characteristics at presentation:

a. Polyarticular: ≥ 5 inflamed joints, Rheumatoid factor negative
b. Pauciarticular: < 5 joints
c. Systemic onset: arthritis with characteristic fever
d. Juvenile rheumatoid arthritis: ≥ 5 joints, rheumatoid factor positive
e. Juvenile ankylosing spondylitis
f. Juvenile psoriatic arthritis

(3) Population Not < 18 Years

For All KQs

- The study sample must consist of children 18 years or younger. If the study includes adults, at least 80% of the sample must be children, or outcomes must be reported separately for the 18 years or younger subgroup.

(4) No Clinical Outcome Measure (Test) of Interest

- Study must report at least one clinical outcome measure for childhood JIA that is commonly used in clinical trials or within the clinical practice setting.

Notes/Further Guidance

The following list of specific measures/instruments was agreed on after discussions with the project's technical expert panel (TEP).

- Measures of disease activity:
  - Active joint count (AJC)
  - Physician global assessment of disease activity (PGA)
  - Parent/patient global assessment of well-being (PGW)
- Measure of functional status/disability:
  - Childhood Health Assessment Questionnaire (CHAQ)
- Measures of health-related quality of life:
  - Child Health Questionnaire (CHQ)
  - Pediatric Quality of Life Inventory (PedsQL) 4.0
  - Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM)
- Composite measures of response to therapy and developing definitions of disease status:
  - American College of Rheumatology Pediatric Response Criteria (ACR Pediatric 30)
  - A consensus-based definition of remission
  - Flare
  - Minimal disease activity (MDA)

(5) No Data Reported on Test Performance

- Outcomes to be evaluated here are:
  - Validity of clinical outcomes measures
  - Reliability of clinical outcomes measures (inter- and intra-rater reliability, test-retest reliability)
  - Responsiveness of clinical outcomes measures (standardized response mean and responsiveness index).
  - Feasibility of clinical outcomes measures (specifically, time to administer).

Appendix C. Data Abstraction Forms

KQ 1–4—Blank ET/Data Abstraction Form

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
StudyID	**Geographical location:** **Study dates:** **Funding source:** **Setting:** **Study design:** RCT Nonrandomized comparative study Other **Intervention(s):** - DMARD name: - Dose: - Titration: - N: **Comparator(s):** **Were additional arthritis medications allowed?:** **If Yes to above, was this done:** Per protocol At discretion of clinician/investigator NR **Study duration:** **Primary outcome(s):** **Secondary outcome(s):**	**Number of patients:** - Screened for inclusion: - Eligible for inclusion: - Randomized: - Began treatment: - Completed treatment: - Withdrawals/losses to followup: **Age:** - Mean (SD): - Median: - Range: **Sex:** - Female: - Male: **Race/ethnicity:** **JIA diagnosis:** JRA JCA JIA Spondyloarthropathy Psoriatic arthritis Other (describe) **Baseline severity:** Active joint count: Duration of disease: Other (specify): NR **Percentage with uveitis:** **Inclusion criteria:** **Exclusion criteria:**	**1) Active joint count:** **2) Quality of life/functional status:** **3) Number of joints with limited range of motion:** **4) Global assessment of current status:** - Physician: - Patient/Parent: **5) Laboratory measures of inflammation:** - ESR: - Other: **6) Radiographic evidence of progression of disease:** **7) Pain control:** **8) Clinical remission:** **9) Flare of disease:** **10) Discontinuation of DMARD due to:** - Remission of disease: - Inefficacy: - Intolerance/AEs: **11) Mortality:** **12) Adverse events reported?:** Yes No **13) Other:**	**Exclusion reasons (if appropriate):** **General comments:** **Quality assessment:** *Primary outcome:* - Overall rating: - Comments: *Adverse events:* - Overall rating: - Comments: **Applicability:** **This article is relevant to:** Question #_____

KQ 5—Blank ET/Data Abstraction Form

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
StudyID	**Geographical location:** **Setting:** Specialty clinic Other [specify] **Study design:** RCT Longitudinal non-RCT Cross-sectional Other [specify] **Study objective(s):** **Duration of followup:**	**Number of patients:** **Age:** - Mean (SD): - Median: - Range: **Sex:** - Female: - Male: **Race/ethnicity:** **JIA diagnosis:** JRA JCA JIA Spondyloarthropathy Psoriatic arthritis Other (describe) **Percentage with systemic JIA:** **Baseline severity:** Time since diagnosis: Active joint count: Other [specify]: NR **Inclusion criteria:** **Exclusion criteria:**	**Instrument(s) evaluated:** **Mode of administration:** Self-administered Interviewer-administered Other [specify]	**1) Reliability:** - Test-retest: - Kappa statistics: - Inter-rater: - Intra-rater: - Intra-class correlation: **2) Validity:** - Versus clinical outcomes: - Versus lab results: - Versus radiological results: - New instrument versus established instrument: **3) Other:** - Feasibility: NR [or report results] - Responsiveness: NR [or report results] - ROC curves: NR [or report results]	**Exclusion reasons (if appropriate):** **General comments:** **Quality assessment:**

Appendix D. Evidence Tables—Main Literature Search

Evidence Table 1. Studies relevant to key questions 1–4

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr>
<td>Brewer, Giannini, Kuzmina, et al., 1986

#1181

AND

Van Kerchove, Giannini, and Lovell, 1988

#1120</td>
<td>Geographical location: US (13 centers; N = 65 patients); Soviet Union (5 centers; N = 97 patients)

Study dates: NR

Funding source: NIH Grant from Winthrop laboratories and funds from Merck Sharp Dohm Laboratories

Setting: 18 pediatric rheumatology centers

Study design: RCT

Intervention(s):
- DMARD name: PCN
- Dose: 5 mg/kg/day
- Titration: Increased at 2 months to 10 mg/kg/day
- N = 54

- DMARD name: HCQ
- Dose: 3 mg/kg/day
- Titration: Increased at 2 months to 6mg/kg/day
- N = 57

Comparator(s): Placebo (N = 51)

Were additional arthritis medications allowed?: Yes: NSAIDs, antibiotics,</td>
<td>Number of patients: N = 162
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: NR
- Began treatment: 162
- Completed treatment:
6 months = 143 (88%)
12 months = 123 (76%)
- Withdrawals/losses to followup: NR

Age:
- Range: 18 months – 17 years
- Mean 9.7 years
Sex:
- Female: 122 (75.3%)
- Male: 40 (24.7%)

Race/ethnicity: NR

JIA diagnosis:
JRA
Polyarticular 142, pauciarticular 11, systemic 9

Baseline severity:
Active joint count:
PCN: 18 ± 13.5
HCQ: 18.6 ± 13.1
Placebo: 16.3 ± 10.6

Duration of disease: Mean 3.2 years

ESR:
PCN: 32 ± 23</td>
<td>1) Active joint count:
Degree of change at 6 months:
<table><tr><th>Drug</th><th>Mean</th><th>Median</th><th>95% CI</th></tr><tr><td>PCN</td><td>-3.0</td><td>-3</td><td>-4.8 to -1.1</td></tr><tr><td>HCQ</td><td>-2.8</td><td>-2</td><td>-5 to - 0.7</td></tr><tr><td>PLA</td><td>-2.9</td><td>-1.5</td><td>-5.6 to 0.2</td></tr></table>Degree of change at 12 months:
<table><tr><th>Drug</th><th>Mean</th><th>Median</th><th>95% CI</th></tr><tr><td>PCN</td><td>-3.7</td><td>-3.5</td><td>-5.6 to -1.9</td></tr><tr><td>HCQ</td><td>-6.7</td><td>-4</td><td>-9.4 to -4</td></tr><tr><td>PLA</td><td>-5.4</td><td>-4.5</td><td>-8 to -2.8</td></tr></table>2) Quality of life/functional status: NR

3) Number of joints with limited range of motion:
Degree of change at 6 months:
<table><tr><th>Drug</th><th>Mean</th><th>Median</th><th>95% CI</th></tr><tr><td>PCN</td><td>-2.5</td><td>-1</td><td>-4.3 to -0.8</td></tr><tr><td>HCQ</td><td>-0.7</td><td>-1</td><td>-2.3 to 1</td></tr><tr><td>PLA</td><td>-3.8</td><td>-2</td><td>-6.2 to -1.3</td></tr></table>Degree of change at 12 months:
<table><tr><th>Drug</th><th>Mean</th><th>Median</th><th>95% CI</th></tr><tr><td>PCN</td><td>-1.4</td><td>-0.5</td><td>-2.9 to -0.04</td></tr><tr><td>HCQ</td><td>-1.9</td><td>-2</td><td>-4.4 to 0.5</td></tr><tr><td>PLA</td><td>-3.4</td><td>-3</td><td>-5.8 to -0.9</td></tr></table>4) Global assessment of current status:
By physician: Number (%) much better / better / same / worse / much worse / NA
6 months:</td>
<td>General comments: Older medications, PCN not used any longer

Quality assessment:
Primary outcome:
- Overall rating: Good

Adverse events:
- Overall rating: Fair
- Comments: Listed by drug

Applicability: Good</td>
</tr>
</table>

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	acetaminophen and codeine NSAIDs given per protocol – had to be steady dose, unchanged during study **Study duration:** 12 months **Primary outcome(s):** NR **Secondary outcome(s):** NR	HCQ: 28 ± 23 Placebo: 30 ± 21 **Percentage with uveitis:** NR **Inclusion criteria:** - Met the criteria for JRA established by the American Rheumatism Association or the criteria used in the Soviet Union and Eastern Europe - Presence of severe, clinically active. poorly controlled disease. - Age ≥18 months and ≤ 17 years **Exclusion criteria:** - Clinically important cardiac disorder or other severe or chronic disease - Pregnant or nursing women - Patients scheduled for surgery	PCN: 4(8) / 24(47) / 18(35) / 5(10) / 0 / 0 HCQ: 3(6) / 25(50) / 16(32) / 5(10) / 0 / 1(2) PLA: 6(14) / 15(36) / 17(41) / 2(5) / 1(2) / 1(2) 12 months: PCN: 9(21) / 15(35) / 12 (28) / 7(16) / 0 HCQ: 11(24) / 22(48) / 12(26) / 1(2) / 0 PLA: 7(21) / 11(32) / 14(41) / 2(6)0 By patient/parent: NR **5) Laboratory measures of inflammation:** ESR: Mean decrease (median) 12 months: PCN: 9.4 (4) HCQ: 10 (4) PLA: 10 (4) **6) Discontinuation of DMARD due to:** Remission of disease: NR Inefficacy (n [%]): PCN: 4(36) HCQ: 5(45) PLA: 4(24) Intolerance/AEs (n [%]): PCN: 2(18) HCQ: 3(27) PLA: 3(18) **7) Mortality:** NR **8) Adverse events reported?:** Yes - leucopenia, anemia **9) Other - Total sum of severity:** Degree of change at 6 months:	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Drug / *Mean* / *Median* / *95% CI* PCN / -23.5 / -15 / -34.7 to -12.3 HCQ / -15.4 / -10 / -23.9 to - 6.8 PLA / -12.7 / -12.5 / -24.8 to -0.6 Degree of change at 12 months: *Drug* / *Mean* / *Median* / *95% CI* PCN / -24.3 / -17.5 / -34.9 to -13.7 HCQ / -23.4 / -14 / -34.2 to - 12.6 PLA / -18.1 / -16 / -24.4 to -11.8	
Giannini, Brewer, Kuzmina, et al., 1992 **#1008**	**Geographical location:** 18 centers in the US and 5 in the Soviet Union **Study dates:** NR **Funding source:** FDA, NIH, National Arthritis Foundation, Children's Hospital Research Foundation, Lederle Laboratories **Setting:** Specialty centers **Study design:** RCT **Intervention(s):** - DMARD name: Methotrexate - Dose: Very low dose (5 mg/m^2/week) or low dose (10 mg/m^2/week) up to 15 mg/week max - N: Planned for 30/group **Comparator(s):** Placebo	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 127 - Began treatment: 127 - Completed treatment: 114 (for efficacy analysis); 108 completed the entire 6-month trial - Withdrawals/losses to followup: 19 discontinued therapy (see under "Results" for details); no reported loss to follow-up **Age:** - Mean (SD): 10.1 years - Median: NR - Range: 2.5 to 17.8 years **Sex:** - Female: 96 (76%) - Male: 31 (24%) **Race/ethnicity:** NR	**1) Active joint count:** Very low dose: -5.2 Low dose: -7.2 Placebo: -5.2 p > 0.3 **2) Quality of life/functional status:** Composite index: Very low dose: 32% improved Low dose: 63% Placebo: 36% **3) Number of joints with limited range of motion:** Very low dose: -0.5 Low dose: -5.4 Placebo: -0.7 p = 0.04 **4) Global assessment of current status:** By physician: Low dose improved over placebo (p = 0.02) Very low dose not improved over placebo (p = 0.06)	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Well-conducted RCT *Adverse events:* - Overall rating: Good - Comments: Thorough explanation **Applicability:** Good

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		JIA diagnosis: JRA		
	Were additional arthritis medications allowed?: Yes: NSAIDs or prednisone Dose of these drugs had to be constant for at least 1 month before randomization and could not be changed **Study duration:** 6 months **Primary outcome(s):** - Physician's global assessment of the patient's response - Articular-severity score - Composite index **Secondary outcome(s):** - Number of joints with swelling - Pain on motion - Tenderness - Limitation of motion - Severity of condition - Duration of morning stiffness - Laboratory changes (hemogram and ESR)	**Baseline severity:** Active joint count (n [SE]): Very low dose: 27 (2) Low dose: 21 (2) Placebo: 24 (2) Duration of disease: Mean 5.1 years Other (specify): Systemic in 32 (25%) **Percentage with uveitis:** NR **Inclusion criteria:** - Criteria for JRA of the ACR or the Soviet Union and Eastern Europe - 3 joints with active arthritis not adequately controlled by NSAIDs or second line agents - At least 18 months and less than 18 years of age **Exclusion criteria:** - Other clinically important severe or chronic disease - Girls who might become pregnant - Receipt of penicillamine, hydroxychloroquine, oral or parenteral gold, or intraarticular or long-acting parenteral steroids within 3 months before randomization - Previous receipt of methotrexate	By patient/parent: NR – results "nearly identical with those of the physician's" **5) Laboratory measures of inflammation:** ESR: Very low dose: 7/28 with an elevated level had a normal value by the final visit Low dose: 13/28 with an elevated level had a normal value by the final visit Placebo: 8/27 with an elevated level had a normal value by the final visit **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** Remission of disease: NR Other reasons: Very low dose: 2 ineffectiveness of drug, 1 AE, 2 intercurrent illness Low dose: 2 AEs, 2 intercurrent illness, 2 "administrative," 1 noncompliance Placebo: 5 ineffectiveness of drug, 1 intercurrent illness, 1 "administrative" reasons **11) Mortality:** None **12) Adverse events reported?:** Yes 8/40 with very low dose: 4 GI problems, 2 headache or dizziness, 2 inflammation of	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			oral mucosa with headache and GI problems 6/47 with low dose: 3 GI problems, 1 ulceration of mucous membranes, 1 headache, 1 headache and abdominal problems 5/41 placebo: All GI problems 15 in very low dose, 15 in low dose, and 5 in placebo had abnormal lab results "judged to be clinically important" – most frequent were alterations in WBC differential, hematuria, and pyuria. Increased aminotransferase levels and anemia were most common with placebo.	
Giannini, Lovell, Silverman, et al., 1996 **#877**	**Geographical location:** 7 centers in US and Canada **Study dates:** Nov 1991-Nov 1994 **Funding source:** FDA, NIH, Immuno AG, Children's Hospital Research Foundation of Cincinnati, Schmidlapp Founation, IRCSS (Italian Research Hospital) **Setting:** Specialty **Study design:** RCT, blinded, with a run-in period between 3 and 6 months. RCT lasted 4 months and had an "escape" provision for those whose symptoms worsened. **Intervention(s):** - DMARD name: IVIG - Dose: 1.5-2.0 g/kg/infusion (100	**Number of patients:** N = 25 in the run-in phase, 19 in the blinded RCT - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 19 - Began treatment: 19 - Completed treatment: 12 completed, 6 "early escape" - Withdrawals/losses to followup: 1 **Age:** - Mean (SD): 10.9 (5.8) (n = 25 in the run-in period) - Median: NR - Range: 2 to 23 years **Sex:** - Female: 22 (88%) - Male: 3 (12%) **Race/ethnicity:** NR **JIA diagnosis:**	**1) Active joint count:** In the RCT, -3% in IVIG group (n = 10), 30% increase in the placebo group (n = 9) **2) Quality of life/functional status:** 19/25 had "clinically important improvement" in the open label and entered the RCT During the RCT, 2/10 in the treatment group "escaped" to higher dosing based on clinically significant worsening. 5/9 in the placebo group escaped to treatment because of clinically significant worsening. **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** By physician: In the RCT, -3% in physician global assessment in the IVIG group (n = 10), 91% increase in global assessment in the placebo group (n = 9)	**General comments:** Includes only subjects who responded to IVIG from the open-label trial – evaluates effectiveness based on lack of "escape" **Quality assessment:** *Primary outcome:* - Overall rating: Fair - Comments: No statistical inference testing; conflict of interest with funding source; main outcome not validated *Adverse events:* - Overall rating: Fair - Comments: No validated AE measure; potential conflict of interest with funding source **Applicability:** Includes only subjects who responded to IVIG from the open-label study

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	g maximum) bimonthly - Titration: After 6 infusions, dose could be increased up to the maximum - N: 25 **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes - NSAIDs, "slow acting antirheumatic drugs (methotrexate, sulfasalazine, hyroxychloroquine), low dose prednisone (< 10 mg/day) **If Yes to above, was this done per protocol or at the discretion of study investigators:** NR **Study duration:** Run-in: 3 to 6 months RCT: 4 months **Primary outcome(s):** - "Clinically important benefit," defined as ≥ 25% improvement in at least 2 of the following: (a) total number of joints with active arthritis, (b) overall articular severity score, (c) physician's global assessment of overall disease activity - "Clinical important worsening," defined as ≥ 25% worse in 2/3 above **Secondary outcome(s):** Juvenile Arthritis Functional	All with poly-JRA Group A: Late onset (> 10 years) but short duration (< 3 years) Group B: ≥ 5 joints with active arthritis, disease before 8 years, short duration (< 3 years) Group C: Longer duration (> 5 years, substantial involvement (≥ 10 joints) **Baseline severity:** Active joint count: 26.7 (± 13.2) at run-in Duration of disease: 4.4 years (± 4.5) at run-in Other (specify): Overall articular severity score: 103 (± 60) Physician global assessment: 5.7 (± 2.0) JAFAR: 11.1 (± 6.5) Elevated ESR: 11/23 **Percentage with uveitis:** NR **Inclusion criteria:** Poly-JRA Between 2 and 23 years **Exclusion criteria:** - Known hypersensitivity to immunoglobulin - Leukopenia (WBC < 1500/mm^3) - Thrombocytopenia (platelets < 100,000/mm^3) - Significant renal or hepatic disease - IgA deficiency - Malignancy	By patient/parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** None **12) Adverse events reported?:** Yes – not broken down by treatment group In the open-label period, 3 patients, and in the RCT, 1 patient experienced AEs associated with the infusion process, namely headache, dizziness, nausea, vomiting, diarrhea, tachycardia, fatigue, and chills. AEs not associated with infusion: In the open-label period, 1 with joint pain, 1 with flare and worsening chronic iritis that required steroids, 1 with fever to 39.9 degrees C related to probable intercurrent illness **13) Other:** Mean time to failure during the RCT in the placebo group was 2.5 months (range 1.8 to	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Assessment Report (JAFAR)	- Chronic infection - Immunized with a live virus in past 2 weeks - Pregnancy	3.2 months) In the RCT, 10% increase in JAFAR in the IVIG group (n = 8), 59% increase in the placebo group (n = 7) – sample size smaller because subjects with JAFAR = 0 at baseline were excluded	
Hoza, Kadlecova, Nemcova, et al., 1991 **#1048**	**Geographical location:** Prague, Czechoslovakia **Study dates:** NR **Funding source:** NR **Setting:** Hospital **Study design:** RCT **Intervention(s):** - DMARD name: Sulfasalazine (SSZ) - Dose: 20-30 mg/kg/day - N: 21 **Comparator(s):** - DMARD name: Chloroquin (DLG) - Dose: 3 to 4 mg/kg/day - N: 18 **Were additional arthritis medications allowed?:** Yes: NSAIDs, prednisone NR whether these were added per protocol or at the discretion of clinician/investigator **Study duration:** 6 months	**Number of patients:** N = 39 - Screened for inclusion: - Eligible for inclusion: 39 - Randomized: SSZ, 21; DLG, 18 - Began treatment: 39 - Completed treatment: 34 - Withdrawals/losses to followup: 5 withdrawals **Age:** NR **Sex:** - Female: 26 (66.7%) - Male: 13 (33.3%) **Race/ethnicity:** NR **JIA diagnosis:** *SSZ:* Poly: 11 Oligo: 8 Systemic: 2 *DLG:* Poly: 12 Oligo: 5 Systemic: 1 **Baseline severity:** NR Percentage with uveitis: NR **Inclusion criteria:**	**1) Number of criteria:** At time 0/6 months: SSZ: 7/6 DLG: 4/3 **2) Number of affected joints:** At time 0/6 months: SSZ: 6/5 DLG: 4/3 **3) AM stiffness (minutes)** At time 0/6 months: SSZ: 29/20 DLG: 37/21 **4) Pain score** At time 0/6 months: SSZ: 5/4 DLG: 5/3 **5) Global assessment of current status:** Improved/no effect/worse SSZ: - Physician: 9/9/3 - Patient: 10/7/3 - Parent: 7/11/3 DLG: - Physician: 8/3/7 - Patient: 7/5/3 - Parent: 8/5/5 **5) Laboratory measures of inflammation:**	**General comments:** - Not controlled, not blinded - Poor description of population **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair/poor - Comments: Poor description of patients; unclear if blinded; some outcomes validated, others not; short study duration *Adverse events:* Overall rating: Poor - Comments: Not characterized by patient or treatment received; no n/% given **Applicability:** - Unclear population in terms of age and disease severity - Study outside US - Not blinded

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Primary outcome(s): - Number of JCA criteria - Number of affected joints - Duration of morning stiffness - Pain score - ESR - Functional capacity - Parent/patient and physician global - Improvement (= when 5 of 6 indices reported improved) **Secondary outcome(s):** NR	Pauci or polyarticular JCA **Exclusion criteria:** NR	- ESR at time 0/6 months: SSZ : 52.7/36.3 DLG: 41.2/28.9 **6) Discontinuation of DMARD due to:** NR **7) Mortality:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: SSZ, 4; DLG, 1 **11) Mortality:** 0 **12) Adverse events reported?:** Yes SSZ: 4 (19%) discontinued due to AEs DLG: 1 (5%)	
Ilowite, Porras, Reiff, et al., 2009 **#62**	**Geographical location:** 17 sites in USA, Canada, Australia, New Zealand, and Costa Rica **Study dates:** July 2000 to February 2004 **Funding source:** Amgen, Inc. **Setting:** NR **Study design:** RCT, blinded, placebo-controlled, multicenter, with a 12-week, open-label, run-in period; 16-week, blinded RCT phase; and a 12-month open-label extension period	**Number of patients:** N = 86 in run-in phase, 50 in blinded RCT phase, 30 in extension phase - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 50 - Began treatment: 50 - Completed treatment: 31 - Withdrawals/losses to followup during blinded phase: 19/50 (38%; Anakinra N = 6 [4 for disease flare], placebo N = 13 [10 for disease flare]) Note: Reasons for withdrawal from blinded phase NR **Age:**	**1) Active joint count:** NR **2) Quality of life/functional status:** CHAQ change at week 28: Anakinra: -0.25 Placebo: 0.13 P value NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR change at week 28: Anakinra: -2.21	**General comments:** - Primary outcome changed from efficacy to safety because of low enrollment - Baseline CHAQ and ESR values NR **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Not powered for efficacy; insufficient reporting of randomization and concealment; no validated AE measure; conflict of interest with funding source, run-in phase *Adverse events:*

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Patients who experienced disease flare during the blinded phase were given the option to switch arms (and remain blinded) **Intervention(s):** - DMARD name: Anakinra - Dose: 1.0 mg/kg/day (max dose 100 mg/day) by daily injection - Titration: NA - N: 86 in run-in phase, 25 in RCT phase (plus 25 who received placebo), and 29 who completed open-label extension phase **Comparator(s):** Placebo (N = 25) **Were additional arthritis medications allowed?:** Yes: NR whether these were added per protocol or at the discretion of study investigators **Study duration:** 12-week run-in phase 16-week blinded phase 12-month extension phase **Primary outcome(s):** Safety, as defined by the incident of treatment-emergent AEs and lab values Assessments done at baseline, week 2, week 4, and every 4 weeks thereafter in blinded phase, then every 3 months in	- Mean (SD): 12 (SD NR) - Range: 3 to 17 **Sex:** - Female: 63 (73%) - Male: 23 (27%) **Race/ethnicity:** White: 46 (53%) Black: 5 (6%) Hispanic: 29 (34%) American Indian/Alaskan native: 3 (3%) Asian: 1 (1%) Other: 2 (2%) **JIA diagnosis:** JRA Anakinra Placebo Onset: N (%) N (%) - Polyarticular 14 (56) 19 (76) - Systemic 9 (36) 2 (8) - Pauciarticular 2 (8) 4 (16) **Baseline severity:** NR **Percentage with uveitis:** NR **Inclusion criteria:** - Presenting with polyarticular-course JRA, independent of onset - Required to have ≥ 5 swollen joints due to active arthritis (not bony overgrowth) and 3 joints with limitation of motion at screening and day 1 visit	Placebo: 13.73 P value NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** By week 28: Anakinra Placebo N (%) N (%) - Polyarticular 2 (14) 8 (42) - Systemic 2 (22) 1 (50) - Pauciarticular 0 1 (25) P = 0.11 "Time to disease flare was greater in patients receiving anakinra, nearly reaching statistical significance (p = 0.057)." **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 27/86 patients (31%) in open-label run-in phase withdrew because of nonresponse - Intolerance/AEs: 4/86 patients (5%) in open-label run -n phase withdrew because of AEs Reasons for withdrawal from blinded phase NR **11) Mortality:** None	- Overall rating: Fair - Comments: Insufficient reporting of randomization and concealment; no validated AE measure; conflict of interest with funding source **Applicability:** Outcomes measured; differential dropout rates (12% vs. 26%)

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	extension phase up to 12 months **Secondary outcome(s):** Response, defined as ≥ 30% improvement in any 3 of 6 JRA core set criteria variables, including: - Physician global assessment of disease activity; - Patient/parent assessment of disease activity; - CHAQ; - Number of joints with active arthritis; - Number of joints with limited range of motion; - ESR. Also assessed: - Proportion of patients with disease flares in the blinded phase; - Time to disease flare; - Changes in the JRA core components at week 28; - Pharmacokinetics.	- Age between 2 and 17 years - Minimum weight of 10 kg - On a stable dose of MTX for 6 weeks before study entry and not receiving biologic therapy within 4 weeks of initiating study drug - Negative pregnancy test of childbearing potential **Exclusion criteria:** - Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal - Creatinine > 1.5 times the upper limit of normal - WBC < 2.0 x 10^9/L - Neutrophil count < 1.5x10^9/L - Platelet count < 150x10^9/L - Receiving treatment with a DMARD other than MTX - Receiving intraarticular or systemic corticosteroid injections within 4 weeks before study entry - Clinically significant systemic disease (such as hepatic, renal, neurological, endocrine, cardiac, gastrointestinal [except NSAID-induced GI problems]) - Hematological disease - Presence of symptoms of systemic disease, such as intermittent fever, rash, hepatosplenomegaly, or pericarditis within 24 weeks of the first dose of anakinra	**12) Adverse events reported?:** Yes **13) Other:** Responders: Anakinra (%) / Placebo (%) - Polyarticular: 53 / NR - Systemic 73 / NR - Pauciarticular 67 / NR	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Kvien, Hoyeraal, and Sanstad, 1985 **#1207**	**Geographical location:** Oslo, Norway **Study dates:** 1979 to 1983 **Funding source:** Norsk Hydro Research Foundation for Rheumatology, Norwegian Women Public Health Association, Astra Syntex Research Foundation at Oslo Sanitersforening Rheumatism Hospital and the Norwegian Medicinal Depot **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Hydroxychloroquine (HC)-Ercoquin - Dose: 5 mg/kg daily, rounded upwards to nearest 25 mg and given twice per day - Titration: Given 9 months then withdrawn - N: 25 - DMARD name: Gold sodium thiomalate (GSTM) - Myocrisin - Dose: 0.7 mg/kg by weekly injection - Titration: After total of 14mg/kg (20 weeks), 0.7mg/kg given monthly through week 50 - N: 23 - DMARD name: D-Penicillamine	**Number of patients:** N = 72 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 72 - Began treatment: 72 - Completed treatment: 44 - Withdrawals/losses to followup: 28 **Age:** - Median: 10.8 years - Range: 3.6 to 15.9 years **Sex:** - Female: 47 (65.3%) - Male: 25 (34.7%) **Race/ethnicity:** NR **JIA diagnosis:** JRA (pauciarticular or polyarticular) **Baseline severity:** Active joint count: 7-9 Duration of disease: Median 16 months (range, 3 to 164) Other: Radiographic erosions or severe growth disturbances in ≥ 1 joint, n = 9 **Percentage with uveitis:** "Chronic iridocyclitis," n = 11 **Inclusion criteria:** - Fulfillment of the diagnostic criteria of JRA - Present pauciarticular or polyarticular disease type - Between 2 and 16 yrs old - Active disease with indication	**1) Active joint count:** Baseline (BL) median and median change values at 12, 24, and 50 weeks: 	Drug	BL	12 wk	24 wk	50 wk
HC	9	-1	-2	-4
GSTM	7	-1	-2	-5
PEN	8.5	-2	-2	-2.5 | P = NS **2) Quality of life/functional status:** "Functional capacity" reported as a 1-20 graphic rating scale – see "Global assessment of current status," below **3) Number of joints with limited range of motion:** Baseline (BL) median and median change values at 12, 24, and 50 weeks: | Drug	BL	12 wk	24 wk	50 wk
HC	3	0	0	0
GSTM	3	0	-1	0
PEN	4	0	-1	-2 | P = NS **4) Global assessment of current status:** By physician (1-20 scale, 20 maximum activity): Baseline (BL) median and median change values at 12, 24, and 50 weeks: | Drug	BL	12 wk	24 wk	50 wk
HC	11	-2	-2.5	-8
GSTM	12	-3	-5	-9
PEN	12	-2	-4	-7.5	 P = NS By physician: HVM ≥ 50% improvement by physician's overall assessment at 12, 24, and 50 weeks	**General comments:** None **Quality assessment:** *Primary outcome:* - Overall rating: Poor - Comments: Allocation concealment not specified; important baseline differences; unclear if outcomes assessed blind to intervention; outcomes not well described *Adverse events:* - Overall rating: Poor - Comments: Allocation concealment not specified; important baseline differences; unclear if outcomes assessed blind to intervention; outcomes not well described **Applicability:** Non-USA

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	(Pen)- Distamin - Dose: Rounded to nearest 25 mg and given twice per day - Titration: 2.5mg/kg weeks 1-4; 5 mg/kg weeks 5-8; 7.5 mg/kg weeks 9-12; 10 mg/kg after week 12 to week 50 - N: 24 **Comparator(s):** Three DMARDs compared, no placebo **Were additional arthritis medications allowed?:** Yes: NSAIDs, preferred to be kept constant; acetaminophen as needed **Study duration:** 50 weeks **Primary outcome(s):** Not stated; outcomes measured at 12, 24, and 50 weeks **Secondary outcome(s):** - Joint counts - Articular indices - Physicians' overall assessment - Goniometric measurements - Various functional tests - Ophthalmological examinations - ESR and other laboratory measures	for use of slow-acting antirheumatic drugs (SAARD), that is, progressive disease with reversible disease manifestations without sufficient effect of NSAID **Exclusion criteria:** - Contraindication for use of either hydroxychloroquine, gold sodium thiomalate, or D-penicillamine - Secondary amyloidosis - Present systemic disease type - Use of either systemic corticosteroids, immunoregulatory drugs, or SAARD during the 6 months prior to the study, or local corticosteroid injections or joint surgery during the preceding 2 months	<table><tr><td>Drug</td><td>12 wk</td><td>24 wk</td><td>50 wk</td></tr><tr><td>HC</td><td>4/25</td><td>9/24</td><td>12/17</td></tr><tr><td>GSTM</td><td>6/19</td><td>8/19</td><td>10/15</td></tr><tr><td>PEN</td><td>0/23</td><td>8/19</td><td>8/12</td></tr></table>P = NS By patient/parent: NR **5) Laboratory measures of inflammation:** - ESR: Baseline (BL) median and median change values at 12, 24, and 50 weeks: <table><tr><td>Drug</td><td>BL</td><td>12 wk</td><td>24 wk</td><td>50 wk</td></tr><tr><td>HC</td><td>28</td><td>-4</td><td>-9.5</td><td>-12</td></tr><tr><td>GSTM</td><td>27</td><td>-7</td><td>-10</td><td>-11</td></tr><tr><td>PEN</td><td>20</td><td>-7</td><td>-6</td><td>-8</td></tr></table>P = NS **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** Pain on movement – Baseline (BL) median and median change values at 12, 24, and 50 weeks: <table><tr><td>Drug</td><td>BL</td><td>12 wk</td><td>24 wk</td><td>50 wk</td></tr><tr><td>HC</td><td>6</td><td>-1</td><td>0</td><td>-1</td></tr><tr><td>GSTM</td><td>4.5</td><td>-1</td><td>-1</td><td>-2</td></tr><tr><td>PEN</td><td>7</td><td>-3</td><td>-2</td><td>-2</td></tr></table>P = NS **8) Clinical remission:** NR **9) Flare of disease:** Withdrawals by week 50 due to disease exacerbation HC: 1 GSTM: 0	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			PEN: 2 **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: HC, 6; GSTM, 4; PEN, 4 - Intolerance/AEs: HC, 0; GSTM, 3; PEN, 6 **11) Mortality:** NR **12) Adverse events reported?:** Yes Number of AEs reported (HC / GSTM / PEN): Dermatitis: 1 / 2 / 1 Stomatitis: 0 / 1 / 0 GI upset: 1 / 0 / 4 Taste disturbances: 0 / 0 / 2 Proteinuria: 0 / 2 / 1 Eosinophilia: 0 / 3 / 0 Thrombocytopenia: 0 / 0 / 3 Antibodies to native DNA: 0 / 0 / 1 Other: 0 / 2 / 4 Withdrawals due to AEs: HC: 0 GSTM: 3 PEN: 6	
Kvien, Hoyeraal, and Sandstad, 1986 **#1188**	**Geographical location:** Oslo, Norway **Study dates:** 1979-83 **Funding source:** Norsk Hydro Research Foundation for Rheumatology, Norwegian Women Public Health Association, Astra Syntex Research Foundation at Oslo Sanitetsforening Rheumatism Hospital, Norwegian Medicinal Depot and Norma and Leon	**Number of patients:** N = 32 (AZA N = 17; PL N = 15) - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 32 - Began treatment: 32 - Completed treatment: NR - Withdrawals/losses to followup: 8 – follow-up rates: Week 8: 15/17 AZA; 15/15 PL Week 16: 13/17 AZA; 11/15 PL **Age:** Median (range):	**1) Active joint count:** Baseline (BL) median and median change values at 8 and 16 weeks: | Drug	BL	8 wk	16 wk
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AZA	17	-5	-7
PL	31	1	-1 | P = 0.45 **2) Quality of life/functional status:** Baseline (BL) median and median change values at 8 and 16 weeks:	**General comments:** Reference 15 in the published report has more information on outcomes assessment **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Allocation concealment not stated; small sample with some potentially important baseline differences and significant dropouts

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Hess' Foundation for Support of Rheumatological Research at Olslo Sanitetsforening Rheumatism Hospital **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Azathioprine (AZA) -Imuran - Dose: 2.5 mg/kg rounded to nearest 12.5 mg, given daily - Titration: NA - N: 17 **Comparator(s):** - Matching Placebo (PL) - N: 15 **Were additional arthritis medications allowed?:** Prednisolone, preferably 0.2 mg/kg at trial start; reduced in 5-8 steps until withdrawal by study end; NSAIDS, preferably maintained at stable dose **Study duration:** 16 weeks **Primary outcome(s):** Not specified **Secondary outcome(s):** Multiple disease activity measures	AZA: 10.2 years (2.4-14.8) Placebo: 9.5 years (4.1-15.0) **Sex:** - Female: AZA 12 (70.6%) Placebo 10 (66.7%) - Male: AZA 5 (29.4%) Placebo 5 (33.3%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Baseline severity:** Active joint count: 17 AZA; 31 PL Duration of disease: 31 months AZA (range 4-139); 21 months PL (range 3-110) Other (specify): Severe radiographic abnormalities: 8 AZA, 7 PL **Percentage with uveitis:** Chronic iridocyclitis: AZA n = 5; PL n = 3 **Inclusion criteria:** - Required therapy with immunomodulatory drugs - Disease was active and progressive (with severe systemic features and/or with severe articular involvement progressing towards irreversible joint abnormalities) - Insufficient response to previous adequate therapy with slow acting antirheumatic drugs	<table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>5</td><td>-2</td><td>-4</td></tr><tr><td>PL</td><td>6</td><td>0</td><td>0</td></tr></table>P < 0.01 **3) Number of joints with limited range of motion:** Baseline (BL) median and median change values at 8 and 16 weeks: <table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>9</td><td>-1</td><td>-1</td></tr><tr><td>PL</td><td>16</td><td>1</td><td>-2</td></tr></table>P = 0.51 **4) Global assessment of current status:** - By physician (1-20 scale, 20 maximum activity): Baseline (BL) median and median change values at 8 and 16 weeks: <table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>13</td><td>-3</td><td>-5</td></tr><tr><td>PL</td><td>16</td><td>1</td><td>-2</td></tr></table>P = 0.12 - By patient ("subjective total assessment, 1-20, 20 maximum activity"): Baseline (BL) median and median changes at 8 and 16 weeks: <table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>5</td><td>-1</td><td>-2</td></tr><tr><td>PL</td><td>6</td><td>1</td><td>0</td></tr></table>P = 0.02 - By patient – HVM "subjective total assessment improved by ≥ 50%: AZA: 6/15 week 8; 8/13 week 16 PL: 1/15 week 8; 1/11 week 16 P = 0.01	*Adverse events:* - Overall rating: Fair - Comments: No details on AE assessments **Applicability:** Not U.S.A.

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		for 6 months for patients with pauci- and polyarticular disease type - Systemic disease patients were included if their responses to previous therapy with corticosteroids were insufficient **Exclusion criteria:** - Previous use of azathioprine or other immunomodulatory drugs - Evidence of concomitant infectious, hematological, or hepatic disease, or other disorders contraindicating use of immunomodulatory drugs - Probably insufficient cooperation and local followup - Joint surgery or corticosteroid injections (both local or systemic) during a period of 2 months before the study - Alterations of the dose of NSAID or corticosteroid during the 7 days before the study - Lack of assent/consent from the patient/parent to take part in the study	**5) Laboratory measures of inflammation:** - ESR: Patients with ≥ 50% improvement AZA: 3/15 week 8; 4/13 week 16 PL: 3/15 week 8; 2/11 week 16 P = 0.36 - ESR: Patients with ≥ 25% improvement AZA: 8/15 week 8; 4/13 week 16 PL: 4/15 week 8; 4/11 week 16 P = 0.41 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** - Pain on movement (1-20, 20 maximum activity): Baseline median and median changes at 8 and 16 weeks: Drug / BL / 8 wk / 16 wk AZA / 3 / -1 / -2 PL / 7 / 0 / -1 P = 0.10 **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy (exacerbation): 1 AZA; 2 PL - Intolerance/AEs: 3 AZA; 0 PL **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Lahdenne, Vahasalo, and Honkanen, 2003 **#530**	**Geographical location:** Finland **Study dates:** NR **Funding source:** NR **Setting:** NR **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Infliximab or etanercept - Dose: Infliximab 3-4 mg/kg IV at weeks 0, 2, 6, and then 4- to 8-week intervals; etancercept (0.4 mg/kg) subcutaneously twice/week - Titration: NR - N: 24 (14 infliximab, 10 etanercept) **Comparator(s):** Open-label comparison to other DMARD **Were additional arthritis medications allowed?:** Yes: One or more of methotrexate, prednisolone, cyclosporine A, sulfasalazine, hydroxylchloroquine, intraarticular corticosteroid injections, NSAIDs NR whether these were added per protocol or at the discretion of study investigators **Study duration:** 12 months	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 24 - Completed treatment: 18 - Withdrawals/losses to followup: Etancerpt (1 noncompliance – switched to infliximab), infliximab (5 noncompliance or adverse events) **Age:** - Mean (SD): 10.2 (NR) - Median: NR - Range: 3.3-16.3 years **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** Polyarticular JIA **Baseline severity:** Active joint count: Etanercept: 10 (5-19) Infliximab: 13 (6-21) Duration of disease: At least 1 year **Percentage with uveitis:** NR **Inclusion criteria:** Refractory to standard treatment for 1 year **Exclusion criteria:** NR	**1) Active joint count:** Etanercept: -9.5 (95% CI -19 to -3) Infliximab: -11.5 (95% CI -17 to -7.5) P = 0.74 **2) Quality of life/functional status:** CHAQ: Etanercept -0.81 (95% CI -1.44 to -0.19) Infliximab: -0.31 (95%CI -0.75 to -0.25) P = 0.12 **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: Etanercept: -29 (95% CI -52 to -14.5) Infliximab: -35 (95% CI -50.5 to -23.5) P = 0.65 - Patient/Parent: Etanercept: -24.5 (95% CI-50.5 to -7.0) Infliximab: -27.5 (95%CI -47.5 to -12) P = 0.81 ACR Paediatric 50: Etancercept: 3 mo (90%), 6 mo (89%), 12 mo (89%) Infliximab: 3 mo(67%) , 6 mo (83%), 12 mo (78%) ACR Paediatric 75: Etancercept: 3 mo (60%), 6 mo (78%), 12 mo (67%) Infliximab: 3 mo(50%) , 6 mo (58%), 12 mo (67%) **5) Laboratory measures of inflammation:** - ESR: Etancercept: -28.5 (95% CI -51.5 to -15) Infliximab: -25 (95%CI: -36 to -15)	**General comments:** - Drug switching makes it hard to interpret the effect of the drugs individually - Not much reported on the subjects **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: No funding source reported, assessment not masked *Adverse events:* - Overall rating: Fair - Comments: No validated AE measure, no funding source reported **Applicability:** Outcomes measured prospectively

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			P = 0.37 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: 0 - Inefficacy: NR - Intolerance/AEs: 3 in the infliximab group – infusion reaction with chest pain, dyspnea and urticaria which could not be controlled by slowing infusion or premedication 1 in infiximab group – possible macrophage activation syndrome 1 in infliximab group – alopecia 3 in the infliximab group switched to etanercept, which was tolerated **11) Mortality:** None **12) Adverse events reported?:** Yes	
Lovell, Giannini, Reiff, et al., 2000 **#721** **AND** **Lovell, Giannini, Reiff, et**	**Geographical location:** Multiple sites in US and Canada **Study dates:** NR **Funding source:** Supported by Immunex Corporation, Seattle, which provided the study drug and grants to investigational sites; by the Children's Hospital Foundation of Cincinnati; and by grants from the National	**Number of patients:** N = 69 - Screened for inclusion: NR - Eligible for inclusion: NR - Enrolled in lead-in phase: 69 - Completed lead-in phase: 64 - Enrolled in RCT phase: 51 - Began treatment: 51 - Completed treatment: 40 - Withdrawals/losses to followup: Lead-in phase: 5/69 (1 AE, 2 withdrew consent, 2 lack of response)	**1) Active joint count:** Placebo N = 26 / Etanercept N = 25 Baseline: 27.0 / 32.0 3 mo: 37.5 / 13.0 7 mo: 13.0 / 7.0 **2) Quality of life/functional status:** CHAQ score:	**General comments:** - Well designed, executed, and reported study - Some potential for conflict of interest **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
al., 2003 **#547**	Institutes of Health (AR42632 and AR44059-P60 MAMDC). **Setting:** NR **Study design:** RCT, multicenter, double-blind, with open-label lead-in and RCT phases (Lovell et al. #721) and ongoing open-label extension phase with 58 patients (Lovell et al. #547) **Intervention(s):** - DMARD name: Etanercept - Dose: 0.4 mg/kg (up to 25 mg) subcutaneously twice weekly, until disease flare occurred or 4 months elapsed - N: 25 **Comparator(s):** Placebo - N: 26 **Were additional arthritis medications allowed?:** Yes: - MTX was discontinued 14 days and other DMARDs 28 days before start of treatment with etanercept - Intraarticular and soft-tissue corticosteroid injections not permitted during or for 1 month prior to the trial - Stable doses of NSAIDs or low doses of corticosteroids permitted, at discretion of clinician - Pain meds allowed except during the 12 hours before joint	RCT phase, etanercept: 6/25 (24%) withdrew because of disease flare RCT phase, placebo: 18/26 (69%) withdrew because of disease flare, and 1 because of parental withdrew consent - Enrolled in open-label extension phase: 58 - Included in analysis of extension phase: 48 - Withdrawals from extension phase: 10 (suboptimal response 7; lost to followup 1; AEs 1; remission 1) **Age:** - Mean (SD): 10.5 (SD NR) - Range: 4-17 years **Sex:** - Female: 43 (62%) - Male: 26 (38) **Race/ethnicity:** White: 52 (75%) Black: 6 (9%) Hispanic: 9 (13%) Other: 2 (3%) **JIA diagnosis:** JRA Lead-in phase, n (%): - Pauciarticular: 7 (10) - Polyarticular: 40 (58) - Systemic: 22 (32) RCT phase, n (%): - Pauciarticular: 3 (6) - Polyarticular: 31 (61)	Placebo N = 26 / Etanercept N = 25 Baseline 1.3 / 1.6 3 mo 0.4 / 0.9 7 mo 1.2 / 0.8 Lead-in phase: 37% median improvement in scores seen for all patients RCT phase: 54% mean improvement in etanercept vs. no change in placebo group (p = 0.01) **3) Number of joints with limited range of motion:** Placebo N = 26 / Etanercept N = 25 Baseline 6.5 / 8.0 3 mo 1.0 / 2.0 7 mo 4.5 / 1.0 **4) Global assessment of current status:** Physician's global assessment of disease severity: Placebo N = 26 / Etanercept N = 25 Baseline 6 / 7 3 mo 1 / 2 7 mo 5 / 2	**Applicability:** No significant issues

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	assessment	- Systemic: 14 (56)	Patient's or parent's global assessment of overall well-being:	
	Study duration:	**Baseline severity:**	Placebo Etanercept	
	Lead-in phase: 3 months	Active joint count: 28	N = 26 N = 25	
	RCT phase: 4 months	Duration of disease: 5.9 years	Baseline	
			5 5	
	Primary outcome(s):	**Percentage with uveitis:** NR	3 mo	
	Number of patients with disease flare, defined as worsening of ≥ 30% in 3 of 6 response variables, with improvement of ≥ 30% in no more than 1 variable		1 2	
		Inclusion criteria:	7 mo	
		- 4-17 years of age	5 3	
		- Polyarticular JRA		
		- Had active disease despite treatment with NSAIDs and with	**5) Laboratory measures of inflammation:**	
	Secondary outcome(s):		- ESR:	
	Assessments at screening, baseline, day 15, and at the end of each month, with final safety assessment 30 days after discontinuation of study drug	methotrexate at doses of at least 10 mg per square meter of body-surface area per week	Placebo Etanercept	
			N = 26 N = 25	
		- Had normal or nearly normal platelet, white-cell, and neutrophil counts, hepatic amino-transferase levels, and results of renal-function tests	Baseline	
			27 41	
			3 mo	
			12 15	
			7 mo	
			30 18	
		Exclusion criteria:	- CRP:	
		- Pregnant or lactating females (girls with childbearing potential were required to use contraception throughout the study)	Placebo Etanercept	
			N = 26 N = 25	
			Baseline	
			1.8 3.5	
			3 mo	
		- Major concurrent medical conditions	0.3 0.2	
			7 mo	
			3.5 0.4	
			"In the double-blind study as compared with the end of the open-label study, a significant proportion of patients who received placebo had shifts from normal levels of CRP and ESR to above-normal values ($p \leq 0.03$ for each variable)."	
			6) Radiographic evidence of progression	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			of disease: NR **7) Pain control:** - Visual analog scale (0 = best, 10 = worst): Placebo N = 26 / Etanercept N = 25 Baseline: 3.5 / 3.5 3 mo: 0.3 / 1.3 7 mo: 3.5 / 1.5 **8) Clinical remission:** NR **9) Flare of disease:** RCT phase: Placebo: 21 (81%) Etanercept: 7 (28%) P = 0.003 Rates of flare remained consistently and significantly lower in the etanercept group ($p < 0.001$) after adjustment for the effects of baseline characteristics. Median time to flare was > 116 days in the etanercept group, and 28 days in the placebo group ($p < 0.001$). **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 2/69 (3%) in lead-in phase - Intolerance/AEs: 1/69 (2%) in lead-in phase **11) Mortality:** None **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Other: Definition of improvement: 30% improvement from baseline on ≥ 3 of 6 core variables, with 30% worsening on no more than 1 variable 51/69 (74%) met the definition of improvement at the end of the lead-in phase. 44 (64%) and 25 (36%) met ACR Pedi 50 and ACR Pedi 70 response criteria, respectively At the end of the RCT phase, 18 patients (72%) in the etanercept group and 6 patients (23%) in the placebo group met ACR Pedi 50 criteria for response	
Lovell, Ruperto, Goodman, et al., 2008 **#100**	**Geographical location:** Multiple centers in US, Italy, France, Czech Republic, Belgium, Germany, and the Slovak Republic **Study dates:** Lead-in and RCT phases, Sep 2002 to Jan 2005; ongoing extension phase **Funding source:** Supported by a research grant from Abbott Laboratories **Setting:** NR **Study design:** RCT, double-blind, placebo-controlled, multicenter, medication-withdrawal study, with lead-in, RCT, and extension phases Random allocation, stratified by MTX use (never received MTX	**Number of patients:** N = 171 (85 on MTX, 86 not on MTX) - Screened for inclusion: 196 - Eligible for inclusion: 171 - Open-label lead-in phase: 171 (85 on MTX, 86 not on MTX) - Completed lead-in phase: 160 (83 on MTX, 77 not on MTX) - Began treatment in RCT phase: 133 (75 on MTX, 58 not on MTX) - Completed RCT phase: 128 (71 on MTX, 57 not on MTX) - Entered extension phase: 128 - Withdrawals/losses to followup: Before RCT phase: 38 During RCT phase: 5 **Age:** - Mean (SD): MTX: 11.4 (3.3) No MTX: 11.1 (3.8) - Range: 4-17 years **Sex:**	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR: NR - Other: CPR measured but NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** Defined as > 30% worsening in ≥ 3 of 6	**General comments:** - Very well designed, executed, and reported study - Potential for conflict of interest, given the funding source and the authors' relationships with industry - Allocation concealment not specified **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good **Applicability:** No significant issues

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	vs. discontinued MTX > 2 weeks before) Patients achieving ACR Pedi 30 response at 16 weeks of the lead-in phase entered RCT phase **Intervention(s):** - DMARD name: Adalimumab - Dose: Based on body-surface area during first part of extension phase; in later part, fixed dose given (20 mg for patients weighing < 30 kg, and 40 mg for patients weighing ≥ 30 kg) During lead-in phase: 24 mg/m^2 (up to 40 mg) subcutaneously every other week for 16 weeks - Titration: As above - N: 68 **Comparator(s):** Placebo - N: 65 **Were additional arthritis medications allowed?:** Yes: - Patients taking MTX were at a stable dose of at least 10 mg/m^2/week for 3 months and continued through lead-in and RCT phases - NSAIDs, low-dose corticosteroids, or pain meds given at the discretion of clinician/investigator **Study duration:** 16-week open-label lead-in	- Female: MTX: 68 (80%) No MTX: 67 (78%) - Male: MTX: 17 (20%) No MTX: 19 (22%) **Race/ethnicity:** White: MTX: 81 (95%) No MTX: 76 (88%) Black: MTX: 0 (0%) No MTX: 3 (3%) Other: MTX: 4 (5%) No MTX: 7 (8%) **JIA diagnosis:** JRA, polyarticular **Baseline severity:** Active joint count: - MTX: 15.0 - No MTX: 19.4 Duration of disease, in years: - MTX, placebo: 4.0 - MTX, adalimumab: 4.3 - No MTX, placebo: 2.9 - No MTX, adalimumab: 3.6 **Percentage with uveitis:** NR **Inclusion criteria:** - Age 4-17 years - Polyarticular JRA with active disease - Inadequate response to NSAIDs	core criteria for JRA and improvement of ≥ 30% in no more than 1 criteria No. of disease flares during RCT phase: | Sub-group	Placebo	Adalim	P value
---	---	---	---
MTX	24/37 (65%)	14/38 (37%)	0.02
No MTX	20/28 (71%)	13/30 (43%)	0.03 | **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR During lead-in phase, 1/85 patients (1%) in the MTX stratum and 2/86 (2%) in the no MTX stratum withdrew because of an AE, and 5/85 (6%) in the no MTX stratum withdrew because of lack of efficacy During the RCT phase, 1/133 (1%) withdrew consent, and 4/133 (3%) withdrew for other reasons **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** ACR 30: "The patients improved according to all levels of ACR Pedi response during the open-label lead-in phase." "More patients treated with adalimumab than patients treated with placebo had ACR Pedi 30, 50, 70, or 90 responses in both the methotrexate stratum and the stratum not receiving MTX."	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	phase, 32-week RCT withdrawal phase, and ongoing open-label extension phase **Primary outcome(s):** Percentage of patients not receiving MTX who had a disease flare during the RCT phase **Secondary outcome(s):** - ACR Pedi 30, 50, 70, 90, and 100 responses - Safety evaluated on basis of physical exams, lab results, vital signs, and AEs	- Either previously treated with MTX or had AEs or no response to MTX **Exclusion criteria:** - Hematologic, hepatic, or renal abnormalities - Ongoing infection or recent severe infection - Recently vaccinated - Previously treated with IVIG, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered IV, IM, or intraarticular	"During the open-label extension phase, ACR Pedi responses were sustained during 2 years of treatment. After 104 weeks of treatment, 40% of patients had an ACR Pedi 100 response."	
Opper-mann and Mobius, 1994 **#937**	**Geographical location:** Cottbus, Germany **Study dates:** NR **Funding source:** NR **Setting:** NR **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Alphaglobulin (AG) - Dose: 400 mg IG/kg daily x 5 days; repeated 3 days each month for 6-8 months - Titration: None - N: 8 **Comparator(s):** - DMARD name: Methylprednisolone (MP)	**Number of patients:** N = 20 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 20 - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** - Range: 2-15 years **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JCA **Baseline severity:** Active joint count: NR Duration of disease: NR **Percentage with uveitis:** NR	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation: (Estimated from graph)** - ESR: MP: Baseline 59, 6 months 21 AG: Baseline 61, 6 months 24 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Open-label, nonrandomized, analyses not adjusted for baseline differences, patients not adequately described *Adverse events:* - Overall rating: NA - Comments: AEs not reported **Applicability:** Not USA

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td>- Dose: 30 mg/kg (max 1.0 g/pulse) x 3 days; pulses repeated monthly for 6-8 months
- Titration: None
- N: 12

Were additional arthritis medications allowed?: Yes:
- NSAIDS continued
- Methotrexate 10 mg/m^2/week
- Glucocorticosteroids ≤ 0.2 mg/kg body weight/day – given on alternate days

Study duration: Unclear, likely 6-8 months

Primary outcome(s): NR

Secondary outcome(s):
ESR, CD4, CD8 counts</td><td>Inclusion criteria:
PJCA or SJCA, characterized by high inflammatory activity of the rheumatic process

Exclusion criteria: NR</td><td>9) Flare of disease: NR

10) Discontinuation of DMARD due to:
- Remission of disease: NR
- Inefficacy: NR
- Intolerance/AEs: NR

11) Mortality: NR

12) Adverse events reported?: No</td><td></td></tr>
<tr><td>Prieur, Piussan, Manigne, et al., 1985

#1212</td><td>Geographical location: France

Study dates: NR

Funding source: Supported by Caisse Nationale de l’Assurance Maladie des Travailleurs Salariés

Setting: Outpatient or 3 specialized centers

Study design: RCT, double-blind

Intervention(s):
- DMARD name: D-penicillamine
- Dose: 5 mg/kg/day x 2months
- Titration: Increased to 10 mg/kg/day x 4 months</td><td>Number of patients: N = 74 (DP 38, placebo 36)
- Screened for inclusion: NR
- Eligible for inclusion: 74
- Randomized: 74
- Began treatment: 74
- Completed treatment: 55
- Withdrawals/losses to followup: 12 (4/8)
Analysis complete on 70 (2 misdiagnosed not included)

Age:
- Mean (SD):
DP: 8.2 (3.9)
Placebo: 9.8 (3.9)
- Range: 3-18 years

Sex:</td><td>1) Morning stiffness (minutes, mean [SD]):
<table><tr><td>Drug</td><td>Time 0</td><td>Final</td></tr><tr><td>DPN</td><td>47.5 (36.2)</td><td>26.8 (38.7)</td></tr><tr><td>Placebo</td><td>48.2 (32.5)</td><td>37.2 (43.8)</td></tr></table>2) Number of painful joints (mean [SD]):
<table><tr><td>Drug</td><td>Time 0</td><td>Final</td></tr><tr><td>DPN</td><td>6.3 (5.5)</td><td>3.3 (3.8)</td></tr><tr><td>Placebo</td><td>7.6 (5.3)</td><td>5.5 (5.5)</td></tr></table>3) Number of inflamed joints (mean [SD]):
<table><tr><td>Drug</td><td>Time 0</td><td>Final</td></tr><tr><td>DPN</td><td>5.2 (5.2)</td><td>2.5 (3.4)</td></tr><tr><td>Placebo</td><td>2.6 (2.7)</td><td>1.7 (2.1)</td></tr></table></td><td>General comments: None

Quality assessment:
Primary efficacy outcome:
- Overall rating: Fair
- Comments: Outcome measures not validated, patients in placebo group may have had worse disease

Adverse events:
- Overall rating: Good

Applicability: Outdated medication</td></tr>
</table>

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- N: 38 **Comparator(s):** Placebo; N = 36 **Were additional arthritis medications allowed?:** Yes: Pyridoxine hydrochloride 10 mg/kg/day **Study duration:** 6 months **Primary outcome(s):** - Functional Steinbrocker class - Duration morning stiffness (minutes) - Number of painful joints - Number of inflamed joints - Number of stiff joints - Sum of severity of pain - Sum of severity of inflammation - Sum of severity of stiffness - Consumption of steroids and --- - ASA - ESR	- Female: 51 (68.9%) - Male: 23 (31.1%) **Race/ethnicity:** NR **JIA diagnosis:** Polyarticular JCA or pauciarticular JCA (but with polyarticular course) or systemic onset JCA **Baseline severity:** Number of inflamed joints: DPN: 10.5 (± 6.5) Placebo: 13.9(± 19.1) Duration of disease: DPN: 3.1 (± 2.3) Placebo: 4.2 (±3.3) **Percentage with uveitis:** NR **Inclusion criteria:** - Met previously established diagnostic criteria - At least 2 of the following inflammatory criteria: erythrocyte sedimentation rate (ESR) > 25 mm/hour, serum fibrinogen > 400 mg/dL, and elevation (> 2 SD) of IgG, IgA, or IgM **Exclusion criteria:** - Persistence of systemic extraarticular symptoms (mainly spiking fever) during the previous 6 months - Arthritic involvement of < 4 joints - Use of NSAIDs not authorized for pediatric use in France	**4) Number of stiff joints (mean [SD]):** | Drug | Time 0 | Final | | --- | --- | --- | | DPN | 11.7 (9.0) | 8.5 (7.9) | | Placebo | 10.6 (7.5) | 11.1 (9.2) | **5)Severity of pain (mean [SD]):** | Drug | Time 0 | Final | | --- | --- | --- | | DPN | 7.2 (5.8) | 3.6 (4.2) | | Placebo | 8.3 (6.6) | 6.5 (6.3) | **6) Functional class 3-4 (time 0/final):** DPN: 9/4 Placebo: 6/6 **7) Remissions (time final):** DPN: 7 Placebo: 4 **8) ESR (mean [SD]):** | Drug | Time 0 | Final | | --- | --- | --- | | DPN | 49 (32) | 31 (26) | | Placebo | 41 (26) | 33 (23) | **9) Physician/parent/patient assessment** Not completed by all **10) Discontinuation of DMARD due to:** - Remission of disease: 0 - Inefficacy: 1 - Intolerance/AEs: 2 **11) Mortality:** NR **12) Adverse events reported?:** Yes Cytopenia (1)	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Systemic corticosteroid therapy > 0.5 mg/kg/day of prednisone or the equivalent -Use of SAARD during the previous 3 months - Any modification of treatment (including physiotherapy) during the past month - Presence of renal, blood, or hepatic disorders during the previous 6 months - History of penicillin allergy	Rash/mouth ulcers (1)	
Riddle, Ryser, Morton ,et al., 2006 **#313**	**Geographical location:** Dallas, Texas **Study dates:** NR **Funding source:** NR **Setting:** Hospital specializing in pediatric rheumatological conditions **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Methotrexate (MTX) - Dose: NR - Titration: NR - N: 20 **Comparator(s):** - NSAID, dose not specified, n = 22 - Methylprednisolone (MP) IV at time 1 and 4 months later; dose not specified, n = 20	**Number of patients:** N = 57 - Screened for inclusion: NR - Eligible for inclusion: 63 - Randomized: NA - Began treatment: 63 - Completed treatment: 57 - Withdrawals/losses to followup: **Age:** - Mean (SD): 8.1 (4.8) **Sex:** - Female: 44 (77.2%) - Male: 13 (22.8%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Baseline severity:** - Active joint count: Mean of 2.8 to 8.6 across groups - Duration of disease: NR **Percentage with uveitis:** NR **Inclusion criteria:** - Diagnosis of JIA	**1) Active joint count:** Baseline and 4-month mean (SD): NSAID: 2.8 (2.6), 2.0 (2.2) MTX: 8.1 (8.9), 4.1 (5.2) MP: 8.6 (7.3), 1.5 (2.5) F (2, 35) = 5.62, p = 0.008, MP greater percent improvement than other two treatments **2) Quality of life/functional status:** - Generic PedsQL Total Score (Parent report) – Baseline and 4-month mean (SD): NSAID: 76.1 (16.8), 77.5 (17.5) MTX: 69.7 (13.3), 74.7 (15.0) MP: 44.9 (19.4), 72.0 (18.9) Time*Medication F(10, 58) = 2.36, p = 0.02; MP greater percent improvement than other two treatments - Rheumatology PedsQL Total Score (Parent Report) – Baseline and 4-month mean (SD): NSAID: 70.8 (23.5), 75.7 (20.5) MTX: 60.3 (16.9), 71.9 (14.7) MP: 45.9 (19.2), 74.2 (20.1) Time*Medication F(10, 52) = 2.86, p = 0.007; MP greater percent improvement than other two treatments	**General comments:** Patient reports of HRQOL also given **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Confounding by indication; analysis adjusts only for baseline scores and not other potential confounders; outcomes not assessed blind to treatment condition; patients not blind to treatment assignment *Adverse events:* - Overall rating: Fair - Comments: Outcomes not assessed blind to treatment condition; patients not blind to treatment assignment **Applicability:** Poor

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Were additional arthritis medications allowed?: NR **Study duration:** 4 months **Primary outcome(s):** - Pediatric Quality of Life Inventory (PedsQL), version 4.0 -Generic Core Scales - Rheumatology Module, version 3.0 **Secondary outcome(s):** - Adverse effects - Joint counts - ESR - Global assessment	- Beginning new medication treatment – NSAIDs, MTX, or steroids - Age 1-18 years **Exclusion criteria:** - Presence of any other major illness or disability, as determined by the pediatric rheumatologist - Lack of proficiency in the English language prohibiting the administration of study questionnaires	**3) Number of joints with limited range of motion:** Baseline and 4-month mean (SD): NSAID: 3.7 (8.0), 3.1 (7.3) MTX: 7.9 (8.5), 4.3 (6.4) MP: 9.5 (9.3), 3.5 (6.9) **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** ESR – Baseline and 4-month mean (SD): NSAID: 22.6 (22.7), 22.1 (21.3) MTX: 40.2 (30.6), 27.7 (23.4) MP: 77.3 (32.3), 19.3 (18.8) F (2, 35) = 12.3, p = 0.001, MP greater percent improvement than other two treatments **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** Reported only as a subscale of Rheumatology PedsQL **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruperto, Lovell, Cuttica, et al., 2007 **#188**	**Geographical location:** 34 sites in North America (9), South America (3), and Europe (22) **Study dates:** Oct 2001 to Apr 2004 **Funding source:** Centocor, Inc. **Setting:** NR **Study design:** RCT, Phase III, international, multicenter, double-blind, placebo-controlled, with double-blind all active treatment extension **Interventions:** DMARD name: Infliximab plus methotrexate Dose: 3 mg/kg Titration: None N: 60 **Comparator:** Placebo + methotrexate for 14 weeks, followed by Inliximab 6 mg/kg plus MTX in weeks 14-52 N: 62 **Were additional arthritis medications allowed:** Yes: Methotrexate 10-15 mg/m^2/week oral or parenteral; other drugs (NSAIDs, opioids, corticosteroids) given at the discretion of the clinician/investigator **Study duration:** 52 weeks	**Number of patients:** N = 122 - Screened for inclusion: NR - Eligible for inclusion: 122 - Randomized: 122 - Began treatment: 122 - Completed treatment: 109 - Withdrawals/losses to followup: 13 (11%) **Age:** Mean (SD): 6 mg/kg: 11.0 (±4.0) 3 mg/kg: 11.3 (±4.0) Range: ≥ 4 to < 18 **Sex:** Female: 6 mg/kg: 49(79.0%) 3 mg/kg: 53(88.3%) Male: 6 mg/kg: 13 (21.0%) 3 mg/kg: 7 (11.7%) **Race/ethnicity:** White: 6mg/kg: 53(88.3%) 3 mg/kg: 50(83.3%) Other: 6 mg/kg: 9 (11.7%) 3 mg/kg: 10 (16.7%) **JIA diagnosis:** JRA Systemic onset: 6 mg/kg: 8 (13.1%) 3 mg/kg: 11 (18.3%) Pauciarticular onset, then polyarticular: 6 mg/kg: 15 (24.6%)	**1) Active joint count:** "At week 14, the number of joints with active arthritis differed significantly between patients in the infliximab 3 mg/kg group and those in the placebo group (p = 0.016), whereas there were no significant differences for the other core set variables." **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR: NR - Other: NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** 0 active joints at 52 weeks: Infliximab 3mg/kg: 26/59 (44.1%) Placebo then Infliximab 6 mg/kg: 25/58 (43.1%) **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: 9 patients infliximab, 1 placebo + MTX	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Results inconsistently, incompletely, and inadequately reported *Adverse events:* - Overall rating: Fair Comments: Results inconsistently, incompletely, and inadequately reported **Applicability:** Good

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		3 mg/kg: 13 (21.7%)	**11) Mortality:** 2 deaths (1 placebo + MTX, 1 Infliximab)	
	Primary outcome: Proportion meeting ACR Pedi 30 criteria at week 14	Polyarticular: 6 mg/kg: 38 (62.3%) 3 mg/kg: 36 (60%)	**12) Adverse events reported?:** Yes	
	Secondary outcome: - Improvement > 50% and > 70% on Pedi 50 and Pedi 70 - At week 52, number of joints with active disease	**Baseline severity:** Duration of disease (mean years ± SD): 6 mg/kg: 3.6 (± 3.4) 3 mg/kg: 4.2 (±3.6) Active joint count (mean ± SD): 6 mg/kg: 18.5 (± 11.5) 3 mg/kg: 19.5 (± 12.3) Rheumatoid factor + (n [%]): 6 mg/kg: 14 (23.7%) 3 mg/kg: 13 (21.7%) **Percentage with uveitis:** 0% **Inclusion criteria:** - Age ≥ 4 years and < 18 years - JRA - Suboptimal response to MTX after ≥ 3 months - ≥ 5 active joints - No active systemic symptoms **Exclusion criteria:** - Active uveitis - Serious infection, including tuberculosis - Malignancy - Prior treatment with TNF inhibitor	**13) Other:** ACR30 (primary study outcome) Week 14: Infliximab 3 mg/kg: 37/58 (63.8%) Placebo + MTX: 29/59 (49.2%) Week 52 (all patients): Pedi 50: 78/112 (69.9%) Pedi 70: 58/112 (51.8%) No significant differences between study groups "By the end of the study, following crossover of placebo-treated patients to infliximab 6 mg/kg, improvement in the JRA core set components was comparable between the treatment groups."	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruperto, Lovell, Quartier, et al., 2008 **#102**	**Geographical location:** Europe, Latin America, USA **Study dates:** Feb 2004-June 2006 **Funding source:** Bristol-Myers Squibb **Setting:** Pediatric rheumatology centers **Study design:** Open-label run-in followed by RCT **Intervention(s):** Open label: Abatacept 10mg/kg (max 1000 mg) on days 1, 15, 29, 57, and 85 of the 4-month open-label period Subjects who met ACR-Ped 30 were randomized to abatacept or placebo Abatacept 10mg/kg in 28-day intervals for 6 months or until a flare **Comparator(s):** Placebo (for RCT) **Were additional arthritis medications allowed?:** Methotrexate (if stable on it), folinic or folic acid, stable oral corticosteroids (10 mg/day or 0.2 mg/kg/day, whichever less), NSAIDs or analgesics for pain control	**Number of patients:** - Screened for inclusion: 214 - Eligible for inclusion: 190, of whom 170 enrolled in open-label trial - Randomized: 123 (based on response in open-label trial) - Began treatment: 122 - Completed treatment: 42 discontinued because treatment not effective - Withdrawals/losses to followup: 1 withdrew consent; 80 completed all visits in the 6-month double-blind period **Age:** Mean (SD) for the double-blind period: Abatacept (n = 60): 12.6(3) Placebo (n = 62): 12.0 (3) Overall age range: 6-17 years **Sex:** For the double-blind period Abatacept: - Female: 72% - Male: 28% Placebo: - Female: 73% - Male: 27% **Race/ethnicity:** For the double-blind period Abatacept: - White: 77% - Black: 8% - Other: 15% Placebo: - White: 79%	**1) Active joint count:** At the end of the RCT (mean [SD]): Abatacept: 4.4 (7.0) Placebo: 6.0 (5.8) P = 0.02 **2) Quality of life/functional status:** CHAQ (mean [SD]): Abatacept: 0.8 (0.9) Placebo: 0.7 (0.6) P = 0.04 **3) Number of joints with limited range of motion (mean [SD]):** Abatacept: 8.8 (12.8) Placebo: 8.6 (12.0) P = 0.01 **4) Global assessment of current status:** By physician (mean [SD]): Abatacept: 14.7 (18.9) Placebo: 12.5 (12.5) P < 0.01 By patient/parent (mean [SD]): Abatacept: 17.9 (22.2) Placebo: 23.9 (21.6) P = 0.70 **5) Laboratory measures of inflammation:** ESR (mean [SD]): Abatacept: 25.1 (26.4) Placebo: 30.7 (30.1) P = 0.96 C-reactive protein (mean [SD]): Abatacept: 0.16 (0.25) Placebo: 0.29 (0.54) P = 0.03	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Potential funding conflict *Adverse events:* - Overall rating: Good - Comments: Potential funding conflict **Applicability:** Good

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Black: 7% - Other: 15%	**6) Radiographic evidence of progression of disease:** NR	
	Study duration: 4 months (open-label), then 6 months (RCT); study also reports a 5-year open-label followup after the RCT component	**JIA diagnosis:** JIA	**7) Pain control:** NR	
	Primary outcome(s): Time to flare (30% or more in at least 3 of 6 core variables, with at least 30% improvement in no more than 1 variable)	**Baseline severity:** For the double-blind period (mean [SD]): Active joint count: Abatacept: 18.2 (11.5) Placebo: 14.7 (12.8)	**8) Clinical remission:** Inactive disease in 30% of abatacept vs. 11% controls (p = 0.02)	
	Secondary outcome(s): ACR Pediatric 30, 50, 70, and 90	Duration of disease: Abatacept: 3.8 (3.7) years Placebo: 3.9 (3.5) years	**9) Flare of disease:** By ACR Pediatric 30 criteria, after 6 months of RCT or time of flare for those who did not complete, 82% in the abatacept improved compared with 69% in the placebo (p = 0.17)	
		CHAQ disability index: Abatacept: 1.3 (0.7) Placebo: 1.2 (0.8)	By ACR Ped 50, 77% in abatacept improved, compared with 52% in controls (p < 0.01)	
		Parent global assessment: Abatacept: 41.8 (22.5) Placebo: 39.9 (24.7)	By ACR Ped 70, 53% in abatacept improved, compared with 31% placebo (p = 0.02)	
		ESR: Abatacept: 31.4 (27.7) Placebo: 30.8 (26.9)	By ACR Ped 90, 40% in abatacept improved, compared with 16% in placebo (p < 0.01)	
		Percentage with uveitis: None	**10) Discontinuation of DMARD due to:**	
		Inclusion criteria: - 6-17 years - JIA - At least 5 active joints - Active disease (at least 2 active joints and 2 joints with limited ROM) - Inadequate response to or intolerance to at least one DMARD (including etanercept, infliximbab, adalimumab)	- Remission of disease: None during RCT - Inefficacy: 10 - Intolerance/AEs: None during RCT	
			11) Mortality: None	
			12) Adverse events reported?: Yes During the run-in: 25 headache (13%), 19 nausea (10%), 17 cough (9%), 17 diarrhea (9%), 14 upper respiratory tract infection	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			(7%), 12 fever (6%), 8 infusional AEs	
		Exclusion criteria: - Active uveitis - Major concurrent medical conditions - Pregnant or lactating - No live vaccine within 3 months of the first dose of study medication - Intraarticular injections 4 weeks before enrollment or throughout the trial	During the RCT: No serious AEs for those with abatacept	
Silverman, Cawkwell, Lovell, et al., 1994 **#914**	**Geographical location:** US **Study dates:** NR **Funding source:** Baxter HealthCare, American Red Cross, Children's Hospital Research Foundation of Cincinnati, The Arthritis Foundation **Setting:** 9 sites in the US **Study design:** RCT **Intervention(s):** - DMARD name: IVIG - Dose: 1.5 g/kg, max 75 g every 2 weeks for the first 2 months then monthly for an additional 4 months - Titration: NR - N: 14 **Comparator(s):** Placebo N: 17	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 31 - Began treatment: NR - Completed treatment: 15 - Withdrawals/losses to followup: 1 dropout in placebo group, 1 placebo who did not meet eligibility criteria, 6 in each group because treatment insufficient, 1 in placebo for logistical reasons, 1 due to AE (noninfectious hepatitis) **Age:** IVIG - Mean (SD): 8.85 (1.3) - Median: 8.32 Placebo - Mean (SD): 9.07 (1.2) - Median: 8.53 **Sex:** IVIG - Female: 5 - Male: 9	**1a) Active joint count (mean change [SE], median):** IVIG: 3 (5), -2 Placebo: 1.5 (3.6), -1 **1b) Overall severity (mean change [SE], median):** IVIG: 21.4 (26.5), -5.5 Placebo: 5.1 (18.9), -18 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** By physician: 50% of the IVIG and 27% of the placebo improved (p > 0.3) By patient/parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR	**General comments:** - Small sample size led to heterogeneity - High dropout rate (50%) **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor. - Comments: Method not described or validated; small sample size *Adverse events:* - Overall rating: Poor - Comments: Rating was used to assign likelihood that the AE was related to IVIG; no AE data reported for the placebo group **Applicability:** Poor (small sample size)

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Were additional arthritis medications allowed?: Yes: - No more than 2 NSAIDs and up to 2 SAARDs – NR whether these were given per protocol or at the discretion of the clinician/ investigator; - Corticosteroids: 2 arms, either no steroids or steroid tapering, given per protocol **Study duration:** 6 months **Primary outcome(s):** Physician's global assessment **Secondary outcome(s):** - Joint count - Hemoglobin - Albumin - Platelet count - ESR	Placebo - Female: 7 - Male: 10 **Race/ethnicity:** NR **JIA diagnosis:** Systemic JRA **Baseline severity:** Active joint count: IVIG: 11.8 (3.2) Placebo: 16.8 (3.5) Duration of disease: IVIG: 1.55 (0.8) years Placebo: 1.89 (0.5) years Sum of severity scores for swelling, pain on motion, tenderness, and limitation of motion: IVIG: 48.1 (11.1) Placebo: 78.5 (17.4) **Percentage with uveitis:** NR **Inclusion criteria:** - Active, refractory systemic JRA, - At least 1 day of fever of 38.5 or greater within 30 days before enrollment - At least 1 of the following: Hb < 10.5 g/dL, albumin < 35 mg/dL, ESR > 20 mm/h, platelet count > 450,000 - Active articular disease **Exclusion criteria:** Intraarticular steroids	**8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: None - Inefficacy: 6 in each group - Intolerance/AEs: 1 (IVIG) **11) Mortality:** None **12) Adverse events reported?:** Yes 4 patients in IVIG group had 10 AEs, of which 6 were considered probably or possibly treatment-related. 9/10 were chills, fever, emesis, or headache; 1 was hepatitis. Most AEs were infusion-related.	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Silverman, Mouy, Spiegel, et al., 2005 **#383**	**Geographical location:** Multinational **Study dates:** NR **Funding source:** Sanofi-Aventis **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Oral leflunomide - Dose: if < 20 kg, 100 mg loading x 1 day and then 10 mg every other day; if 20-40 kg, 100 mg loading x 2 days, then 10 mg daily; if > 40 kg, loading 100 mg x 3 days, then 20 mg daily **Comparator(s):** Oral methotrexate 0.5 mg/kg/week (max 25 mg), and placebo **Were additional arthritis medications allowed?:** Yes: Folic acid or folinic acid (everyone), NSAIDs, prednisone (in unchanged), up to 2 doses of intraarticular corticosteroid – all given at the discretion of the clinician/investigator **Study duration:** 16 weeks with an optional 32-week extension **Primary outcome(s):**	**Number of patients:** - Screened for inclusion: 103 - Eligible for inclusion: 94 - Randomized: 94 - Began treatment: 47 in each group - Completed treatment: 86 completed 16-week study and 54 completed 48-week extension - Withdrawals/losses to followup: For the 16-week study, 3 in the methotrexate group withdrew (1 AE, 1 lack of efficacy, 1 lost), 5 in the leflunomide group withdrew (3 AEs, 1 lack of efficacy, 1 declined to take drug). For the extension, in the methotrexate group, 7 did not enroll (3 at nonparticipating site, 2 for lack of efficacy, 2 declined consent). In the leflunomide group, 9 did not enroll (4 at nonparticpating site, 4 lack of efficacy, 1 declined consent). **Age:** Leflunomide: - Mean (SD): 10.1 (4.0) - Median: 11 - Range: 3-17 Methotrexate: - Mean (SD): 10.2 (3.8) - Median: 11 - Range: 3-17 **Sex:** Leflunomide: - Female: 75% - Male: 26%	**1) Active joint count:** At 16 weeks: -8.1 in leflunomide group versus -8.9 in methotrexate group (NS) **2) Quality of life/functional status:** At 16 weeks: ACR Pedi 30 responses were 68% in leflunomide and 89% in methotrexate (p = 0.02) Median time to ACR Pedi 30 response was 52 days in leflunomide and 56 days in methotrexate group ACR Pedi 50 responses were 60% in leflunomide and 77% in methotrexate (p = 0.1) ACR Pedi 70 responses were 43% in leflunomide and 60% in methotrexate (p = 0.14) Mean percent improvement index -44.41 for leflunomide and -52.87 for methotrexate (p = 0.18) CHAQ: -0.44 in leflunomide group and -0.39 in methotrexate group Similar findings described for the extension **3) Number of joints with limited range of motion:** -5.2 in leflunomide group vs. -5.3 in methotrexate group (NS) **4) Global assessment of current status:** Change at 16 weeks: By physician: Leflunomide -31.5, methotrexate -32.1 (overlapping 95% CIs)	**General comments:** Lacks placebo group **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Percent improvement index lacks validation *Adverse events:* - Overall rating: Good **Applicability:** Good

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- ACR Pedi 30 - Percent Improvement Index (mean of the percent changes from baseline in each core set of disease activity measures, with negative values indicating improvement and positive values set to 0 indicating no improvement) **Secondary outcome(s):** - Rates of ACR Pedi 50 and ACR Pedi 70 responses - Time to an ACR Pedi 30 response - Area under the curve analyses - Mean changes in the core set of disease activity measures and - C-reactive protein concentrations	Methotrexate: - Female: 72% - Male: 28% **Race/ethnicity:** Leflunomide: - White: 87% - Black: 2% - Asian: 2% - Other: 9% Methotrexate: - White: 74% - Black: 4% - Asian: 0% - Other: 21% **JIA diagnosis:** JRA **Baseline severity:** Active joint count: - Leflunomide: 14.4 (7.9) - Methotrexate: 14.0 (9.9) Duration of disease: - Leflunomide: 1.69 (3.21) - Methotrexate: 1.37 (1.97) ESR: - Leflunomide: 30.8 (18.2) - Methotrexate: 34.5 (21.7) **Percentage with uveitis:** NR **Inclusion criteria:** - Active polyarticular disease - Not received methotrexate or leflunomide - Sexually active female patients	By patient/parent: Leflunomide -15.9 methotrexate -22.0 **5) Laboratory measures of inflammation:** ESR: Decrease in leflunomide group -6.5; decrease in methotrexate group -7.2 (non-significant) C-reactive protein: decreased -3.9 in leflunomide group vs. -11.4 in methotrexate group (p = 0.04) **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 1 in methotrexate group and 1 in leflunomide group during the first 16 weeks; 2 in the methotrexate group during the extension; 4 in the leflunomide group during the extension - Intolerance/AEs: 1 in the methotrexate group during the first 16 weeks, 3 in the leflunomide group during the first 16 weeks **11) Mortality:** None **12) Adverse events reported?:** Yes In the first 16 weeks leading to withdrawal: 1 methotrexate = LFT abnormalities 1 leflunomide = LFT abnormalities 1 leflunomide = parapsoriasis	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		negative serum pregnancy studies throughout the study **Exclusion criteria:** - ACR Functional class IV disease - Active systemic symptoms within 4 weeks before entry - Persistent or severe infection within 3 months before entry - Inflammatory disease other then JRA or a history of such a disease	1 leflunomide = Crohn's disease (not thought to be related) Other serious AEs Leflunomide: 1 with suspected salmonellosis None in the methotrexate group	
Smith, Thompson, Whitcup, et al., 2005 **#400**	**Geographical location:** Bethesda, MD **Study dates:** Sep 17,1999-Sep 28, 2001 (enrollment) **Funding source:** Immunex Corp **Setting:** NIH **Study design:** 1year duration – 2 phases: 1st phase: RCT, double-blind 2nd phase: Single arm, open-label Randomized 2:1 etanercept/placebo **Interventions:** DMARD name: Etanercept Dose: 0.4mg/kg twice weekly N: 7 **Comparator:** Placebo N: 5	**Number of patients:** N = 12 - Screened for inclusion: 24 - Eligible for inclusion: 12 - Randomized: 12 (7 to DMARD, 5 to placebo) - Began treatment: 12 - Completed treatment: 12 - Withdrawals/losses to followup: 0 **Age:** Mean (SD): 11 Median: 11 Range: 6-15 years **Sex:** Female: 9 (75%) Male: 3 (25%) **Race/ethnicity:** Hispanic: 4 (33.3%) Black: 1 (8.3%) White: 6 (50%) Pacific Islander: 1 (8.3%) **JIA diagnosis:** JRA	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 1 - Intolerance/AE: 0	**General comments:** - Uveitis patients only - Pilot study **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Small sample size; potential conflict from sponsor *Adverse events:* Fair - Comments: Small sample size; potential conflict from sponsor **Applicability:** All uveitis patients; only ophthalmic outcomes

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Were additional arthritis medications allowed: Yes, if stable MTX and prednisone and at the discretion of the clinician/investigator **Study Duration:** 1 year **Primary outcome:** Ophthalmic outcomes: - Reduction of anterior chamber cells to 0 or trace while using steroids < 3x/day - 50% reduction in number or dose of other anti-inflammatory medication **Secondary outcomes:** - 10-letter change in best corrected visual acuity - 2-step change in anterior chamber cell count, vitreous haze, or anterior chamber cells - Presence of cystoid macular edema	**Baseline severity:** NR **Percentage with uveitis:** 100% **Inclusion criteria:** - 2-18 years of age - ACR criteria for JRA - Active uveitis - No change in arthritis meds for at least 8 weeks prior **Exclusion criteria:** - Media opacities - Periocular injections of steroids within 2 months - DMARD therapy except MTX or prednisone - Spondylarthropathy/enthesitis	**11) Mortality:** None **12) Adverse events reported?:** Yes **13) Ophthalmic outcomes:** Successful outcome: 6 months DMARD: 6/12 12 months DMARD: 4/7 6 months placebo: 2/5 Failures: 6 months DMARD: 1/12 12 months DMARD: 1/7 6 months placebo: 1/5	
Van Rossum, Fiselier, Franssen, et al., 1998 **#798**	**Geographical location:** 7 pediatric rheumatology centers in The Netherlands **Study dates:** Aug 1992 – Dec 1994 **Funding source:** NR **Setting:** Pediatric rheumatology centers **Study design:** RCT **Intervention(s):**	**Number of patients:** N = 69 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 69 - Began treatment: 69 - Completed treatment: 52 - Withdrawals/losses to followup: 17 (1 excluded postrandomization, not eligible) **Age:** - Mean (SD): SSZ: 8.4 (4.4) Placebo 9.7 (3.6)	**1) Active joint count:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): SSZ: -5.54 (1.16) PL: -0.78 (1.22) P = 0.005 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments):	**General comments:** Pain scores not reported, but number of painful joints reported **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good **Applicability:** Non-USA

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- DMARD name: Sulfasalazine (SSZ) - Dose: 50 mg/kg/day in 2 doses; max 2000 mg/day - Titration: ¼ total dose, increased weekly by ¼'s until target dose reached. Dose could be modified to highest dose tolerated, but no less than 50% of initial prescribed dose. - N: 35 **Comparator(s):** Placebo, N = 34 **Were additional arthritis medications allowed?:** Yes - NSAIDS continued in type and dose - Corticosteroids (oral or intraarticular) and other DMARDS not permitted - Other therapy considered necessary for patient's welfare allowed at the discretion of the clinician/investigator **Study duration:** 24 weeks **Primary outcome(s):** Response, defined as ≥ 2 grade improvement in joint swelling severity score or score of 0 in ≥ 50% of joints involved at baseline and, if applicable, development of disease activity in ≤ 10% of the other joints, with the restriction that the number of deteriorated joints had to be ≤ 50% of the number of improved joints	- Range: SSZ: 2.5-17.6 Placebo: 2.5-15.1 **Sex:** - Female: SSZ: 23 (66%) Placebo: 23 (68%) - Male: SSZ: 12 (34%) Placebo: 11 (32%) **Race/ethnicity:** NR **JIA diagnosis:** JCA **Baseline severity:** Active joint count (median [range]): 5 (2-11) SSZ; 7 (3-12) PL **Percentage with uveitis:** NR **Inclusion criteria:** - Met EULAR criteria for oligoarticular- or polyarticular-onset JCA - Age between 2-18 years, with onset of JCA before age 16 - At least 1 joint with active arthritis (defined as the presence of swelling or limitation of motion, with either pain on movement or tenderness) - An insufficient response to NSAID therapy at an optimal dosage for at least 3 months and, if applicable, to intraarticular corticosteroid injections - Intraarticular corticosteroid	SSZ: -2.49 (1.12) PL: -1.97 (0.80) P = 0.64 **4) Global assessment of current status:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): By physician: SSZ: -1.95 (0.18) PL: -0.99 (0.19) P = 0.0002 By patient: SSZ: -0.92 (0.18) PL: -0.24 (0.18) P = 0.008 By parent: SSZ: -0.98 (0.14) PL: -0.44 (0.16) P = 0.010 **5) Laboratory measures of inflammation:** ESR (mm/hour): SSZ: -0.74 (0.07) PL: -0.04 (0.08) P < 0.0001 - Other: CRP given **6) Radiographic evidence of progression of disease:** Mean number of improved joints: SSZ: 0.71 (range, 0-3) PL: 0.53 (range 0-3) P = NS **7) Pain control:** NR	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Secondary outcome(s): - Overall articular severity score (sum of swelling, tenderness/pain and limitation of movement scores) - Patient's general impression of disease activity (1-5) - Parent's general impression of disease activity (1-5) - Physician's general impression of disease activity (0-5) - ESR, C-reactive protein - Radiological evaluation	injections were not permitted 8 weeks prior to the start of the study - There was a 4-week washout period for DMARDs **Exclusion criteria:** - Previous treatment with SSZ - Known hypersensitivity to sulfa preparations or salicylates - Known glucose-6-phosphate dehydrogenase deficiency or porphyria - Leukopenia < 3.0a10^9/L or granulopenia < 1.0x10^9/L or thrombocytopenia < 100x10^9/L - Liver transaminase levels more than twice the upper limit of normal - Renal impairment, defined as creatinine clearance < 90 mL/minute/1.73m^2 (determined as an elevated serum creatinine level more than 2 SD above the mean value for age) - Unwillingness or inability of parent/children to adhere to the protocol - Females who might become pregnant and if sexually active, not practicing effective birth control	**8) Clinical remission ("response"):** Can be estimated from graph at multiple time points. At 24 weeks: SSZ: 69% (9% SEM) PL: 45% (9% SEM) No significant difference for oligoarticular- and polyarticular-onset patients. Pavia criteria for improvement: SSZ: 44% (9% SEM) PL: 21% (8% SEM) **9) Flare of disease:** NR **10) Discontinuation of DNRMARD due to:** - Remission of disease: NR - Inefficacy: 3 (all PL) - Intolerance/AEs: 10 (all on SSZ) **11) Mortality:** NR **12) Adverse events reported?:** Yes **13) Medication compliance:** > 80% for 83% of subjects	
Woo, South-wood, Prieur, et al., 2000 **#693**	**Geographical location:** UK and France **Study dates:** NR **Funding source:** Supported by Arthritis Research Campaign grant WO-120; MTX and placebo	**Number of patients:** N = 88 - Screened for inclusion: NR - Eligible for inclusion: 88 - Randomized: 88 - Began treatment: 88 - Completed treatment: 79 - Withdrawals/losses to followup: 9 (7 from systemic group, 2 from	**1) Global assessment of current status:** When analyzed separately, no statistically significant differences between MTX and placebo; when combined, statistically significant improvement with MTX *Assessment by physician:* MTX (EOA/systemic):	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Cross-over with adequate washout; validated outcomes

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	tablets provided by Lederle Laboratories **Setting:** NR **Study design:** RCT, double-blind, cross-over design **Intervention(s):** - DMARD name: Methotrexate - Dose: 15 mg/m^2 PO weekly - Titration: increase to 20 mg/m^2 after 2 months if no improvements in global - N: Goal 44 per group; actual 43 and 45 **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes: Prednisolone, steroid injections, and NSAIDs NR whether these were added per protocol or at the discretion of clinician/investigator **Study duration:** 12 months (4 months treatment, 2 months washout, 4 months treatment, 2 months washout) **Primary outcome(s):** - > 30% improvement in 3 or more core variables and > 30% worsening in no more than 1 Core clinical variables: Physician	EOA = extended oligoarticular arthritis) **Age:** - Mean ± SD (range): EOA: Male: 7.4 ± 3.0 (5.0-11.7) Female: 8.53 ± 3.43 (3.3-15.5) Systemic: Male: 8.5 ± 3.3 (3.7-14.1) Female: 8.0 ± 4.25 (2.5-15.7) **Sex (male):** EOA: 5 (12%) Systemic: 22 (49%) **Race/ethnicity:** NR **JIA diagnosis:** JIA: extended oligoarticular and systemic **Baseline severity:** Active arthritis in past 3 months: EOA: 45 (100%) Systemic: 43 (96%) Duration of disease (months): EOA: 53.8 (4-132) Systemic: 33.7 (4-116) **Percentage with uveitis:** NR **Inclusion criteria:** - Under 16 years of age - Fulfilled the ILAR/WHO criteria for systemic or extended oligoarticular arthritis **Exclusion criteria:** NR	Very active: 28%/28%, -23/-15 Mildly active: 21/28%, +50/+43 Placebo (EOA/systemic) Very active: 24%/33%, -6/-14 Mildly active: 32/23%, +11/+10 P < 0.001 *Assessment by parent:* MTX (EOA/systemic): Very active: 29%/26%, -22/-15 Mildly active: 19/32%, +50/+35 Placebo (EOA/systemic): Very active: 29%/30%, -14/-19 Mildly active: 27/32%, +11/+4 P < 0.001 *Assessment by patient:* MTX (EOA/systemic): Very active: 28%/31%, -18/-24 Mildly active: 13/41%, +39/+28 Placebo (EOA/systemic) Very active: 26%/31%, -13/-17 Mildly active: 29/24%, +11/10 *Systemic core features (outcome = systemic score of 0):* MTX (start/end): 32%/61% Placebo (start/end): 27%/45% **2) Limited joint range:** Treatment effect (mean [SEM]): EOM: 4.47 (3.67) Systemic: 2.57 (6.68) **3) Limited joint score:** Treatment effect (mean [SEM]): EOA: -3.0 (1.8)	*Adverse events:* - Overall rating: Good **Applicability:** - Study outside US- may be more homogeneous population - Long duration of disease at baseline (average 3-4.4 years)

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	global, parent/child global, number of joints with active disease, range of joint motion For systemics, 8 core measures were: Rash; fever; cervical, axillary, ingunial lymphadenopathy; hepatomegaly; splenomegaly; pericarditis **Secondary outcome(s):** - Steroid dose - For systemics, presence of systemic features		Systemic: -3.3 (3.5) **4) Laboratory measures of inflammation:** ESR (baseline mean [SD], treatment effect mean [SEM]): EOA: 49 (28), -16.6 (3.6) Systemic: 57 (31), -12.4 (6.5) C-reactive protein (baseline mean, treatment effect mean [SEM]): EOA: 2.7, -45% (-27%) Systemic: 6.9, -29%(-51%) **5) Steroid dose (mg/day, baseline mean [SD], treatment effect mean [SEM]):** EOM: 1.2 (2.4), -0.012 (0.012) Systemic: 11.6 (6.5), -0.55 (0.92) **6) Overall clinical improvement (MTX/placebo)** EOA: 48/18 Systemic: 25/16 **7) Discontinuation of DMARD due to:** - Inefficacy: 6 systemic, 1 EOA - Intolerance/AEs: 1 systemic, 1 EOA **8) Mortality:** NR **9) Adverse events reported?:** Yes	
Yokota, Imagawa, Mori, et al., 2008 **#138**	**Geographical location:** Japan **Study dates:** NR **Funding source:** Chugai Pharmaceuticals supplied study medication and was responsible for data processing and management, statistical analysis, and reporting of serious adverse	**Number of patients:** N = 56 - Screened for inclusion: NR - Eligible for inclusion: NR - Began lead-in phase: 56 - Completed lead-in phase: 50 - Randomized: 44 - Began RCT phase: 43 (23 placebo; 20 tocilizumab) - Completed RCT: 41 - Began extension phase: 50 (44	**1) Active joint count, median (range):** - Lead-in phase: - Baseline: 4 (0-39) - 6 weeks: 0 (0-34) - Improvement: 73% - RCT, placebo (N = 23): - Baseline: 4 (0-21) - Last observation: 0 (0-34) - RCT, tocilizumab (N = 20): - Baseline: 3.5 (0-18)	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Potential for significant conflict of interest, given that the data were analyzed by the sponsor of the study, which has a financial interest in tocilizumab;

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	events **Setting:** 8 university hospitals and children's hospitals in Japan **Study design:** RCT, double-blind, multicenter, withdrawal design **Intervention(s):** - DMARD name: Tocilizumab - Dose: 8 mg/kg IV every 2 weeks - Titration: None - N: 20 **Comparator(s):** Placebo - N: 23 **Were additional arthritis medications allowed?:** Some: - Not allowed: Intraarticular corticosteroids, methylprednisolone, immunosuppressive drugs, TNF agents, and other DMARDs - Doses of oral corticosteroids had to be stable for 2 weeks before the trial **Study duration:** Open-label lead-in phase: 6 weeks RCT phase: 12 weeks Open-label extension phase: 48 weeks Patients had to achieve an ACR Pedi 30 response and CRP	randomized, plus 6 not randomized) - Withdrawals: - Lead-in phase: 6/56 (3 antibodies; 2 AEs; 1 lack of efficacy) - RCT placebo: 19 (1 AE; 18 early escape) - RCT tocilizumab: 4 (1 AE; 3 early escape) - Extension phase: 2 withdrawn because of AE - Loss to followup: 0 **Age:** - Mean (SD): 8.3 (4.4) - Range: 2-19 years **Sex:** - Female: 35 (62.5%) - Male: 21 (37.5%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Baseline severity:** Active joint count (median [range]): Start of lead-in phase: 4 (0-39) Start of RCT phase, placebo: 4 (0-21) Start of RCT phase, tocilizumab: 3.5 (0-18) Duration of disease, years (SD): Placebo: 4.7 (4.0) Tocilizumab: 4.6 (3.5) Past treatments (number [SD]):	- Last observation: 0 (0-4) - Extension phase: - 48 weeks: 0 (0-4) - Improvement: 88% **2) Quality of life/functional status:** CHAQ score, median (range): - Lead-in phase: - Baseline: 0.88 (0-3) - 6 weeks: 0.38 (0-3) - Improvement: 43% - RCT, placebo (N = 23): - Baseline: 0.63 (0-3) - Last observation: 0.38 (0-3) - RCT, tocilizumab (N = 20): - Baseline: 0.88 (0-2.38) - Last observation: 0.38 (0-1.63) - Extension phase: - 48 weeks: 0.13 (0-2.13) - Improvement: 67% **3) Number of joints with limited range of motion, median (range):** - Lead-in phase: - Baseline: 0.5 (0-47) - 6 weeks: 0 (0-45) - Improvement: 54% - RCT, placebo (N = 23): - Baseline: 0 (0-37) - Last observation: 0 (0-42) - RCT, tocilizumab (N = 20): - Baseline: 0.5 (0-47) - Last observation: 0 (0-46) - Extension phase: - 48 weeks: 0 (0-62) - Improvement: 72% **4) Global assessment of current status:** - Physician, visual analog scale, 0 mm (best) to 100 mm (worst), median (range):	screening and randomization procedures not described *Adverse events:* - Overall rating: Fair - Comments: Same issues as above **Applicability:** No significant issues

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	concentrations < 5 mg/L at end of lead-in phase to be eligible for RCT phase **Primary outcome(s):** Proportion of patients who maintained an ACR Pedi 30 response and CRP concentrations < 15 mg/L **Secondary outcome(s):** - ACR Pedi responses, systemic feature score, and CRP assessed every 2 weeks - Active disease defined by an increase in CRP and an inadequate response to corticosteroids for longer than 3 months - Safety monitored by physical exam daily during hospital stay	Placebo: 2.0 (1.0) Tocilizumab: 2.1 (1.0) **Percentage with uveitis:** NR **Inclusion criteria:** - 2-19 years of age - Onset of disease before 16th birthday - Met the ILAR classification criteria for systemic-onset JIA **Exclusion criteria:** - Important concurrent medical or surgical disorders - Leucopenia (< $3.5x10^9$/L) or thrombocytopenia (< $100x10^9$/L) - Cardiac disease (assessed by a pediatric cardiologist before enrollment) - Developed macrophage-activation syndrome during the prestudy hospital admission	- Lead-in phase: - Baseline: 52 (18-100) - 6 weeks: 8.5 (0-97) - Improvement: 75% - RCT, placebo (N = 23): - Baseline: 51 (18-95) - Last observation: 14 (0-84) - RCT, tocilizumab (N = 20): - Baseline: 51.0 (21-96) - Last observation: 5.5 (0-47) - Extension phase: - 48 weeks: 3.5 (0-22) - Improvement: 89% - Patient or parent's, visual analog scale, 0 mm (best) to 100 mm (worst), median (range): - Lead-in phase: - Baseline: 53 (0-90) - 6 weeks: 13.5 (0-69) - Improvement: 63% - RCT, placebo (N = 23): - Baseline: 55 (18-85) - Last observation: 39 (2-94) - RCT, tocilizumab (N = 20): - Baseline: 51.5 (0-76) - Last observation: 4.5 (0-34) - Extension phase: - 48 weeks: 8.5 (0-70) - Improvement: 75% **5) Laboratory measures of inflammation:** - ESR, mm/h (range): - Lead-in phase: - Baseline: 44.5 (8-125) - 6 weeks: 4.0 (0-64) - Improvement: 82% - RCT, placebo (N = 23): - Baseline: 35 (8-68) - Last observation: 11 (1-41)	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			- RCT, tocilizumab (N = 20): - Baseline: 39.5 (8-103) - Last observation: 4.0 (0-7) - Extension phase: - 48 weeks: 3.0 (0-12) - Improvement: 91% - CRP, mg/L (range): - Lead-in phase: - Baseline: 43.5 (16-190) - 6 weeks: 0.5 (0-99) - Improvement: 90% - RCT, placebo (N = 23): - Baseline: 38 (17-131) - Last observation: 15 (0-101) - RCT, tocilizumab (N = 20): - Baseline: 35 (16-190) - Last observation: 0.1 (0-22) - Extension phase: - 48 weeks: 0.1 (0-2) - Improvement: 99% **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: Lead-in phase: 2/56 (4%); RCT placebo: 1/23 (5%); RCT tocilizumab: 1/20 (5%) Early escape (switched to another medication due to poor response):	

Evidence Table 1. Studies relevant to key questions 1–4 (continued)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			- Placebo: 18/23 (78%) - Tocilizumab: 3/20 (15%) "Median time to early escape was 4.9 weeks in the placebo group, but longer than 12 weeks in the tocilizumab group" (significance test NR) **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** ACR Pedi Responses: - Lead-in phase, N (%): - ACR Pedi 30: 51 (91%) - ACR Pedi 50: 38 (86%) - ACR Pedi 70: 38 (68%) - Both ACR Pedi 30 response and CRP < 5 mg/L: 44 (79%)	

Evidence Table 2. Studies relevant to key question 5

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Bazso, Consolaro, Ruperto, et al., 2009 **#1524**	**Geographical location:** Genoa, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT (1 sample, MTX) Cross-sectional (2 samples, Clinic and PRINTO) **Study objective(s):** "… to devise and test several reduced joint counts …" **Duration of followup:** MTX sample = 6 months	**Number of patients:** Clinic: 434 PRINTO: 3324 MTX: 595 Data given below are for these 3 samples **Age:** - Mean (SD): NR - Median (IQ range): 7.2 (3.9 to 11.2); 10.6 (7.2 to 14), 7.8 (4.2 to 11.3) **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis, median (IQ range): 2 (0.8, 5.4); 3.8 (1.6, 6.7); 2.2 (0.4, 3.4) Active joint count: 2 (0, 4); 2 (0,5), 9 (6;16) CHAQ: 0.1 (0, 0.3); 0.4 (0, 1.1); 1.2 (0.6, 1.7) **Inclusion criteria:** - Clinic: NR - PRINTO (need ref 13) - MTX (need ref 14)	**Instrument(s) evaluated:** Childhood Health Assessment Questionnaire (CHAQ), likely an Italian version **Mode of administration:** NR	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Spearman correlations for CHAQ compared to counts of joints with restricted movement (67 joints) Clinic sample (n = 232): 0.40 PRINTO sample (n = 2739): 0.47 MTX sample (488): 0.27 for 6-month change scores Results were virtually identical for reduced joint counts. - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** - The PRINTO (ref 13) and MTX (ref 14) have been reported previously - This report focused on reduced joint counts (10, 27, 35, and 45) vs. full count of 71 but for our purposes the data of interest were for the CHAQ - Report also contains correlations between physician global assessments, parent global assessments, and joint counts (Table 4) - Report also includes effects of substituting reduced joint counts in the ACR Peds score and how it affects response ratings – but not of primary interest (Table 7) **Quality assessment:** - Spectrum: 3 samples ranging from mild to moderate/severe disease - Blinding to criterion: Can't tell - Blinding to instrument: Can't tell - Validated criterion: Partial, joint counts are a relevant but incomplete clinical outcome - FU > 80%: Can't tell - 95% CI not appropriate for baseline measures (should give SD or range)

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Exclusion criteria: - Clinic: NR - PRINTO (need ref 13) - MTX (need ref 14)			
Bekkering, ten Cate, van Rossum, et al., 2007 **#1552**	**Geographical location:** Leiden, The Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** "…to compare the measurement properties of the JFAS and the CHAQ.." **Duration of followup:** NA	**Number of patients:** 28 **Age:** - Mean (SD): NR - Median: 10 - Range: 7-13 **Sex:** - Female: 16 - Male: 12 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 3/28 **Baseline severity:** Median (range): Time since diagnosis: 3.3 years (0.1-10.2) Active joint count: JC swollen 1.0 (0-28); JC tender 0.8 (0-8); JC limited ROM 1.0 (0-17) Other: JAFAS 0 (0-13); CHAQ 0.125 (0-2.6) NR **Inclusion criteria:** - Age 7-12 years - JIA and no other medical conditions interfering with	**Instrument(s) evaluated:** JAFAS, range 0-20 CHAQ, 30 items, total score ranges from 0-3 CHAQ-9: 9 items selected to correspond to the JAFAS **Mode of administration:** Interviewer-administered	**1) Reliability:** (n = 28) - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: JAFAS 0.91; CHAQ 0.96; CHAQ-9 0.92 **2) Validity:** (n = 28) Spearman correlation coefficients; *p < 0.05, **p < 0.01 - Versus clinical outcomes: Pediatrician-rated disease activity (VAS): JAFAS 0.41*, CHAQ 0.56**, CHAQ-9 0.34 JC swollen: JAFAS 0.47*, CHAQ 0.65 **, CHAQ-9 0.48* JC tender: JAFAS 0.07, CHAQ 0.41*, CHAQ-9 0.09 JC limited ROM: JAFAS 0.44*, CHAQ 0.64**, CHAQ-9 0.59** - Versus lab results: ESR: JAFAS 0.37; CHAQ 0.62*, CHAQ-9 0.75** - Versus radiological results: NR - New instrument versus established instrument: JAFAS score correlation with CHAQ score, Spearman's r = 0.55; JAFAS correlation with CHAQ-9, Spearman's r = 0.56 **3) Other:** - Feasibility: NR	**General comments:** - Sample had very little functional disability - Joint counts could range from 0-30 **Quality assessment:** - Blind criterion: Can't tell - Blinded instrument: Can't tell - Validated criterion: Partial (joint counts yes, ESR no) - F/U ≥ 80%: NA - Analyses appropriate: Yes

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		functional ability **Exclusion criteria:** NR		- Responsiveness: NR - ROC curves: NR	
Bekkering, ten Cate, van Suijle-kom-Smit, et al, 2001 **#1784**	**Geographical location:** Leiden, Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** To investigate the relationship between joint impairments and disabilities in children with systemic JIA. The relationship was studied at the level of (1) complete instruments, (2) upper and lower limb function separately, (3) the individual joints and items. **Duration of followup:** NA	**Number of patients:** 21 **Age:** - Mean (SD):9.3 (4.1) - Median: NR - Range: 3.6-16.4 **Sex:** - Female:10 - Male: 11 **Race/ethnicity:** NR **JIA diagnosis:** JIA-systemic **Percentage with systemic JIA:** 100% **Baseline severity:** Time since diagnosis: 4.8 (3.6), range 0.8-12.6 Other (n, mean ± SD, range): CHAQ: 18, 1.7 ± 0.7 (0.4-2.9) Pain-VAS: 17, 1.0 ± 0.8 (0-2.8) JAFAS: 15, 5.1 ± 4.6 (0-16) **Inclusion criteria:** - Systemic JIA - Children treated with steroids for more than a year	**Instrument(s) evaluated:** *Joint impairment :* JCS (joint count on swollen joints) JCT (joint count on tender joints) JAM (Joint Alignment and Motion Scale) *Functional performance and ability:* JAFAS (Dutch) and CHAQ (Dutch) **Mode of administration:** Self-administered: CHAQ-c Interviewer-administered: JAFAS, JCT, JCS, JAM	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Spearman correlation JAM, CHAQ: 0.66, $p < 0.01$ JAM, JAFAS: 0.77, $p < 0.01$ JCS, CHAQ: 0.45, $p < 0.05$ JCS, JAFAS: 0.52, $p < 0.05$ JCT, CHAQ: 0.028 JCT, JAFAS: 0.14 Other results reported include: Correlations between joint impairment and extremity-specific parts of CHAQ (CHAQ-arm, CHAQ-leg) and JAFAS (JAFAS-arm, JAFAS-leg) Correlation between a compounded measure for the range of motion of shoulder, elbow, and wrist and specific items of CHAQ, JAFAS **3) Other:** - Feasibility: NR - Responsiveness: NR	**General comments:** - Small sample size - All patients with systemic disease **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- Children included in the study constituted a subset from an early study on effect of corticosteroids on BMD and growth **Exclusion criteria:** NR		- ROC curves: NR	
Brown, Wright, Lang, et al., 2005 **#337**	**Geographical location:** Ottawa, Toronto, Halifax and Winnipeg, Canada **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** "…to compare the ability of these 3 self-report functional questionnaires to measure clinically important change…" and "…to determine the extent of agreement between parent report and child report on each of the 3 questionnaires" **Duration of followup:** 6 weeks and 6 months	**Number of patients:** 74 with intra-articular steroid treatment (IAS); 18 with methotrexate, hip-tendon release or total hip replacement (MTX/Hip) **Age:** Mean (SD): 12.8 (3.0) IAS; 12.9 (3.1) MTX/Hip **Sex:** - Female: 68 - Male: 24 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 12 (13%) **Baseline severity:** Time since diagnosis: 27 ≤ 1 yr; 17 1-3 yrs; 11 4-5 yrs; 23 6-10 yrs; 14 ≥ 11 yrs Active joint count: Mean tender joints 6.7 (IAS), 18.0 (MTX/Hip) Mean swollen joints: 4.3	**Instrument(s) evaluated:** Juvenile Arthritis Functional Assessment Report (JAFAR) Childhood Health assessment Questionnaire (CHAQ) Juvenile Arthritis Functional Status Index (JASI) **Mode of administration:** "Questionnaire" - Other: joint count assessed by pediatric rheumatologist; grip strength, functional ROM and timed walk test measured by physiotherapies or occupational therapist; demographics by research assistant. JAFAR, CHAQ, JASI – uncertain	**1) Reliability:** - Test-retest: NR - Inter-rater: Mean difference for child vs. parent at baseline, 6 weeks, 6 months: JAFAR: 0.93 (p = 0.45), 0.99 (p = 0.38), 0.87 (p = 0.20) CHAQ: -0.1 (p = 0.016), -0.065 (p = 0.08), -0.089 (p = 0.027) JASI: 0.83 (p < 0.0001), 0.72 (p < 0.0001), 0.77 (p = 0.0005) - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: Standardized response mean (95% CI) at 6 weeks and 6 months - Child as respondent: JAFAR: 0.34 (0.13, 0.54), 0.41(0.19, 0.63) JASI: 0.40 (0.19, 0.61); 0.24 (0.03, 0.45)	**General comments:** - Calculated a sample size - Few patients on DMARDs **Quality assessment:** - Spectrum: Limited; consecutive patients - Blind criterion: NA, no analyses compared instruments to a criterion - Blinded instrument: Completed blind to global assessments - Validated criterion: NA, no criterion standard - FU > 80%: Yes 84/92 - Appropriate analysis: Partial; didn't compare change scores to global status - Subgroup analyses based on very small numbers for MTX/Hip group

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		(IAS), 7.5 (MTX/Hip) **Inclusion criteria:** - Age 8 to 20 - JIA - Active inflammation of ≥ 1 joint - IAS injection, MTX treatment or orthopedic hip surgery planned - Fluent in English - Agree to 3 assessment visits **Exclusion criteria:** Comorbid medical condition that might independently affect physical function		CHAQ: 0.39 (0.18, 0.60); 0.48 (0.27, 0.69) Differences not statistically significant; results similar when parent respondent , CHAQ appear higher, but not statistically significant when parent is respondent Relative efficiency (RE; ratio of paired t-test for JAFAR or JASI compared to CHAQ in the denominator): JAFAR (IAS subgroup apt 6 weeks) parent; child respondents: 0.55; 0.34 JAFAR (MTX/Hip subgroup at 6 months) parent; child respondents: 1.45; 15.11 JASI (IAS subgroup at 6 weeks) parent; child respondents: 0.53; 0.27 JASI (MTX/Hip subgroup at 6 months) parent; child respondents: 0.73; 3.94 - ROC curves: NR	
Brunner, Johnson, Barron, et al., 2005 **#1591**	**Geographical location:** Cincinnati, OH **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** ".. to perform an initial validation of the	**Number of patients:** 77 parents 52 children aged 8 or older **Age:** - Mean (SD): NR - Median: 10.3 - Range: 2-18 **Sex:**	**Instrument(s) evaluated:** GISSK, CHAQ **Comparators:** Pain during prior week; (VAS-pain), 0-100, higher scores worse PedsQL Generic Core Sacle version 4 (PedsQL-GC), 0-100, higher scores	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity: (Spearman correlation coefficients, p value for association between CHAQ and outcome)** - Versus clinical outcomes:	**General comments:** Data on GISSK not abstracted, as not a priority instrument **Quality assessment:** - Appears to be skewed to somewhat more severe spectrum (second-line agents) but appropriate to our study question - Parents and children

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	Gastrointestinal Symptom Scale for Kids (GISSK) in children with juvenile rheumatoid arthritis…" **Duration of followup:** NA	- Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: Median 1 (range 0-46) Other: CHAQ (parent) mean 0.12 (0.66); (child) mean 0.24 (0.46) 42 (55%) were taking etanercept or infliximab, and 65 (94%) were taking methotrexate **Inclusion criteria:** Children with JRA requiring second-line agents **Exclusion criteria:** NR	better functional status PedsQL Rehueumatology Module (PedsQL-RM), 0-100, higher scores better functional status Parent global rating of health during prior week, (VAS-health), 0-100, higher scores better Physician global rating of disease activity, (VAS-DA), 0-100, higher scores worse Active joint count (AJC) Joints with limited range of motion (LROM) **Mode of administration:** Self-administered by parents (n = 77) or child (n = 52)	AJC: 0.39, p = 0.0010 LROM: 0.33, p = 0.0062 VAS-pain: 0.57, p < 0.0001 VAS-DA: 0.20, p < 0.0859 VAS-health: -0.59, p < 0.0001 PedsQL-GC: -0.62, p < 0.0001 PedsQL-RM: -0.63, p < 0.0001 - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	completed questionnaires independently but unclear if CHAQ results available to examining clinician who completed VAS-DA - FU >80%: NA - Small sample size; no sample size calculations
Brunner, Klein-Gitelman, Miller, et al., 2004 **#1779**	**Geographical location:** Cincinnati, Ohio **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT	**Number of patients:** 119 families **Age:** - Mean (SD): 10.5 (4.3) - Range: 3-18 **Sex:**	**Instrument(s) evaluated:** Physician-rated disease severity (DS), VAS 100 mm Childhood Health Assessment Questionnaire (CHAQ),	N varied: n = 119 for parent ratings on Health, Global, CHAQ, VAS pain; n = 87 for child ratings JAQQ n = 58; PedsQL-RM n = 94, PedsQL-GC n = 60 parents, n = 46 children **1) Reliability:**	**General comments:** None **Quality assessment:** - Sample semi-consecutive - Parents and patients completed instruments independently; instrument order varied

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	Study objective(s): To examine the strength of association between HRQOL and disability, pain, or well-being and whether HRQOL changes importantly as a function of the disability status **Duration of followup:** Mean 3.5 months (0.6)	- Female: 91 - Male: 28 **Race/ethnicity:** NR **JIA diagnosis:** JRA n = 102 Spondyloarthropathy n = 2 Psoriatic arthritis n = 8 Other (describe): Juvenile dermatomyositis (1), Castleman syndrome (1), arthritis with inflammatory bowel disease (1), sacroidosis (1), SLE (2), mixed connective tissue disease (1) **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: mean 3.5 years (range, 0.3 to 14.2) Active joint count: NR **Inclusion criteria:** - Children between 1-18 year of age - Symptoms of chronic arthritis irrespective of a specific underlying diagnosis - Arthritis present for at least 3 months continuously **Exclusion criteria:**	includes VAS pain, 100 mm Parent and patient global rating of health (Health) and well being (Global WB), VAS 100 mm Juvenile Arthritis Quality of Life Questionnaire (JAQQ) Pediatric Quality of Life Questionnaire Inventory version 4.0 (PedsQL-c, child rating) PedsQL-rheumatology module (PedsQL-RM) Standard Gamble (SG) **Mode of administration:** Self-administered P-parent; C-child)	- Test-retest: NR - Inter-rater: Parent vs. Child (intraclass correlation coefficient) Health: 0.53 JAQQ: 0.69 PedsQL-GC: 0.48 PedsQL-RM: 0.57 CHAQ: 0.51 Global WB: 0.47 VAS Pain: 0.26 - Intra-rater: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Spearman correlation coefficients for CHAQ vs: VAS Pain: 0.28 (P), 0.31 (C) Global WB: -0.45 (P), -0.23 (C) Health: -0.52(P), -0.64 (P) JAQQ: -0.65 (P), -0.64 (C) PedsQL-GC: -0.22 (P), -0.32 (C) PedsQL-RM: -0.42 (P), -0.47 (C) Statistically significant for all Spearman correlation coefficients for JAQQ vs: VAS Pain: -0.54 (P), -0.45 (C) Global WB: 0.59 (P), 0.36 (C) Health: 0.57(P), 0.66 (P) PedsQL-GC: 0.73 (P), 0.78 (C) PedsQL-RM: 0.79 (P), 0.76(C) Statistically significant for all	- Analysis appropriate

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- Diagnosis of fibromyalgia, nonspecified myalgias, or arthralgias - Symptoms were < 3 months in duration		except PedsQL-GC parent Spearman correlation coefficients for PedsQL-GC vs: VAS Pain: 0.12 (P), -0.36 (C) Global WB: 0.64 (P), 0.44 (C) Health: 0.53(P), 0.66 (P) PedsQL-RM: 0.81 (P), 0.80 (C) Statistically significant for all except VAS pain, Global WB parent Spearman correlation coefficients for PedsQL-RM vs: VAS Pain: -0.27 (P), -0.60 (C) Global WB: 0.66 (P), 0.45 (C) Health: 0.62 (P), 0.60 (P) Statistically significant for all When disability was classified by the CHAQ as none (0), mild (0-0.25), mild to moderate (0.25-1.25), or moderate (1.26-2.0), mean HRQOL scores differed significantly on the PedsQL-RM, JAQQ, Health, Global WB, VAS Pain, but not for the PedsQL-GC or number of involved joints **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Brunner, Klein-Gitelman, Miller, et al., 2005 **#1606**	**Geographical location:** Cincinnati, HO **Setting:** NR **Study design:** Longitudinal non-RCT	**Number of patients:** 92 (67 age ≥ 8) **Age:** - Mean (SD): 8.7 years - Median: NR - Range: 1-18	**Instrument(s) evaluated:** CHAQ compared to the 6 core response variables (using the Juvenile Arthritis Quality of Life Questionnaire to measure functional status)	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR	**General comments:** None **Quality assessment:** - Parents and patients completed questionnaires independently; order of questionnaires randomized

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	Study objective(s): "…to estimate the minimum clinically important difference of the CHAQ for children who were experiencing changes in their health and well being…" **Duration of followup:** Mean 3.5 (2.3) months	**Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: NR Other: 33 (36%) "no disability CHAQ parent (n = 92): Median 0.25 (IQR 0-0.91), mean 0.53 (0.61) CHAQ child (n = 67): Median 0.25 (0-0.66), mean 0.46 (0.56) **Inclusion criteria:** - Convenience sample of children age 1-18 with JRA - Symptoms of chronic arthritis for ≥ 2 months **Exclusion criteria:** NR	Minimum clinically important difference (MCID) analyses constrained to those with small improvement or decline (10-30 mm change on 100 mm VAS, or 1-2 points on 0-10 Likert scale, or "better" or "worse" on a 5-point Likert scale). Depending on definition used, these analyses used 25-44% of the overall sample. **Mode of administration:** Self-administered: Parents and children >7 years old Interviewer-administered: Children < 8 years old	**2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: CHAQ median (IQR) change for worsening in well-being for the 3 definitions ranged from 0 (0.375) to 0.25 (0.75)-child ratings; 0 (0.25) to 0.125 (0.75)-parent ratings; and worsening in disease activity as rated by physician -0.125 (0.375) CHAQ median (IQR) change for improvement in well-being for the 3 definitions ranged from -0.188 (0.5) to 0.0 (0.875)-child ratings; 0 (0.125) to 0 (1.0)-parent ratings; and worsening in disease activity as rated by physician 0 (0.375) to 0 (0.125) - ROC curves: NR Authors' conclusion: The MCID of the CHAQ for both improvement and worsening are often at or close to the level of the smallest potential difference, suggesting that the CHAQ is relatively insensitive to important short term changes in children with JRA	- Unclear if raters (e.g., AJC) blinded to CHAQ results - FU rate > 80%: Inclear, this was a convenience sample and not study flow given - Analyses: Small sample; no power calculation but otherwise appropriate - Conclusion is appropriate

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Brunner, Lovell, Finck, et al., 2002 **#598** **AND** **Lovell, Giannini, Reiff, et al., 2000** **#721**	**Geographical location:** Cinncinati, OH **Setting:** Specialty clinic (confirm in ref 3) **Study design:** Randomized discontinuation trial among etanercept responders; 90 days post initiation of open-label etanercept **Study objective(s):** "…to develop preliminary criteria for defining disease flare in patients with polyarticular-course JRA by using the core response variables for JRA…" **Duration of followup:** Median to disease flare 30 days (range 6-126)	**Number of patients:** Placebo 26; etanercept 25 **Age:** - Mean (SD): 10.6 (SD NR) - Median: NR - Range: 4-17 **Sex:** - Female: 34 (67%) - Male: 17 (33%) **Race/ethnicity:** White: 37 (73%) Black: 4 (8%) Hispanic: 8 (16%) Other: 2 (4%) **JIA diagnosis:** JRA **Percentage with systemic JIA:** 17 (33%) **Baseline severity:** Time since diagnosis: 5.8 years (SD NR) CHAQ: Mean 0.825 (SD NR), median 1.0 Active joint count (AJC): Mean 11 (SD NR), median 9 (range 0-29) Limited ROM joints (LROM): Mean 18, median 15 (range 0-53) **Inclusion criteria:**	**Instrument(s) evaluated:** Definitions of flare using 6 core response variables: AJC, LROM, Physician global-disease severity (0-10), Patient or Parent global overall well-being (0-10), ESR, functional status (CHAQ, 0-3) Flare definitions tested: Varied from 20% to 50% change on 2 to 4 of the core response variables. Some definitions allowed for up to 30% improvement on 1 of the remaining CRV. All 26 patients in placebo arm were assumed to flare; therefore sensitivity of flare definition = # relapsed by candidate definition/total in placebo group All 25 in etanercept arm were presumed not to flare; therefore specificity of flare definition = # without relapse by candidate definition/total in etanercept group **Mode of administration:** Self-administered Interviewer-administered Other [specify]	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Worsening in ≥ 2 CRV by ≥ 40%, allows 1 CRV to improve: Sensitivity: 85% (95% CI 71 to 99) Specificity: 80% (64 to 94) ROC AUC: 0.677 (0.57 to 0.78) Other definitions had statistically significantly lower ROC AUC - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: See above	**General comments:** Variables well defined **Quality assessment:** - Appears to be skewed to somewhat more severe spectrum (failed NSAID and/or MTX) - Assessors were blind to treatment assignment (the de facto criterion) - FU >80%: Yes - Small sample size; no sample size calculations; problems with multiple testing - Criterion standard (assumptions about flare based on treatment) is suspect

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- Active polyarticular JRA despite treatment with NSAID or MTX - Age 4-17 - Normal or near normal platelet, WBC, ALT/AST, creatinine - Contraception if girl of child-bearing age **Exclusion criteria:** Major concurrent medical conditions			
Cespedes-Cruz, Gutierrez-Suarez, Pistorio, et al., 2008 **#142**	**Geographical location:** 11 sites in Western Europe, USA and Australia **Setting:** Specialty clinic **Study design:** RCT **Study objective(s):** "..to compare the effect of MTX therapy on the HRQOL of patients with JIA…" **Duration of followup:** 6 months	**Number of patients:** 521 JIA 3315 healthy controls **Age:** - Mean (SD): 8.2 (4.6) JIA; 11.2 (3.8) healthy controls - Median: NR - Range: NR **Sex:** - Female: 375 (72%); 1730 (52.2%) healthy controls - Male: 146 (28%); 1585 (47.8%) healthy controls **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 75 (14%) **Baseline severity:** Time since diagnosis: Mean 2.8 (3.4)	**Instrument(s) evaluated:** Child Health Questionnaire (CHQ): 15 domains and physical (PhS) and psychosocial (PsS) summary scores Childhood Health Assessment Questionnaire (CHAQ) in multiple languages **Mode of administration:** Self-administered: CHAQ Completed by parent: CHQ	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: CHQ distinguished between healthy controls and subjects with JIA on all 15 domains (Fig 2) - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Baseline CHAQ values > 1.33 were associated with poor HRQOL at 6 months as measured by the CHQ physical (OR for PhS < 30 = 5.2, 95% CI 3 to 8.9) and psychosocial (OR for PsS < 30 = 3.9, 1.5 to 10) summary scores **3) Other:**	**General comments:** Limited useful information; measure validation was not the primary purpose of the study **Quality assessment:** - Large sample, participating in RCT of MTX - Comparisons to healthy controls bias towards greater sensitivity/specificity - Analysis: No sample size calculation but large sample for most analyses - No responsiveness indices calculated

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Active joint count: Mean 12.0 (9.1) Other: CHAQ: 1.2 (0.8) Parent global assessment of well-being (0-10 VAS): Mean 4.4 (2.6) **Inclusion criteria:** -PRINTO database-participants in RCT of MTX - Completed ≥ 6 months treatment - Polyarticular JIA - HRQOL assessment at baseline and 6 month followup **Exclusion criteria:** NR		- Feasibility: NR - Responsiveness: CHQ scores improved in all 15 subscales from baseline to 6 months (Fig 2, responsiveness statistics not reported); PhS scores changed more than PsS scores - ROC curves: NR	
Cosolaro, Vitale, Pistaro, et al., 2007 **#1556**	**Geographical location:** Genova, Italy **Setting:** Specialty clinic and hospitalized patients **Study design:** Cross-sectional **Study objective(s):** To investigate "the discrepancy between the physicians' and parents' ratings of inactive disease in children with JIA and attempt to identify factors explaining it"	**Number of patients:** 636 patients; 537 with complete data; 265 with rating of inactive disease by physician and/or parent constituted the analytic sample **Age:** - Mean (SD): NR - Median: NR - Range: NR **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR	**Instrument(s) evaluated:** Physician global assessment of overall disease activity (10 cm VAS, 0 = no activity, 10 = maximum activity) Parent global assessment of overall well being (10 cm VAS, 0 = very good, 10 = very poor) **Mode of administration:** Self-administered: Parent Physician global is presumably based on history, physical examination and	**1) Reliability:** - Test-retest: NR - Inter-rater: Score of 0 by parent and physician (40%); among discordant ratings, physicians rated > 0 (35.5%) when parent rated 0, physicians rated 0 (24.5%) when parents rated > 0 - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR	**General comments:** The relevance of parent ratings of overall well-being vs. physician rating of disease activity is uncertain **Quality assessment:** - Sample: Not well described, eligibility criteria not well described - Blinding: Unclear if physician global rating completed blind to parent rating - FU rate > 80%: NA - Analysis: No chance corrected agreement

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
			laboratory data (ESR, CRP, joint counts, CHAQ completed)	- New instrument versus established instrument: NR	
	Duration of followup: NA	**JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: NR Other: NR **Inclusion criteria:** - Patients included in the clinical database from January 1992 through December 2006 - JIA by ILAR criteria **Exclusion criteria:** NR		**3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Dempster, Porepa, Young, et al., 2001 **#1782**	**Geographical location:** Toronto, Canada **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** To determine cutoff levels on the CHAQ for different disability levels; to determine the minimum clinically important change and whether these change scores were similar for parent-reported and child-reported assessments **Duration of followup:**	**Number of patients:** 131 **Age:** - Mean (SD): 9.6 (NR) - Range: 1-18 **Sex:** - Female: 90 (69%) - Male: 41 (31%) **Race/ethnicity:** NR **JIA diagnosis:** JRA, n = 101 Spondyloarthropathy, n =10 Psoriatic arthritis, n = 14 Other: Reactive or unclassified arthritis, n = 5 **Percentage with**	**Instrument(s) evaluated:** CHAQ **Comparators:** Quality of My Life Questionnaire (QOMLQ), VAS 100 mm measuring overall quality of life and health-related QOL Categorical disability Scale (CDS): 6 response categories ranging from no disability (“can do everything other kids can do with no problems”) to severe disability (“everything is hard for me”) Categorical change scale	**1) Reliability:** - Test-retest: NR - Inter-rater: Parent vs. child (n = 56) CHAQ intraclass correlation coefficient = 0.83; CDS weighted kappa = 0.58 - Intra-rater: NR - Internal reliability: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Median (IQR) CHAQ scores by parent described CDS: None: 0 (0)	**General comments:** None **Quality assessment:** - Consecutive patients, not all had JIA, moderate to no disability so full spectrum of disease not included - Instruments completed independently - Validity of hypothetical scenario for minimal change uncertain - Categorical change score done cross-sectionally based on current status compared to remembered status

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	NA	**systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: 4 (NR) Other: Median Steinbrocker score 1 (range 1-4) **Inclusion criteria:** - Inflammatory arthritis - Consecutive attendees to participating rheumatology clinics **Exclusion criteria:** NR	(CCS): Rates "ability to do things" on 5-point scale ranging from "a lot worse" to "a lot better" Hypothetical situation where new medication reduces disability by "just enough to make a difference" – adjusted activities on the original CHAQ to show how scores would change; same approach but for increased disability and made adjustments on QOMLQ Active joint count Steinbrocker functional assessment scale **Mode of administration:** Self-administered by parents and independently by children age ≥ 10	Mild: 0.13 (0.41) Mild to moderate: 0.63 (0.88) Moderate: 1.75 (0.59) No patients classified as moderate-to-severe or severe Differences statistically significant, F = 45.5, 3 df, p < 0.0001 Median values for children's ratings were not statistically significantly different from parent ratings **3) Other:** - Feasibility: NR - Responsiveness: Using hypothetical situation, median CHAQ minimal change for improvement = -0.13 and for worsening = 0.75. However, threshold varied by disability class, with higher disability patients requiring larger changes for improvement and smaller changes for deterioration. Using CCS scores, median values (IQR, range): Improvement (n = NR): 0 (0.27, -1.38-1.25) Worsening (n = NR): 0.13 (0.31, -0.50-2.38) - ROC curves: NR	
Filocamo, Davi, Pistorio, et al., 2010	**Geographical location:** **Genoa, Italy** **Setting:** Pediatric Rheumatology	**Number of patients:** First sample: 397 patients seen between Sep 2002 and Feb 2007 who had Physician Global, Parent	**Instrument(s) evaluated:** 21-numbered circle VAS vs. 10-cm horizontal line VAS	**1) Reliability:** NR **2) Validity:** - Versus clinical outcomes:	**General comments:** None **Quality assessment:** Used different quality of life and functional measures between

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
#6554	clinic **Study design:** Cross-sectional. Investigators studied two patient samples in whom physician global rating of overall disease activity, parent global rating of the child's overall well-being, and parent rating of intensity of child's pain were performed using traditional 10-cm horizontal line VAS (n = 397) or 21-numbered circle VAS (n = 471). The measurement performances of the 2 VAS formats were examined by assessing construct validity, score distribution, responsiveness to change over time, and minimal clinically important difference. **Study objective(s):** To evaluate the measurement properties of 21-numbered circle VAS and traditional 10-cm horizontal line VAS for physician and parent subjective ratings in children with JIA **Duration of followup:** 3-9 months for second	Global, and Parent Pain rated on a traditional 10-cm horizontal line VAS. Second sample: 471 patients seen from Mar 2007 to Dec 2008, who had the same ratings performed on 21-numbered circle VAS **Age:** NR **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** *21-Numbered Circle VAS (n = 471)* Values for various measures (N; mean [SD]; median): Physician Global, cm (n = 437): 2.5 (3.1); 0.5 Parent Global, cm (n = 453): 2.4 (2.7); 1.0 Parent Pain, cm (n = 454): 2.2 (2.8); 0.5 JAFS score (n = 460): 2.3 (4.1); 0 CHAQ score: NR Swollen joint count (n = 444): 1.7 (3.7); 1 Tender joint count (n =	**Mode of administration:** Self-administered Parent rating and Physician rating	10-cm VAS: MD Global Spearman correl: Parent global: 0.54 Parent pain: 0.61 CHAQ: 0.39 Active joint count: 0.77 CHQ phys: -0.53 CHQ psych: -0.13 Parent global correlations: MD global: 0.54 Parent pain: 0.82 CHAQ: 0.53 Active joint count: 0.49 CHQ phys: -0.7 CHQ psych: -0.29 - Versus lab results: ESR correlation with: MD global Parent global **3) Other:** - Feasibility: Report easier scoring, though no data reported - Responsiveness: Reported for 21 point scale only: SRM MD Global Improved: 1.21 (0.98; 1.42) Stable: 0.19 (0.00; 0.40) Worsened: 1.08 (0.78; 1.35) Parent global Improved: 0.83 (0.60; 1.05) Stable: 0.00 (0.00; 0.24) Worsened: 0.66 (0.34; 0.97) Parent pain:	the two populations examined (one getting the 21-numbered VAS and the other the 10-cm line) in addition to differences in baseline disease activity, making comparisons difficult

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	sample; no followup for first	444): 2.3 (5.0); 0 Restricted joint count (n =444): 2.0 (4.9); 0 Active joint count (n = 466): 2.2 (5.0); 1 PRQL-PhH score (n = 452): 2.5 (2.8); 1.5 PRQL-PsH score (n = 451): 1.7 (2.0); 1 CHQ-PhS: NR CHQ-PsS: NR ESR, mm/h (n = 327): 20.6 (16.7); 15 CRP, mg/dL (n = 334): 1.1 (2.2); 0.46 *10-cm Horizontal Line* VAS (n = 397) Values for various measures (N; mean [SD]; median): Physician Global, cm (n = 389): 2.9 (3.3); 1.5 Parent Global, cm (n = 382): 2.0 (2.5); 0.7 Parent Pain, cm (n = 380): 1.9 (2.5); 0.9 JAFS score: NR CHAQ score (n = 391): 0.3 (0.5); 0.0 Swollen joint count (n = 397): 2.6 (5.0); 1 Tender joint count (n = 397): 3.1 (6.3); 1 Restricted joint count (n = 397): 3.6 (8.3) 1 Active joint count (n = 397): 3.6 (6.5); 1 PRQL-PhH score: NR PRQL-PsH score: NR		Improved: 0.81 (0.53; 1.07) Stable: 0.14 (0.00; 0.35) Worsened: 0.75 (0.43; 1.05) - ROC curves: NR	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		CHQ-PhS (n = 212): 46.4 (11.5); 50. CHQ-PsS (n = 212): 48.5 (8.1); 49.4 ESR, mm/h (n = 348): 20.6 (18.3); 14.5 CRP, mg/dL (n = 346): 1.2 (2.9); 0.5 **Inclusion criteria:** Patients seen at study units and fulfilling the International League of Associations for Rheumatology (ILAR) criteria for JIA7 **Exclusion criteria:** NR			
Filocamo, Sztajnbok, Cespedes-Cruz, et al., 2007 **#1555**	**Geographical location:** 1 or 2 sites in Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** "to develop and validate a new short and simple measure of physical function in children with JIA" **Duration of followup:** Mean 6 (3) months	**Number of patients:** 211, 114 with longitudinal follow-up **Age:** - Mean (SD): 8.8 (4.5) - Median: 8.2 - Range: 2.2-18.0 **Sex:** - Female: 154 (73%) - Male: 57 (27%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 15 (7.1%) **Baseline severity:** Time since diagnosis:	**Instrument(s) evaluated:** Juvenile Arthritis Functionality Scale (JAFS), 15 items scored 0-30, three 5-question domains (lower limbs, hand/wrist, upper segment) each scored 0-10; in Italian **Measured for construct validity** Child Health Questionnaire Physical (CHQP) and Psychosocial (CHQPsy) subscales Childhood Health Assessment Questionnaire (CHAQ) – Italian	**1) Reliability:** - Test-retest: NR - Inter-rater: (see General comments) - Intra-rater: NR - Intra-class correlation: Cronbach's alpha for JAFS total (0.82), JAFS lower limb (0.86), JAFS hand/wrist (0.81), JAFS upper segment (0.62) **2) Validity:** Spearman correlations (n varies from 158 to 204) - Versus clinical outcomes: PGDA 0.54; PGWB 0.49; CHQP -0.58; CHQPsy -0.25 - Versus lab results: ESR 0.39, CRP 0.39	**General comments:** Inter-rater reliability was assessed using Cronbach's alpha **Quality assessment:** - Consecutive patients with JIA CHAQ and JAFS were completed in random order - Sample sizes not calculated - Analysis is appropriate with possible exception of inter-rater reliability

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Mean 4.4 (3.4) Active joint count (0-67): Mean 3.26 (6) Other: CHAQ: Mean 0.31 (0.4) JAFS: Mean 1.9 (2.7) **Inclusion criteria:** - Consecutive patients with JIA by ILAR criteria seen at study units between April and September 2005 - Parental informed consent **Exclusion criteria:** - Musculoskeletal abnormalities other than JIA - Other diseases that affected functional health status	Parent global assessment of well-being (PGWB), VAS 0-10 Physicians global assessment of disease activity (PGDA), VAS 0-10 **Mode of administration:** Self-administered: JAFS and CHAQ	- Versus radiological results: NR - New instrument versus established instrument: CHAQ correlation with JAFS, spearman 0.73. The JAFS total and 3 subscales showed statistically significant differences for patients grouped into Steinbrocker functional classes I and II Subgroup analysis for patients with CHAQ > 0.5 showed higher correlations for JAFS and all measures except physician's global assessment **3) Other:** - Feasibility (n = 54 parents): JAFS mean 1.4 minutes (range 1-4), CHAQ 5.3 minutes (3-10). Among 136 parents, 89 (65.4%) preferred the JAFS, 40 (29.4%) preferred the CHAQ, 7 (5.2%) judged equivalent. No missing responses for JAFS. - Responsiveness (n = 114): Standardized response mean among improved patients as rated by physician (n = 20): JAFS 0.56 (95% CI 0-1.49) CHAQ 0.60 (0.24-0.94) Results similar using parent ratings. Standardized response mean among worsened patients as	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				rated by physician (n = 26): JAFS 0.42 (95% CI 0.17-0.68) CHAQ 0.15 (0-0.55) Results similar using parent ratings. - ROC curves: NR	
Geerdink, Prince, Looman, et al., 2009 **#1515**	**Geographical location:** Rotterdam, The Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** ".. to develop a reliable and user-friendly digital CHAQ…" **Duration of followup:** NA	**Number of patients:** 51 **Age:** - Mean (SD): NR - Median: 11.2 - Range: IQ 8.1-15.0 **Sex:** - Female: 36 - Male: 15 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 7 (13.7%) **Baseline severity:** Time since diagnosis: NR Active joint count: NR **Inclusion criteria:** Consecutive patients at outpatient pediatric rheumatology clinic **Exclusion criteria:** Insufficient knowledge of written Dutch language	**Instrument(s) evaluated:** Childhood Health Assessment Questionnaire – Dutch language, digital Modifications: Some change in question order; use of help or helping devices assessed after each of the 8 domains instead of twice; parent (CHAQ-PV) and child (CHAQ-CV) versions with "minor" differences in language **Mode of administration:** Other: Physician assistant completes patient's personal data; all remaining information self-administered (patient or parent) by computer	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Digital vs. paper correlation: 0.974 Median values: Digital 0.72 (IQ range 0.13-1.25), paper 0.66 (IQR 0.13 to 1.13); digital gives statistically significant higher values (p = 0.032) VAS-Pain (correlation 0.989) and VAS-Well-being (correlation 0.951) correlated for digital and paper version; medians did not differ significantly **3) Other:** - Feasibility: Mean administration time: Digital version 5.06 minutes (SD 1.91) vs. 3.75 minutes (SD 1.84) for paper version; 75% of patients	**General comments:** None **Quality assessment:** - Spectrum: Consecutive; severity uncertain - Blinding: NA; order of administration randomized - Validated criterion: NA - FU > 80%: NA - Analysis appropriate: Yes

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				preferred the digital version; 14% no preference; 11% paper version - Responsiveness: NR - ROC curves: NR	
Giannini, Ruperto, Ravelli, et al., 1997 **#1734**	**Geographical location:** Multinational; patient valdiation: Cincinnati, Ohio and Pavia, Italy **Setting:** Specialty clinics Other: Subjects' data for this study were taken from a previously published study (Giannini, Brewer, Kuzmina, 1992, #1008) **Study design:** Consensus process with comparison to study data **Study objective(s):** To identify a core set of outcome variables for the assessment of children with JA **Duration of followup:** NA	**Number of patients:** 78 **Age:** NR **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** NR **Percentage with systemic JIA:** NR **Baseline severity:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Instrument(s) evaluated:** Definition of improvement based on percent improvement and worsening as defined using the core variables including: physician global assessment, parent/patient assessment of well-being, functional ability, number of joints with active arthritis, number of joints with limited range of motion, and ESR **Mode of administration:** Consensus: mailed surveys Retrospective analysis using existing data from a previous study	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** 240 definitions of improvement considered, the sensitivity and specificity calculated using the physicians' consensus rating of improvement as the reference standard. Nine of the definitions with a sensitivity and specificity greater than 80% were retained, and each of these was tested on sample of patients from previously reported placebo controlled trial of methotrexate. Selected definition was at least 30% improvement from baseline in 3 of 6 variables in core set and no more than one with worsening by > 30% selected based on highest face validity rating and performance on patient sample. In a trial of methotrexate vs. placebo, 63.3% of those in the treatment group (n = 38) and 40% of those in the placebo group (n = 39) had improvement according to this instrument	**General comments:** The main goal of this study was to identify the criteria. Minimal validation data. Although rates of improvement based on the instrument were presented using data from a previous study, there was no data to assess the degree to which these subjects had improvement using alternative methods of assessment. **Quality assessment:** - Poor (for validation component) - Some variables had to be derived or converted for validation in patient population - No comment on if pts in study of MTX defined as improved or worsened using previous conventions.

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				3) Other: - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Len, Golden-berg, Ferraz, et al., 1994 **#1748**	**Geographical location:** Brazil **Setting:** Pediatric Rheumatology departments in 2 public hospitals **Study design:** Cross-sectional **Study objective(s):** To translate CHAQ into Portuguese and evaluate the reliability of the Portuguese version **Duration of followup:** NA	**Number of patients:** 53 **Age:** - Mean (SD): 11.1 - Range: 7-17 **Sex:** - Female: 28 (52.9%) - Male: 25 (47.1%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA (JRA):** 7.6% **Baseline severity:** Time since diagnosis: Mean 4.9 years (range 0.5-10.0) Number of involved joints: Mean 6.8 (range 1-24) Mean ESR: 29.9 mm (Westergren) **Inclusion criteria:** - Patients with JRA between 7 and 17 years old - Diagnosis of JRA according to the American Rheumatism Association	**Instrument(s) evaluated:** CHAQ (Portuguese version) **Mode of administration:** Interviewer-administered "First administered to children and then to parents by physiotherapist"	**1) Reliability:** - Test-retest: Pearson's correlation coefficient (n =26): Children = 0.96, parents = 0.96 - Kappa statistics: NR - Inter-rater: NR - Intra-rater:NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Number of involved joints: CHAQ-children = 0.64 ($p < 0.01$) CHAQ-parents = 0.66 ($p < 0.01$) - Versus lab results: ESR: CHAQ-children = 0.55 ($p < 0.01$) CHAQ-parents = 0.54 ($p < 0.01$) - Versus radiological results: NR - New instrument versus established instrument: Disease Activity Index: CHAQ-children = 0.60 ($p < 0.01$) CHAQ-parents = 0.61 ($p < 0.01$) ACR Functional Class: CHAQ-children = 0.61($p < 0.01$) CHAQ-parents = 0.68 ($p < 0.01$) **3) Other:** - Feasibility: NR - Responsiveness: NR	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		1977 criteria **Exclusion criteria:** NR		- ROC curves: NR	
Lurati, Pontikaki, Teruzzi, et. al., 2006 **#301**	**Geographical location:** Milan, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** Compare 4 sets of criteria (ACR 30, ACR 20, DAS and DAS 28) to evaluate clinical response criterion in JIA patients treated with methotrexate and/or anti-tumor necrosis factor α drugs **Duration of followup:** 6 months Patients evaluated at baseline and after 6 months of therapy with MTX or anti-TNFα drugs.	**Number of patients:** 75; patients aged > 16 years = 21; patients aged ≤ 16 years = 54 **Age:** - Mean (SD): 12.8 - Range: 2-32.9 years **Sex:** - Female: 61/75 - Male: 14/75 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 16/75 **Baseline severity:** Stated that variables recorded were tender joint count, swollen joint count in 44 and 28 joints, limited joint count Ritchie Articular Index, ESR , pain evaluation (VAS) as reported by patient or parent/guardian, CHAQ, patients and physicians global disease activity score (VAS), but baseline values not presented in the article **Inclusion criteria:**	**Instrument(s) evaluated:** ACR Pediatric 30 ACR 20 EULAR disease activity score (DAS) 28-joint DAS (DAS28) **Mode of administration:** Other: Investigation of indices of disease activity combining several variables with different modes of administration	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater:NR - Intra-class correlation: NR - Kohen's kappa for various comparison pairs (all patients, age < 16 years, age > 16 years): DAS/ACR Ped 30: 0.71 ± 0.1, 0.72 ± 0.1, 0.69 ± 0.2 DAS28/DAS: 0.68 ± 0.1, 0.65 ± 0.1, 0.73 ± 0.1 DAS28/ ACR Ped 30: 0.55 ± 0.1, 0.61 ± 0.1, 0.39 ± 0.2 DAS/ACR20: 0.53 ± 0.1, 0.61 ± 0.1, 0.21 ± 0.3 ACR20/ACR Ped 30: 0.53 ± 0.1, 0.56 ± 0.1, 0.33 ± 0.3 DAS28/ACR 20: 0.38 ± 0.1, 0.51 ± 0.1, invalid comparison, p > 0.05 - Fleiss Agreement Index: DAS/ACR Ped 30: Good/excellent DAS28/DAS: Good/excellent DAS28/ ACR Ped 30: Good DAS/ACR20: Good ACR20/ACR Ped 30: Good DAS28/ACR 20: Marginal/Good - Landis and Koch reproducibility index: DAS/ACR Ped 30: Substantial DAS28/DAS: Substantial	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		JIA patients being treated with either MTX or anti-TNFα drugs **Exclusion criteria:** NR		DAS28/ ACR Ped 30: Moderate DAS/ACR20: Moderate ACR20/ACR Ped 30: Moderate DAS28/ACR 20: Slight Somers' Δ for various comparison pairs (all patients, age < 16 years, age > 16 years): DAS/ACR Ped 30: 0.75 ± 0.1, 0.69 ± 0.1, 0.72 ± 0.2 DAS28/DAS: 0.73 ± 0.1, 0.61 ± 0.1, §) DAS28/ ACR Ped 30: 0.39 ± 0.1, §, §) DAS/ACR20: 0.35 ± 0.1,§ ,§ ACR20/ACR Ped 30: 0.30 ± 0.1, §, § DAS28/ACR 20: 0.33 ± 0.1, §, § § = Value not computable, because P > 0.05 **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: The concordance of different instruments using ACR Ped 30 as the gold standard: DAS (71% concordance) DAS 28- (55% concordance) ACR 20 (53% concordance) Sensitivity and specificity using ACR Ped 30 as the gold standard: DAS28: Sensitivity 0.9, Specificity 0.66	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				DAS: Sensitivity 0.93, Specificity 0.8 ACR20: Sensitivity 0.81, Specificity 0.84 **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: Mean area under the curve for: (a) DAS28: 0.702 (b) DAS: 0.735 (c)ACR20: 0.562	
Magni-Manzoni, Cugno, Pistorio, et al., 2005 **#1595**	**Geographical location:** Genova, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** Responsiveness of JIA clinical measures (physician and parent global assessment, the global articular severity score, and the morning stiffness to relevant increase in disease activity (disease flare) Disease flare defined as the presence of at least one of the following criteria: 1. New start, restart, or dose increase of ≥ 0.2 mg/kg/day of prednisone	**Number of patients:** 115 **Age:** - Mean (SD): NR - At onset: 4.9 (3.6) **Sex:** - Female: 91 (79%) - Male: 24 (21%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 10% **Baseline severity:** All values expressed as Mean (SD): Time since diagnosis (years): 8.9 (4.1) Active joint count: 3.2 (4.8) Number of swollen joints:	**Instrument(s) evaluated:** Physician global assessment Parent global assessment Parent pain assessment CHAQ score (Italian version) **Mode of administration:** Self-administered Interviewer-administered Other	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness of clinical measures of JIA activity in the detection of disease flare in terms of Standardized Response Mean (SRM) and effect sizes (ES): Physician global assessment: Mean change: 5.4 (2.6) Effect size: 2.32	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		1.9 (3.5)		SRM: 2.07 95% CI: 0.67-3.17	
	2. New start, restart, or dose increase of ≥ 5 mg/m^2/week of MTX or new start or restart of sulfasalazine	Number of joints with pain/tenderness: 1.7 (3.0)		Parent global assessment: Mean change: 1.5 (2.0) Effect size: 0.97 SRM: 0.80 95% CI: 0.19-1.28	
		LROM score: 4.1 (7.3)			
	3. Association to MTX or sulfasalazine of a second-line drug including biologic agent	Number of joints with LROM + POM/TD: 1.5 (2.5)		Parent pain assessment: Mean change: 1.0 (2.5) Effect size: 0.47 SRM: 0.4 95% CI: 0-0.98	
		Global articular severity score: 8.4 (12.0)			
	4. Association with increase in physician global assessment of overall disease activity ≥ 3 cm on VAS with respect to previous evaluation	ESR (mm/h): 18.9 (14.7)		CHAQ score: Mean change: 0.2 (0.4) Effect size: 0.50 SRM: 0.60 95% CI: 0.25-0.96	
		C-reactive protein: 1.8 (3.5)			
	Duration of followup: Mean (range): 2.8 years (0.5 to 6.2 years)	Physician global assessment: 1.8 (2.3)		- ROC curves: NR	
		Parent global assessment: 1.8 (1.6)			
		Parent pain assessment: 1.2 (2.1)			
		CHAQ score: 0.2 (0.5)			
		Inclusion criteria: - Diagnosis of JIA by ILAR criteria - Experience of disease flare - At least 6 months of follow up			
		Exclusion criteria: NR			

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Moretti, Viola, Pistorio, et al., 2005 **#401**	**Geographical location:** Genova, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** To "…compare the relative responsiveness of traditional condition specific measures with that of a generic pediatric HRQoL instrument" **Duration of followup:** 6 months	**Number of patients:** 44 **Age:** - Mean (SD): 7.2 years - Range 2.6 to 14.8 yrs **Sex:** - Female: 35 - Male: 9 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** None **Baseline severity:** Time since diagnosis: Mean 3.4 years (range 1.2-10.4) Active joint count: Median 2.0 (range 1 to 4) Other: 24 no systemic medication; 20 NSAIDs; 8 methotrexate CHQ disability: Mean (SD) 0.36 (0.49) CHQ physical: 39.67 (13.79) CHQ psychosocial: 44.52 (9.58) **Inclusion criteria:** - JIA - ≤ 4 joints involved - Received an intra-	**Instrument(s) evaluated:** Italian version of the Child Health Questionnaire (CHAQ, range 0-3) Italian version of the Child Health Questionnaire (CHQ) reported as physical and psychosocial subscales Physician global assessment (PGA) of overall disease activity (0-10 VAS) Parent global assessment (PGW) of overall well-being (0-10 VAS) **Mode of administration:** NR External criterion: Improved = complete remission or much improved; stable = slightly improved or unchanged; worse = slightly worse or much worse – rated by clinician and parent (results reported separately for physician and parent ratings)	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Mean change scores (6 month – baseline) for groups classified by physician as improved (n = 23), stable (n = 14), worsened (n = 7): CHAQ disability index: -0.12, -0.13, 0.11 CHQ physical score: 4.99, 0.92, -6.00 CHQ psychosocial score: 4.69, 2.01, -10.10 PGA: -5.14, -1.37, 1.12 PGW: -1.65, 0.14, -0.16 (Note: SDs not reported) - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: Standardized responsiveness, effect size, Guyatt statistic: CHAQ disability index: 0.25, 0.17, 0.29 CHQ physical score: 0.19, 0.18, 0.33 CHQ psychosocial score: 0.28, 0.23, 0.72 PGA: 0.82, 1.46, 2.24 PGW: 0.30, 0.33, 0.54	**General comments:** - Physician's global assessment not independent from physician's external criterion - Narrow spectrum of disease **Quality assessment:** - Spectrum: Limited - Blind criterion: Physician's "external criterion" independent and blind to CHAQ and CHQ but not physicians global assessment - Blinded instrument: Can't tell - Validated criterion: Uncertain - F/U ≥ 80%: Yes - Analyses appropriate: Yes

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		articular corticosteroid injection at baseline **Exclusion criteria:** Further intra-articular corticosteroid injection during followup		ROC curves: CHAQ disability index: 0.56 (95% CI 0.40 to 0.71) CHQ physical score: 0.67 (0.50 to 0.81) CHQ psychosocial score: 0.71 (0.54 to 0.85) PGA: 0.86 (0.72 to 0.95) PGW: 0.63 (0.46 to 0.78)	
Oliveira, Ravelli, Pistorio, et al., 2007 **#1777**	**Geographical location:** 32 countries in South America, Europe, Israel, Korea, Russia, Turkey and the UK **Setting:** Healthy children were siblings of JIA children or from schools; JIA participants not described **Study design:** Cross-sectional **Study objective(s):** To investigate proxy-reported HRQOL **Duration of followup:** NA	**Number of patients:** - 3324 JIA - 3315 healthy **Age:** - Mean (SD): 11.2 (3.9) healthy; 10.0 (4.4) JIA - Median: NR - Range: NR **Sex:** - Female: 1694 (51%) healthy; 2250 (68%) JIA - Male: 1621 (49%) healthy; 1074 (32%) JIA **Race/ethnicity:** NR **JIA diagnosis:** JIA: - 655 had systemic - 1130 had polyarthritis - 579 had extended oligoarthritis - 960 had persistent oligoarthritis **Percentage with**	**Instrument(s) evaluated:** Childhood Health Assessment Questionnaire (CHAQ) – in patient's national language (includes VAS for pain) Child Health Questionnaire (CHQ), physical summary score (PhS) and psychosocial summary score (PsS) **Comparators:** Attending physician assessed: Active joint count, joints with swelling, joints with tenderness, joints with limited ROM, global assessment of overall disease activity on 10 cm VAS ESR **Mode of administration:** Self-administered Interviewer-administered	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Internal validity: NR **2) Validity:** - Versus clinical outcomes: Mean score for JIA vs. healthy controls: PhS: 44.5 (10.6) vs. 54.6 (4.0) PsS: 47.6 (8.7) vs. 51.9 (7.52) Patients with "persistent oligoarthritis" had better HRQOL on all CHQ subscales and summary scores than those with extended oligoarthritis, polyarthritis, or systemic arthritis; $p < 0.001$ for all comparisons Spearman correlation coefficient for PhS: Active joints: -0.42 - Versus lab results: Spearman correlation coefficient for PhS: ESR: -0.36 - Versus radiological results: NR - New instrument versus	**General comments:** None **Quality assessment:** - Large multinational sample - Unclear if measures completed independently from clinical assessments; unclear if order randomized - Analysis appropriate

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		systemic JIA: 19.7% of those with JIA **Baseline severity:** Time since diagnosis: 4.1 years (3.5) Active joint count: 5.8 (8.1) ESR: 30.4 (25.4) CHAQ disability index: 0.8 (0.8) **Inclusion criteria:** - Patients (JIA by ILAR criteria) and healthy children enrolled in the PRINTO study - Age ≤ 18 years **Exclusion criteria:** - Psoriatic arthritis - Enthesitis related arthritis		established instrument: Spearman correlation coefficient for PhS: CHAQ: -0.63 Parent VAS pain: -0.63 Parents rating of overall well-being: -0.61 Physician global: -0.52 "All Spearman's correlations between the PsS and JIA severity measures were poor (r = -0.13, 0.36)" **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: CHAQ score of > 1 determined to discriminate best between JIA and healthy controls. 838 (29%) of 2883 JIA patients had scores > 1; all healthy controls had scores < 1	
Palmisani, Solari, Magni-Manzoni, et al., 2006 **#1569**	**Geographical location:** Genoa, Italy **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** Comparing the correlation between JIA measures of disease activity and damage in patients with early and late stage disease. Comparison is across 3 cohorts classified as: (1)	**Number of patients:** Total number of patients: 223 (ED = 70, AD = 114, LD = 39) **Age:** - Median (Range) ED: 0.6 (0.1-1.5) AD: 6.5 (5.0-9.9) LD: 12.5 (10-25) **Sex:** - Female: ED: 52 (74%) AD: 90 (79%) LD: 29 (74%) - Male:	**Instrument(s) evaluated:** CHAQ **Mode of administration:** Self-administered	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: ED (early stage): No. of joints with tenderness/pain on movement (0.33) No. of swollen joints (0.22) No. of joints with LROM (0.33) No. of active joints (0.14) AD (advanced disease):	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	early disease (ED) (disease duration ≤ 1yr); (2) advanced disease (AD) (duration 5-9.9 yrs); (3) longstanding disease (LD) (disease duration ≥ 10 yrs) **Duration of followup:** NA	ED: 18 (26%) AD: 24 (21%) LD: 10 (26%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 10% **Baseline severity:** ED = 70, AD = 114, LD = 39 Time since diagnosis: ED: 0.6 (0.1-1.5) AD: 6.5 (5.0-9.9) LD: 12.5 (10-25) Active joint count: ED: 2.5 (0-19) AD: 2 (0-30) LD: 2.0 (0-39) **Inclusion criteria:** JIA patients fulfilling the ILAR criteria for JIA **Exclusion criteria:** NR		No. of joints with tenderness/pain on movement (0.58) No. of swollen joints (0.41) No. of joints with LROM (0.47) No. of active joints (0.53) LD (late stage): No. of joints with tenderness/pain on movement (0.73) No. of swollen joints (0.28) No. of joints with LROM (0.76) No. of active joints (0.61) - Versus lab results: ED (early stage): ESR: 0.31 CRP: 0.22 AD (advanced disease): ESR: 0.27 CRP: 0.26 LD (late stage): ESR: 0.23 CRP: 0.55 - Versus radiological results: ED Poznanski score (-0.31) AD Poznanski score (-0.02) LD Poznanski score (-0.62) **- New instrument versus established instrument:** Physician global: ED-0.45 AD-0.46 LD-0.38 Parent global: ED-0.62	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				AD-0.70 LD-0.51 **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Pouchot, Larbre, Lemelle, et al., 2002 **#1650**	**Geographical location:** France **Setting:** Outpatient clinics across 16 participating hospitals in a multi-center study in France **Study design:** Cross-sectional **Study objective(s):** Translate, cross-culturally adapt, and validate CHAQ in children with JIA **Duration of followup:** NR	**Number of patients:** 500 children including 306 patients and 194 healthy controls **Age:** - Mean (SD): Systemic: 9.4 ± 5.0 Polyarticular:11.1 ± 4.5 Extended oligoarticular: 10.0 ± 4.2 Persistent oligoarticular: 7.6 ± 3.8 Healthy children (controls): 11.4 ± 3.9 **Sex:** - Female: 77% - Male: 33% **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 23% **Baseline severity:** Time since diagnosis: Systemic: 4.0 ± 3.8 Polyarticular: 4.9 ± 4.0 Extended oligoarticular: 6.4 ± 3.9	**Instrument(s) evaluated:** CHAQ (French version) **Mode of administration:** Self-administered	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: 0.91 (0.87-0.94) - Cronbach's alpha ≥ 0.70 for 7 of the 8 domains (0.69-0.90; 0.69 for Arising) **2) Validity, evaluated by calculating Pearson's coefficient, n = 306** - Versus clinical outcomes: Swollen joint count: 0.4 (0.0001) Painful joint count: 0.43 (0.0001) Stiff joint count: 0.57 (0.0001) - Versus lab results: ESR: 0.32 (0.0001) - Versus radiological results: NR - New instrument versus established instrument: NR -Overall physician's assessment (VAS)-0.49 (0.0001) Pain (parent's assessment, VAS)-0.49 (0.0001)	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Persistent oligoarticular: 3.7 ± 3.2 Healthy children (controls): 11.4 ± 3.9 Active joint count: NR **Inclusion criteria:** Children with JIA meeting Durban's 1997 criterion *and* with systemic, polyarticular, extended oligoarticular, or persistent oligoarticular disease **Exclusion criteria:** Patients with psoriatic arthritis or juvenile spondyloarthritis		Overall impact (parent's assessment, VAS): 0.54 (0.0001) **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves:	
Pouchot, Ecosse, Coste, et al., 2004 **#1612**	**Geographical location:** France **Setting:** Specialty clinic – outpatient pediatric clinics of 16 pediatric referral centers **Study design:** Cross-sectional **Study objective(s):** Assessment of the validity of CHAQ in two age groups of children, using Rasch model scoring to determine variation in item level difficulty by age group **Duration of followup:**	**Number of patients:** 306 Age 1-9: n = 156 Age ≥ 10: n = 151 **Age:** - Mean (SD): Systemic: 9.4 ± 5.0 Polyarticular: 11.1 ± 4.5 Extended oligoarticular: 10 ± 4.2 Persistent oligoarticular: 7.6 ± 3.8 **Sex:** - Female: 238 - Male: 68 **Race/ethnicity:** NR **JIA diagnosis:** JIA	**Instrument(s) evaluated:** CHAQ (French Version) **Mode of administration:** Self-administered (completed by parent)	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** Spearman correlation coefficients are reported for the two age groups (1-9 years and ≥ 10 years), P < 0.0001 for all - Versus clinical outcomes: Number of swollen joints (0.44, 0.31) Number of painful joints (0.32, 0.47) Number of joints with limited range of motion (0.47, 0.52) Number of active joints (0.45,	**General comments:** Assessment of the validity of CHAQ in two age groups of children, using Rasch model scoring to assess bias due to variation of item difficulty across age **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	NA	**Percentage with systemic JIA:** 70/306 (23%) **Baseline severity:** Time since diagnosis (mean ± SD, yrs): Systemic: 4.0 ± 3.8 Polyarticular: 4.9 ± 4.0 Extended oligoarticular: 6.4 ± 3.9 Persistent oligoarticular: 3.7 ± 3.2 Active joint count: Systemic: 7.3 ± 10 Polyarticular: 7.4 ± 10.2 Extended oligoarticular: 3.9 ± 4.8 Persistent oligoarticular: 1.2 ± 2.1 ESR: Systemic: 37.7 ± 26.0 Polyarticular: 16.2 ± 14.2 Extended oligoarticular: 26.1 ± 18.4 Persistent oligoarticular: 21.2 ± 17.2 Physician VAS: Systemic: 3.1 ± 2.8 Polyarticular: 2.9 ± 2.8 Extended oligoarticular: 2.7 ± 2.1 Persistent oligoarticular: 1.8 ± 1.6 **Inclusion criteria:**		0.53) - Versus lab results: ESR (0.37, 0.41) - Versus radiological results: NR - New instrument versus established instrument: Physician global assessment (0.45, 0.53) **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Children with systemic, polyarticular (5 or more joints affected), extended oligoarticular, or persistent oligoarticular JIA satisfying the Durban criteria **Exclusion criteria:** NR			
Ruperto, Ravelli, Falcini, et al., 1998 **#812**	**Geographical location:** Italy, multicenter **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** Investigate performance of core set of outcome measures and the preliminary definition of improvement in JIA population treated with MTX Variables assessed: (1) physician global assessment of disease activity; (2) parent or patient (if appropriate in age) global assessment of overall well being; (3) functional ability; (4) number of joints with active arthritis; (5) number of joints with limited range of motion; (6) erythrocyte sedimentation rate	**Number of patients:** 111 **Age:** NR **Sex:** - Female: 74 (67%) - Male: 37 (33%) **Race/ethnicity:** NR **JIA diagnosis:** JCA (all poly) **Percentage with systemic JIA:** 40 (31%) **Baseline severity:** Time since diagnosis: 3.4 years (0.5-14.9) Active joint count: NR **Inclusion criteria:** -Diagnosis of JCA according to the criteria of the European League Against Rheumatism (EULAR) -Disease duration of at least 6 months - At least five joints with	**Instrument(s) evaluated:** The physician global was scored on a 5-point ordered categorical scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe), not the VAS* Parent/patient global was assessed by asking parents to judge their child's overall well being at 6 months as compared with baseline according to a 3-point categorical scale (better, same, worse), not VAS* Functional status: CHAQ, JAFAR, or Modified Lee Index Joint count: 64 joints **Mode of administration:** Mixed	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity, by Spearman's correlation coefficient:** - Versus clinical outcomes: Physician global versus: Parent global: 0.56 ESR: 0.47 Functional ability: 0.51 LROM: 0.40 Active joints: 0.54 Active joint count versus: Parent global: 0.36 Functional ability: 0.31 LROM: 0.7 Parent global versus: Functional ability: 0.25 LROM: 0.30 - Versus lab results: ESR versus: Physician global: 0.47 Active joint count: 0.34 Parent global: 0.27 Functional ability: 0.24	**General comments:** - No comment on sample size or blinding - Unclear number lost to followup/dropout - Used different scales for parent and physician global assessments instead of VAS **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	Duration of followup: 6 months	active arthritis (defined as the presence of swelling or limitation of movement with either pain upon movement or tenderness) that was not adequately controlled by NSAIDs or DMARDs **Exclusion criteria:** NR		LROM: 0.29 - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Ruperto, Ravelli, Miglia-vacca, et al., 1999 **#1717**	**Geographical location:** Italy **Setting:** NR **Study design:** Longitudinal non-RCT **Study objective(s):** Examine the responsiveness of outcome variables used in clinical trials in children with oligoarticular JCA **Duration of followup:** 3 months	**Number of patients:** 26 **Age:** - Mean (SD): NR - Median: 4.7 years - Range: 1.5-14.8 years **Sex:** - Female: 22 (85%) - Male: 4 (15%) **Race/ethnicity:** NR **JIA diagnosis:** JCA-oligoarticular **Percentage with systemic JIA:** 0 **Baseline severity:** Disease duration: Median 2.5 years (range 0.2-13.2) Active joint count: NR **Inclusion criteria:** Diagnosed with oligoarticular JCA **Exclusion criteria:** NR	**Instrument(s) evaluated:** Physician global (15 cm VAS) Parent global (15 cm VAS) Parent assessment of pain (15 cm VAS) CHAQ – Italian language version Articular (64 joints): Number and score of painful joints Number and score of swollen joints Number and score of joints with LROM Number of active joints Global severity score Clinical improvement defined by PAVIA criteria: 30% improvement in 3 of 6 core variables with ≤ 1 variables worsening by > 30% **Mode of administration:** NR for patient and parent instruments All clinical assessments	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: SRM: Physician global: 0.9 Parent global: 0.5 Parent assessment of pain: 0.3 CHAQ: 0 Articular: Number and score of painful joints: 0/0.7 Number and score of swollen joints: 0.7/1.3 Number and score of joints with	**General comments:** None **Quality assessment:** - Consecutive patients but small sample - Single rater completed all physician assessments and unclear if assessments completed blind to parent/patient reported outcomes - Followup rates not explicitly reported - No sample size calculation - All assessments on individual patients made by a single rater

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
			on individual patients made by a single rater	LROM: 0.7/0.7 Number of active joints: 1.3 Global severity score: 1.3 Effect sizes: Physician global: 1.0 Parent global: 0.5 Parent assessment of pain: 0.2 CHAQ: 0 Articular: Number and score of painful joints: 0/0.4 Number and score of swollen joints: 1.3/0.9 Number and score of joints with LROM: 0.7/0.4 Number of active joints: 0.7 Global severity score: 0.9 Guyatt responsiveness statistics: Physician global: 2.5 Parent global: 1.3 Parent assessment of pain: 1.2 CHAQ: 0.5 Articular: Number and score of painful joints: -/1.3 Number and score of swollen joints: 1.3/1.3 Number and score of joints with LROM: -/1.3 Number of active joints: 2.7 Global severity score: 2.4 - ROC curves: NR 5 measures most responsive: Physician global Number swollen joints	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				Score swollen joints Active joint count Global articular severity score	
Saad-Magalhaes, Pistorio, Ravelli, et al., 2010 **#1510**	**Geographical location:** European, U.S.A and South American sites **Setting:** NR **Study design:** Cross-sectional cohort and a longitudinal cohort **Study objective(s):** Examine whether CHAQ disability index (DI) scoring systems and its responsiveness to change differed significantly when calculated without aids/devices or help **Duration of followup:** Cross section cohort - NA Longitudinal 6 months	**Number of patients:** 2786 in cross-sectional cohort screened, 65 excluded due to age >19, 31 for missing baseline CHAQ, 27 because CHAQ incomplete Total N = 2663 (96%) 595 longitudinal cohort 54 excluded incomplete CHAQ, 9 because > 19 years, 2 for missing baseline CHAQ Total N = 530 (89%) **Age:** Cross-sectional median (range): 10.5 (7.1-13.9) Longitudinal median (range): 7.9 (4.3-11.4) **Sex:** Cross-sectional: - Female: 1779 (66.8%) - Male: 884 (33.2%) Longitudinal: - Female: 381 (71.9%) - Male: 149 (28.1%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** Cross-sectional: 557	**Instrument(s) evaluated:** CHAQ and CHAQDI in participant's national language **Mode of administration:** Self-administered (parent) CHAQ scored using 4 methodologies: - Original scoring system - Omitting 14 items related to use of aids/devices - Omitting 8 items specific to the need for help from another person - Omitting both aids/devices items and need for help items	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus radiological results: NR - Versus clinical outcomes Spearman's correlation coefficient for the 4 scoring approaches Physician global: Cross: 0.43 all 4 Long: 0.31 to 0.33 Number of active joints: Cross: 0.36-0.37 Long: 0.33 Child pain VAS: Cross: 0.54 Long: 0.50-0.51 Child well-being VAS Cross: 0.56-0.58 Long: 0.52-0.54 - Versus lab results: ESR: Cross: 0.34-0.35 Long: 0.18-0.20 - New instrument versus established instrument: No differences across the 4	**General comments:** No comment on blinding **Quality assessment:** - Large sample - Blinding not reported - High followup in longitudinal sample - Good quality **-** No race/ethnicity specified, but multinational

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		(20.9%) Longitudinal: 73 (13.8%) **Baseline severity:** Disease duration: Cross-sectional: 3.7(1.7-6.6) Longitudinal: 1.3 (0.7-3.6) Active joint count: Cross-sectional: 1 (0-5) Longitudinal: 9 (6-16) ESR: Cross-sectional: 20 (10-36) Longitudinal: 40 (22-62) **Inclusion criteria:** - JIA-all subtypes for cross-sectional sample; JIA-polyarticular for longitudinal sample - Age ≤ 19 years - Completion of at least 6 functional areas of the CHAQ **Exclusion criteria:** NR		CHAQs **3) Other:** - Feasibility: NR - Responsiveness: Used longitudinal cohort: SRM large (≥ 0.8, 95% CI 0.77-0.96) for responders (ACR 30 criteria) to MTX and unchanged by 4 different measures, and poor for those who didn't respond (SRM: 0.01), no difference by 4 different measures - ROC curves: NR Mean change in score: Removing aids/help decreased score by 0.1 from cross-sectional cohort (0.64 original to 0.54 with aids/help removed; $p < 0.0001$) and by 0.15 for longitudinal cohort (1.23 to 1.07; $p < 0.0001$)	
Sawyer, Carbone, Whitham, et al., 2005 **#1592**	**Geographical location:** South Australia **Setting:** Specialty clinic – rheumatology clinic **Study design:** Longitudinal non-RCT **Study objective(s):** - Compare ratings of	**Number of patients:** 81 screened 64 (79%) agreed to participate 54 completed study **Age:** - Mean (SD): 12.8 (3.3) - Median: NR - Range: NR	**Instrument(s) evaluated:** HRQL per PedsQL 4.0 Generic Core Scales and PEDS QL 3.0 Arthritis Module of the pediatric Quality of Life inventory Pain by VAS (10 cm) from the Varni-Thompson Pediatric Pain Questionnaire (PPQ)	**1) Reliability:** - Test-retest: NR - Inter-rater: Children in 3 of 4 subscales reported higher scores (better QL) than parent reports PedsQL generic: Differences in mean scores (child vs. parent) ranged from 7.1 (social functioning) to 12.5 (emotional functioning) points	**General comments:** - Questionnaires completed independently - Standard measures used **Quality assessment:** - Good quality - Small sample but selected consecutively - Limited measures for construct validity (only associated with

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	children's HRQL from parents and children with JIA - Investigate extent to which these ratings change over time - Examine relationship between children's HRQL and pain and use of pain coping skills **Duration of followup:** 12 months	**Sex:** - Female: 31 (57.4%) - Male: 23 (42.6%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 7% **Baseline severity:** Time since diagnosis: (phrased duration of care): Mean (SD) = 5.7 ± 2.8 Active joint count: NR **Inclusion criteria:** All children 8-18 diagnosed with JIA at least 6 months prior to study and attending the rheumatology clinic **Exclusion criteria:** Insufficient English to complete questionnaires	CHAQ **Mode of administration:** Self-administered – but research assistant available for questions	higher. Correlation coefficients between parent and child for the 4 subscales ranged from 0.5 to 0.8 for the 4 subscales. Children reported higher scores than parents for 1 (daily activities) of 4 subscales Peds QL- disease specific, Daily activities: Parent: 80.9 (22.8) Child: 87.9 (17.2) Correlation coefficients ranged from 0.5 to 0.9 for 3 subscales; 0.3 for the Worry scale - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Peds QL-generic: 3 of 4 subscales (not social functioning) were significantly associated with pain reported by parent, and all subscales were associated with child-reported pain Peds QL-disease specific: 3 of 4 subscales (not daily activities) were significantly associated with pain reported by parent, and all subscales were associated with child-reported pain - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR	pain scores) - F/U rate good - No sample size calculation

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				3) Other: - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Selvaag, Flato, Lien, et al., 2003 **#1628**	**Geographical location:** Oslo **Setting:** Pediatric Rheumatology **Study design:** Longitudinal cohort **Study objective(s):** Identify determinants of the CHQ in JIA and assess the responsiveness of the instrument **Duration of followup:** Mean follow up 10.0 ± 3.8 months	**Number of patients:** 166 approached; 12 declined, 4 with inadequate Norwegian language skills, and 34 with incomplete data; 116 (69.9%) out of 166 children with JIA and 116 matched healthy controls **Age:** Mean (SD) JIA: 9.2 (3.4) Controls: 9.3 (3.5) **Sex:** JIA: - Female: 70 (60.3%) - Male: 46 (39.7%) Controls: - Female: 70 (60.3%) - Male: 46 (39.7%) **Race/ethnicity:** NR **JIA diagnosis:** JRA (n = 105); Juvenile spondyloarthropathy (n = 11) **Percentage with systemic JIA:** 5 (4.3%) **Baseline severity:** Disease duration (mean [SD]): 12.1 (7.5) months	**Instrument(s) evaluated:** Child Health Questionnaire (CHQ) Physical (Phs) and Psychosocial (PsS) subscales – Norwegian version **Mode of administration:** Self administered: "Most of the data in this study are taken from the parents' questionnaires" Improvement defined using ACR criteria: 30% improvement from baseline to followup in at least 3 of 6 core variables and a maximum of one variable worsening by > 30%	**1) Reliability:** - Test-retest: NR - Inter-rater: Parent vs. patient: Intraclass correlation coefficient for child vs. parent ranged from 0.69 to 0.87 ($p < 0.001$) for concepts related to physical functioning Ranged from 0.38 to 0.53 for mental health, self esteem, and behavior ($p = 0.038$ to 0.003) Compared to controls, scores for JIA patients showed statistically significantly poorer physical health and parental concepts but no difference in psychosocial factors (except role emotional/behavioral) - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus radiological results: NR - Versus clinical outcomes: Pearson's correlation coefficients (PhS; PsS): Parent's pain VAS: -0.624*; -0.143 ($p = 0.129$) Parent's global: -0.661*; -0.315* Physician global: -0.556*; -0.048 ($p = 0.609$) No active joints: -0.360*; -0.024 ($p = 0.802$)	**General comments:** - No comment on blinding - Multiple JIA subtypes included, but small number of subtypes other than oligoarticular and polyarticular - < 80% at followup - Discriminate validity vs. health controls is not particularly useful for our question of the validity/reliability/ responsiveness as used in trials of children with JIA **Quality assessment:** - Fair quality - Blinding not addressed - Followup rate uncertain but approximately 116/150 (77%) - No sample size calculation

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Active joint count (mean [CI]): 2.2 (1.5, 2.8) Arthritis activity index (mean [CI]): 6.8 (4.8, 8.8) Physician global (mean [CI]): 2.4 (2.3, 2.6) on a scale of 1-5 **Inclusion criteria:** - JIA - Disease duration < 2.5 years **Exclusion criteria:** NR		- Versus lab results: ESR: -0.479*; 0.006 (p = 0.951) - New instrument versus established instrument: CHQ vs CHAQ: -0.57; -0.219 (p = 0.018) * p < 0.001 **3) Other:** - Feasibility: NR - Responsiveness: Standardized response mean (SRM) for CHQ if pts Improved (n = 45): 0.96 Worsened (n = 14): -0.60 Unchanged (n = 57): 0.16 - ROC curves: NR	
Singh, Athreya, Fries, et al., 1994 **#1747**	**Geographical location:** Palo Alto, Philadelphia **Setting:** Subspecialty (pediatric rheumatology) **Study design:** Cross-sectional **Study objective(s):** Develop and validate a self/parent administered instrument for measuring functional status in children with JRA **Duration of followup:** Mean of 12.8 days in a	**Number of patients:** 72 JRA patients; 22 healthy controls (face validity only) **Age:** JRA patients: - Mean (SEM): 9.1years (0.6) - Median: NR - Range: 1-19 Controls: - Mean (SEM): 7.9 years (0.8) - Median: NR - Range: 1-17	**Instrument(s) evaluated:** CHAQ **Mode of administration:** Self-administered	**1) 1) Reliability:** - Test-retest (N = 13): Mean time between surveys: 12.8 days Survey #1 mean (SEM): 0.96 (0.26) Survey #2 mean (SEM): 0.96 (0.23) Paired t-test no difference in means (p > 0.9) Spearmans' Correlation: 0.79 (p < 0.002) - Inter-rater (n = 29): Parent vs. patient: Mean (SEM) Parent score = 0.83 (0.26) Patient score = 0.76 (0.16) Paired t-test = no difference in	**General comments:** - No comment on blinding - Face validity assessed by multidisciplinary group **Quality assessment:** - Small sample and eligibility criteria not specified - Blinding not addressed - No sample size calculation

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	subgroup (n = 13)	**Sex:** JRA patients: - Female: 45 (62.5%) - Male: 27 (37.5%) Controls: - Female: 13 (59%) - Male: 9 (41%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA:** 16 (22%) **Baseline severity:** Disease duration: NR Active joint count: NR Other: 4-point scale: Inactive: 9 (13%) Mild: 32 (44%) Moderate: 24 (33%) Severe: 7 (10%) Steinbrocker Functional Class: I: 38 (53%) II: 18 (25%) III: 14 (19%) IV: 2 (3%) **Inclusion criteria:** NR **Exclusion criteria:** NR		means ($p > 0.4$) Spearman's correlation = 0.84 ($p < 0.001$) - Intra-rater: NR - Internal reliability: Cronbach's alpha = 0.94 **2) Validity:** - Versus radiological results: NR - Versus clinical outcomes (Kendall's tau b): Steinbrocker functional class: 0.77 Number of involved joints: 0.67 - Physician assessment of disease activity: 0.67 - Versus lab results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Stephens, Singh-Grewal, Bar-Or, et al., 2007 **#1548**	**Geographical location:** Toronto, Ontario **Setting:** Specialty clinic **Study design:** RCT **Study objective(s):** To determine the reliability of formal exercise testing and of functional and activity questionnaires in children with JIA **Duration of followup:** 2-6 weeks	**Number of patients:** 80 enrolled 74 completed (5 dropped out after test 1, 1 patient dropped out due to change in diagnosis) **Age:** - Mean (SD): 11.4 (2.3) - Median: NR - Range: 8-16 years **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 5 (7%) **Baseline severity:** Time since diagnosis (disease duration): 3.74 (3.21) Active joint count (mean [SD]): 2.84 (5.8) **Inclusion criteria:** Children with JIA **Exclusion criteria:** - Unstable disease (defined as being likely to change medication regimen within the next 12 weeks) - Cardiac, pulmonary, or metabolic disease	**Instrument(s) evaluated:** CHAQ-DI **Mode of administration:** Self-administered	**1) Reliability:** - Test-retest: ICC = 0.82 - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- Moderate or severe hip pain when walking - Active systemic features - Engaged in > 3 hours per week of structured physical activity			
Sztajnbok, Coronel-Martinez, Diaz-Maldo-nado, et al., 2007 **#1568**	**Geographical location:** Genova, Italy **Setting:** Subspecialty **Study design:** Cross-sectional cohort **Study objective(s):** Examine the discrepancy between the physician's and parent's global assessments of disease status and the factors explaining discordance **Duration of followup:** NA	**Number of patients:** 197 **Age:** - Mean: 8.4 (4.5) - Median: 8.2 - Range: 1.2-22.3 **Sex:** - Female: 146 (74.1%) - Male: 51 (25.9%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 15 (7.6) **Baseline severity:** Disease duration (mean [SD]): 3.9 (3.7) Active joint count: Mean (SD): 3.9 (4.5) Median: 2.0 Range: 0-26.0 ESR: Mean (SD): 28.8 (24.4) Median: 20.0 Range: 1.0-130 **Inclusion criteria:**	**Instrument(s) evaluated:** Physician Global disease activity (VAS, 10 cm, 10 is worst) Parent Global well-being, (VAS, 10cm, 10 is worst) Parent Pain (VAS, 10 cm, 10 is worst) **Mode of administration:** Physician global – pediatric rheumatologist exam Self-administered (parent)	**1) Reliability:** - Inter-rater: On average, global physician rating higher (worse) than parent Differences (parent-physician rating) ranged from -9.4 to 4.5 (mean -2 ± 2.8, median -1.3) Discordance defined as > 1 cm difference in physician and parent rating: 0 (no discord): 80 (40.6%) Parent < physician = negative discord: 101 (51.3%) Parent > physician = positive discord: 16 (8.1%) Predictors of discord: Duration of disease (shorter disease with positive discord) Second-line drug (greater frequency in those with 0 or positive discord) Patients with no discord or marked positive (> 3 points difference) had significantly lower extension and severity of arthritis based on joint count -Test-retest: NR - Intra-rater: NR	**General comments:** - Much study information obtained from chart review - No comment on if blinded - Are "global disease activity" and "well being" measuring the same constructs? **Quality assessment:** - Large sample, well described - Blinding not addressed - No sample size calculation; discordance definition arbitrary - Issue of looking at discordance of 2 measures when they are actually measuring 2 different things

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- JIA - Seen in study unit between Feb 2002 and Oct 2004 - Had to have physician and parent global at first visit, only mothers filled out parent global **Exclusion criteria:** - CHAQ completed by father		**2) Validity:** - Versus radiological results: NR - Versus clinical outcomes Spearman's correlation coefficient (no p values given): Physician Global versus: Parent pain assessment = 0.53 CHAQ = 0.38 No. of swollen joints = 0.51 No. of joints with pain on ROM/tenderness = 0.47 No. of joints with LROM = 0.4 No. of active joints = 0.47 - Versus lab results: ESR = 0.33 CRP = 0.29 Parent global versus: Physician pain assessment = 0.70 CHAQ = 0.44 No. of swollen joints = 0.42 No. of joints with pain on ROM/tenderness = 0.46 No. of joints with LROM = 0.38 No. of active joints = 0.40 - Versus lab results: ESR = 0.27 CRP = 0.31 - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Takken, van den Eijkhof, Hoijtnik, et al., 2006 **#1578**	**Geographical location:** Netherlands **Setting:** Specialty clinic **Study design:** Cross sectional: 13 Longitudinal cohort: 63 **Study objective(s):** Examine the psychometric characteristics of the CHAQ-DI **Duration of followup:** NR	**Number of patients:** 76 total, 321 measures **Age:** - Mean (SD): 9.19 years (2.54) - Median: NR - Range: 4.8-15.8 years **Sex:** - Female: 56 (74%) - Male: 20 (26%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Instrument(s) evaluated:** CHAQ (DI) original CHAQ (DI) 29 items CHAQ (DI) 18 itmes **Mode of administration:** Self-administered in Dutch	**1) Reliability:** Test-retest: Partial correlation with severity “average partial correlation with pain and severity within children” Parial correlation pain: CHAQ (DI) original = 0.43 CHAQ (DI) 29 items = 0.54 CHAQ (DI) 18 itmes = 0.57 Partial correlation severity: CHAQ (DI) original = 0.45 CHAQ (DI) 29 items = 0.54 CHAQ (DI) 18 itmes = 0.57 Inter-rater: NR Intra-rater: NR Internal - Cronbach’s alpha: CHAQ (DI) original = 0.88 CHAQ (DI) 29 items = 0.93 CHAQ (DI) 18 itmes = 0.93 **2) Validity:** - Versus clinical outcomes: Correlation with pain (VAS): CHAQ (DI) original = 0.60 CHAQ (DI) 29 items = 0.62 CHAQ (DI) 18 itmes = 0.68 Correlation with severity: CHAQ (DI) original = 0.64 CHAQ (DI) 29 items = 0.64 CHAQ (DI) 18 itmes = 0.67 - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR	**General comments:** Check to ensure citations # 8, 9 10 , 11, 12, 18, 19, 20 are in our database **Quality assessment:** - Fair quality - Small sample - Blinding not reported; severity measure not specified - No sample size; measures not independent

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				3) Other: - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Tennant, Kearns, Turner, et al., 2001 **#1665**	**Geographical location:** Leeds, UK **Setting:** Sub-specialty clinic **Study design:** Cross-sectional **Study objective(s):** Compare and validate four measures of disability and a locally developed functional test. **Duration of followup:** NA	**Number of patients:** 53 **Age:** - Mean (SD): 10.4 (3.1) - Median: 4.7 years - Range: 5-16 years **Sex:** - Female: 37 (70%) - Male: 16 (30%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 7 (14%) **Baseline severity:** Disease duration: Mean (SD): 4 yrs (3.4) Active joint count: Mean (SD): 1.8 (2.6) **Inclusion criteria:** Children with JIA attending a regional JIA center with their parents **Exclusion criteria:** NR	**Instrument(s) evaluated:** CHAQ JAFAR-P JAFAR-C JAFAS TOFT(Turner Observed Functional Test) **Mode of administration:** CHAQ: Self-completed JAFAR-P: Self-completed JAFAR-C: Administered JAFAS: Observed TOFT: Observed Observations made by two experienced occupational therapists	**2) Reliability**: Test-retest: NR Inter-rater (n = 21): Kappa (range for individual items) JAFAS: 0.07-1.00 TOFT: 0.17-1.00 - Intra-rater: NR - Internal – Cronbach's α (n = 38 to 53): CHAQ: 0.90 JAFAR-P: 0.96 JAFAR-C: 0.83 JAFAS: 0.81 TOFT: 0.89 **2) Validity:** - Versus clinical outcomes (n = 37 to 51): Correlation (physician global and active joint count) CHAQ: 0.42*/0.45* JAFAR-P: 0.34^/0.30 (p = ns) JAFAR-C: 0.36^/0.29^ JAFAS: 0.38*/0.40* TOFT: 0.29*/0.20 (p = ns) *p < 0.01; ^p < 0.05 - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness (n = 24):	**General comments:** None **Quality assessment:** - Small sample size; eligibility criteria poorly specified - Blinding not reported - No sample size calculation - Good distribution of JIA subtypes and standard instruments (except TOFT)

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				Effect sizes: CHAQ: 0.22 JAFAR-P: 0.10 JAFAR-C: 0.06 JAFAS: 0.10 - ROC curves: NR Correlation between the JAFAR-P and JAFAR-C: 0.5	
van der Net, Prakken, Helders, et al., 1996 **#1776**	**Geographical location:** Utrecht, The Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** "…to assess the impact of disease on the functional outcomes of patients with polyarticular juvenile chronic arthritis…" **Duration of followup:** NA	**Number of patients:** 23 **Age:** - Mean (SD): 9.8 (4.8) - Median: NR - Range: 2-16 **Sex:** - Female: 17 - Male: 6 **Race/ethnicity:** Caucasian: 20 Asian: 1 Mediterranean: 2 **JIA diagnosis:** JCA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: 4.6 years (SD 4.2; range 0.8-14.2) Active joint count: NR Joint count-tender: Median	**Instrument(s) evaluated:** All in Dutch Childhood Health Assessment Questionnaire (CHAQ); n = 23 parent, n = 16 child Juvenile Arthritis Functional Assessment Report (JAFAR); n = 17 parent, n = 16 child Juvenile Arthritis Functional Assessment Scale (JAFAS), n = 17 **Mode of administration:** NR	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity: Spearman correlation coefficients** - Versus clinical outcomes: Joint count on tenderness (scored 0-198): CHAQ-c: 0.50 CHAQ-p: 0.51* JAFAR-c: 0.49 JAFAR-p: 0.47 JAFAS: 0.10 - Versus lab results: NR - Versus radiological results: Radiographic evaluation score of both wrists (scored 0-5): CHAQ-c: 0.21 CHAQ-p: 0.48* JAFAR-c: 0.31 JAFAR-p: 0.32 JAFAS: 0.22 - New instrument versus established instrument: NR	**General comments:** Also correlates measures with RF seropositivity, disease duration, and active inflammatory disease **Quality assessment:** - Small sample, uncertain how recruited, eligibility criteria not well specified - Blinding: Not stated - F/U: NA - Analysis: OK

Evidence Table 2. Studies relevant to key question 5 (continued)

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		7.0 (IQR 15.8) CHAQ parent: Median 1.8 (IQR 2.8) JAFAR parent: Median 4.0 (IQR 10.8) JAFAS: Median 1.0 (IQR 3.0) **Inclusion criteria:** Registered in Department of Pediatric Rheumatology as having polyarticular onset JCA **Exclusion criteria:** NR		**3) Other:** - Feasibility: 5 children were too young to complete questionnaires; 2 were unable to complete the JAFAR and CHAQ because of mental disability (Downs syndrome, lack of concentration) - Responsiveness: NR - ROC curves: NR	

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Appendix E. Adverse Events—Wider Literature Search

Note: In Parts 1-5 of the following table, the first six columns contain identical information; only the adverse events listed in columns 7-12 vary. A list of studies cited is provided at the end of Part 5 of the table.

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	66	-	-	71	30	-
				Total	**191**	**66**	**-**	**-**	**71**	**30**	**-**
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Cimaz et al., 2010[4]	Case report	1	Adalimumab	1	-	-	-	-	1	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab	85	-	5	-	4	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab + MTX	86	-	5	-	6	-	-
				Total	**343**	**-**	**10**	**-**	**10**	**1**	**-**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
Anakinra	Canna et al., 2009[6]	Case reports	3	Anakinra	3	3	-	-	-	-	-
	Ilowite et al., 2009[7]	RCT	86	Anakinra	86	15	86	-	-	-	-
	Kone-Paut et al., 2007[8]	Case report	1	Anakinra	1	-	1	-	-	-	-
	Lequerre et al., 2008[9]	Series	20	Anakinra	20	-	2	-	2	-	-
	Ohlsson et al., 2008[10]	Series	7	Anakinra	7	1	1	-	1	-	-
	Zeft et al., 2009[11]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**149**	**19**	**90**	**-**	**3**	**-**	**-**
Etanercept	Bloom, 2000[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Bout-Tabaku et al., 2007[13]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Dallocchio et al., 2010[14]	Case reports	8	Etanercept	8	8	-	-	-	-	-
	Elwood et al., 2003[15]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[16]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	103	Etanercept	103	-	-	-	-	3	-
	Horneff et al., 2009[18]	Series	20	Etanercept	20	1	15	-	1		

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Horneff et al., 2009[19]	Series	604	Etanercept	100	-	2	-	-	-	2
	Hung et al., 2005[20]	Case reports	3	Etanercept	3	-	-	-	1	-	-
	Kimura et al., 2005[21]	Series	82	Etanercept	82	-	-	3	-	-	-
	Kunzmann et al., 2005[22]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Lepore et al., 2003[23]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[24]	Case report	1	Etanercept	1	-	2	-	-	-	-
	Lovell et al., 2000[25]	Series	69	Etanercept	69	10	7	-	38	-	-
	Lovell et al., 2003[26]	Series	58	Etanercept	58	-	16	-	80	-	5
	Mangge et al., 2003[27]	Case report	1	Etanercept	1	-	1	-	-	-	-
	Mene et al., 2010[28]	Case report	1	Etanercept	1	-	-	1	-	-	-
	Mori et al., 2005[29]	Series	22	Etanercept	22	4	2	-	12	-	-
	Morishita et al., 2010[30]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Peek et al., 2006[31]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Prince et al., 2009[32]	Series	146	Etanercept	146	6	2	-	-	1	-
	Quartier et al., 2003[33]	Series	61	Etanercept	61	10	11	-	-	-	3

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Ramanan et al., 2003[34]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Robinson et al., 2003[35]	Series	21	Etanercept	21	-	-	-	-	-	-
	Skytta et al., 2000[36]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[37]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[38]	Series	8	Etanercept	8	-	-	-	6	-	-
	Tauber et al., 2005[39]	Case reports	2	Etanercept	2	-	-	-	-	-	2
	Tauber et al., 2006[40]	Case reports	2	Etanercept	2	-	-	-	-	-	2
	Tynjala et al., 2007[41]	Series	45	Etanercept	24	-	1	-	1	-	3
	Tzaribachev et al., 2008[42]	Series	25	Etanercept	25	-	-	-	-	-	-
	Wiegering et al., 2010[43]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Aikawa et al., 2009[44]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Billiau et al., 2010[45]	Series	16	Etanercept + MTX	16	-	-	-	-	-	-
	Fitch et al., 2006[46]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	294	Etanercept + MTX	294	-	-	-	1	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Holl-Wieden et al., 2008[47]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2004[48]	Series	322	Etanercept +MTX	322	3	11	-	1	2	1
	Horneff et al., 2009[19]	Series	604	Etanercept + MTX	504	2	16	3	3	15	9
	Kuemmerle-Deschner et al., 2007[49]	Series	12	Etanercept + MTX	12	-	1	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Correspondence	1	Etanercept + MTX	1	-	-	-	-	-	-
				Total	**1929**	**46**	**87**	**7**	**144**	**22**	**27**
				Incidence – Etanercept		**2%**	**5%**	**0%**	**7%**	**1%**	**1%**
IVIG	Aggarwal et al., 2004 [51]	Series	214	IVIG	1	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Prieur et al., 1990[53]	Series	16	IVIG	16	-	-	1	-	-	-
	Silverman et al., 1994 [54]	RCT	31	IVIG	14	-	-	-	-	-	-
	Uziel et al., 1996 [55]	Series	27	IVIG	27	-	-	1	-	-	-
				Total	**60**	**-**	**-**	**2**	**-**	**-**	**-**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
Infliximab	Armbrust et al., 2004[56]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Becker et al., 2004[57]	Case reports	3	Infliximab	3	-	3	-	-	-	-
	Corona et al., 2004[58]	Series	9	Infliximab	9	-	2	2	-	-	-
	Billiau et al., 2002[59]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Katsicas et al., 2005 [60]	Series	6	Infliximab	6	-	1	-	-	-	-
	Lahdenne et al., 2003 [61]	Series	24	Infliximab	14	-		-	-	-	-
	Mangge et al., 2003 [62]	Case report	1	Infliximab	1	-	1	-	-	-	-
	Morishita et al., 2010[30]	Case reports	2	Infliximab	2	-	-	-	-	-	-
	Pipitone et al., 2005 [63]	Case report	1	Infliximab	1	-	1	-	-	-	-
	Simonini et al., 2008[64]	Series	15	Infliximab	15	-	-	-	-	-	-
	Tutar et al., 2004[65]	Case reports	2	Infliximab	2	-	-	-	-	-	1
	Tyler et al., 2007[66]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[41]	Series	45	Infliximab	21	-	-	-	-	-	-
	Ruperto et al., 2007[67]	RCT	122	Infliximab + MTX	60	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Ruperto et al., 2010[68]	Post-RCT open-label trial	78	Infliximab + MTX	78	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Case reports	2	Infliximab + MTX + etanercept	2	-	-	-	-	-	-
				Total	**219**	**-**	**8**	**2**	**-**	**-**	**1**
Leflunomide	Foeldvari and Wierk, 2010[69]	Series	58	Leflunomide	58	4	-	-	-	-	-
	Silverman et al., 2005[70]	RCT	94	Leflunomide	47	3	3	-	21	-	3
	Silverman et al., 2005[71]	Series	27	Leflunomide	27	8	5	-	9	-	
				Total	**132**	**15**	**8**	**-**	**30**	**-**	**3**
Tocilizumab	Woo et al., 2005[72]	RCT	18	Tocilizumab	18	-	-	-	-	-	-
	Yokota et al., 2008[73]	RCT	56	Tocilizumab	56	17	-	-	52	-	-
				Total	**74**	**17**	**-**	**-**	**52**	**-**	**-**
				Total – Biologics	**3097**	**163**	**203**	**11**	**310**	**53**	**31**
				Incidence – Biologics		**5%**	**7%**	**0%**	**10%**	**2%**	**1%**
NON-BIOLOGIC AGENTS											

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
Azathioprine	Aggarwal et al., 2004[51]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[74]	RCT	32	Azathioprine	17	-	1	-	-	-	-
	Lin et al., 2000[75]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[76]	Series	129	Azathioprine	129	-	2	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	**-**	**3**	-	-	-	-
Cyclosporine A	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[77]	Case reports	50 35 w/ JRA	Cyclosporine A	50	3	-	16	-	-	-
	Gerloni et al., 2001[78]	Series	41	Cyclosporine A	41	2	-	16	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[79]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Mateicka et al., 1994[80]	Series	3	Cyclosporine A	3	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Murphy et al., 1993[81]	Case report	1	Cyclosporine A	1	1	-	-	-	-	-
	Ostensen et al., 1988[82]	Series	14	Cyclosporine A	14	-	-	17	-	-	-
	Pistoia et al., 1993[83]	Series	9	Cyclosporine A	9	-	-	-	-	-	-
	Ruperto et al., 2006[84]	Series	329	Cyclosporine A	329	6	-	6	-	2	-
	Ravelli et al., 2002[85]	Series	17	Cyclosporine A + MTX	17	4	-	1	-	-	-
				Total	**468**	**16**	**-**	**56**	**-**	**2**	**-**
Penicillamine	Aggarwal et al., 2004[51]	Series	214	Penicillamine	23	-	2	1	-	-	-
	Kvien et al., 1985[86]	RCT	77	Penicillamine	38	7	1	1	-	-	-
	Prieur et al., 1985[87]	RCT	74	Penicillamine	74	6	3	-	-	-	-
	Sahn et al., 1989[88]	Case report	1	Penicillamine	1	-	-	-	-	-	-
	Brewer et al., 1986[89]	RCT	162	Penicillamine	54	-	4	-	-	-	1
	Kvien et al., 1985[90]	RCT	72	Penicillamine	24	4	1	1	-	-	-
	Swartz et al., 1984[91]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	**17**	**11**	**3**	**-**	**-**	**1**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
Methotrexate	Aggarwal et al., 2004[51]	Series	214	Methotrexate	118	5	-	-	-	-	-
	Arakawa et al., 2003[92]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	Becker et al., 2010[93]	Series	220	Methotrexate	220	-	-	-	-	-	-
	Chedeville et al., 2005[94]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Cleary et al., 2002[95]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	Corona et al., 1993[96]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[97]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	de Castro et al., 2003[52]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Douglas Graham et al., 1992[98]	Series	62	Methotrexate	62	4	0	-	0	-	-
	Falcini et al., 1997[99]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[100]	RCT	127	Methotrexate	86	-	1	1	-	-	-
	Giannini et al., 2009[17]	Series	197	Methotrexate	197	-	-	-	2	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Gottlieb et al., 1997[101]	Series	25	Methotrexate	25	1	-	-	-	-	-
	Graham et al., 1992[102]	Series	62	Methotrexate	62	4	-	-	-	-	-
	Halle et al., 1991[103]	Series	30	Methotrexate	30	-	-	-	-	-	-
	Huang et al., 1996[104]	Series	26	Methotrexate	26	1	-	-	-	-	-
	Hunstad et al., 2007[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[106]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2006[107]	Series	84	Methotrexate	46	4	-	-	-	-	-
	Lee et al., 2009[108]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	Lin et al., 2000[109]	Series	52	Methotrexate	52	11	-	-	-	-	-
	Londino et al., 1998[110]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[111]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[112]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[113]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[114]	Case report	1	Methotrexate	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Ravelli et al., 1996[115]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[116]	Series	256	Methotrexate	256	44	1			26	
	Ravelli et al., 2001[117]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[118]	Series	57	Methotrexate	20	6	-	-	1	-	-
	Rose et al., 1990[119]	Series	29	Methotrexate	29	2	-	-	-	-	-
	Ruperto et al., 2004[120]	RCT	595	Methotrexate	595	-	-	-	-	-	-
	Russo et al., 2000[121]	Series	20	Methotrexate	20	-	-	-	-	-	-
	Savolainen et al., 2001[122]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Schmeling et al., 2005[123]	Series	58	Methotrexate	58	20	-	-	-	-	-
	Silverman et al., 2005[70]	RCT	94	Methotrexate	47	1	3	-	25	-	2
	Speckmaier et al., 1989[124]	Series	12	Methotrexate	12	1	-	-	-	-	-
	Takeyama et al., 2006[125]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Truckenbrodt et al., 1986[126]	Series	19	Methotrexate	12	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	van der Meer et al., 2007[127]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Wallace et al., 1992[128]	Series	13	Methotrexate	13	-	-	-	-	-	-
	Yildirim et al., 2000[129]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Kocharla et al., 2009[130]	Series	588	Methotrexate + folic acid	198	-	-	-	-	-	-
				Total	**2411**	**100**	**5**	**-**	**32**	**26**	**2**
				Incidence – Methotrexate		**4%**	**0%**	**-**	**3%**	**2%**	**0%**
Sulfasalazine	Balci et al., 2009[131]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[132]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[133]	Series	24	Sulfasalazine	24	-	1	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzbergerten Cate et al., 1991[134]	Series	3	Sulfasalazine	3	-	3	-	-	-	-
	Imundo et al., 1996[135]	Series	139	Sulfasalazine	139	8	18	-	-	-	-
	Joos et al., 1991[136]	Series	41	Sulfasalazine	41	2	1	-	-	-	-
	van Rossum et al., 1998[137]	RCT	69	Sulfasalazine	35	-	9	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	van Rossum et al., 2007[138]	Series	61	Sulfasalazine	32	-	1	-	-	-	-
	Aggarwal et al., 2004[51]	Series	214	Sulfasalazine	28	-	3	-	-	-	-
	Ansell et al., 1991[139]	Series	51	Sulfasalazine	51	-	6	-	-	-	-
	Gedalia et al., 1993[140]	Series	10	Sulfasalazine	10	-	1	-	-	-	-
	Gunnarson et al., 1997[141]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[142]	Series	15	Sulfasalazine	15	-	-	-	-	-	-
	Huang et al., 1998[143]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Kummerle-Deschner et al., 1995[144]	Case report	1	Sulfasalazine	1	-	1	-	-	-	-
	Ozdogan et al., 1986[145]	Series	18	Sulfasalazine	18	-	1	-	-	-	-
	Pinana et al., 2010[146]	Case report	1	Sulfasalazine	1	-	1	-	-	-	-
	Settas et al., 1991[147]	Series	18	Sulfasalazine	18	4	2	-	-	-	-
	Varbanova et al., 1999[148]	Series	32	Sulfasalazine	32	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 1 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
				Total	**476**	**14**	**48**	**-**	**-**	**-**	**-**
				Incidence – Sulfasalazine		**3%**	**10%**	-	-	-	-
OTHER											
	Flato et al., 1998[149]	Series	117	DMARDs	28	-	3	1	-	-	2
	Lomater et al., 1994[150]	Series	7	Plaquenil + MTX + gold salts	7	-	-	-	-	-	-
	Barash et al., 199[151]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	12	19	-	17	35	-
				Total	**191**	**12**	**19**	**-**	**17**	**35**	**-**
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Cimaz et al., 2010[4]	Case report	1	Adalimumab	1	-	-	-	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab	85	-	2	-	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab + MTX	86	-	4	-	-	-	-
				Total	**343**	**-**	**6**	-	-	-	-
Anakinra	Canna et al., 2009[6]	Case reports	3	Anakinra	3	-	-	-	-	-	-
	Ilowite et al., 2009[7]	RCT	86	Anakinra	86	14	13	-	7	92	26
	Kone-Paut et al., 2007[8]	Case report	1	Anakinra	1	1	-	-	-	-	1
	Lequerre et al., 2008[9]	Series	20	Anakinra	20	-	-	-	-	2	-
	Ohlsson et al., 2008[10]	Series	7	Anakinra	7	-	-	-	-	-	3
	Zeft et al., 2009[11]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**149**	**15**	**13**	**-**	**7**	**94**	**30**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
Etanercept	Bloom, 2000[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Bout-Tabaku et al., 2007[13]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Dallocchio et al., 2010[14]	Case reports	8	Etanercept	8	-	-	-	-	-	-
	Elwood et al., 2003[15]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[16]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	103	Etanercept	103	-	-	-	-	1	-
	Horneff et al., 2009[18]	Series	20	Etanercept	20	2	2	-	-	3	1
	Horneff et al., 2009[19]	Series	604	Etanercept	100	-	4	-	-	2	-
	Hung et al., 2005[20]	Case reports	3	Etanercept	3	2	-	-	-	-	-
	Kimura et al., 2005[21]	Series	82	Etanercept	82	-	-	-	-	12	3
	Kunzmann et al., 2005[22]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[23]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[25]	Series	69	Etanercept	69	-	10	-	-	25	1

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Lovell et al., 2003[26]	Series	58	Etanercept	58	6	8	-	-	63	
	Mangge et al., 2003[27]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mene et al., 2010[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mori et al., 2005[29]	Series	22	Etanercept	22	-	2	-	-	5	-
	Morishita et al., 2010[30]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Peek et al., 2006[31]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[32]	Series	146	Etanercept	146	7	9	1	-	7	-
	Quartier et al., 2003[33]	Series	61	Etanercept	61	-	-	1	1	9	-
	Ramanan et al., 2003[34]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Robinson et al., 2003[35]	Series	21	Etanercept	21	-	-	-	-	-	-
	Skytta et al., 2000[36]	Case reports	2	Etanercept	2	-	-	-	-	-	2
	Smith et al., 2005[37]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[38]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[39]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[40]	Case reports	2	Etanercept	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Tynjala et al., 2007[41]	Series	45	Etanercept	24	-	-	-	-	-	-
	Tzaribachev et al., 2008[42]	Series	25	Etanercept	25	1	-	-	-	-	-
	Wiegering et al., 2010[43]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Aikawa et al., 2009[44]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Billiau et al., 2010[45]	Series	16	Etanercept + MTX	16	-	-	-	-	-	-
	Fitch et al., 2006[46]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	294	Etanercept + MTX	294	-	-	-	-	6	-
	Holl-Wieden et al., 2008[47]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2004[48]	Series	322	Etanercept + MTX	322	5	2	-	-	12	6
	Horneff et al., 2009[19]	Series	604	Etanercept + MTX	504	2	3	-	4	19	-
	Kuemmerle-Deschner et al., 2007[49]	Series	12	Etanercept + MTX	12	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Correspondence	1	Etanercept + MTX	1	-	-	-	-	-	-
				Total	**1929**	**25**	**40**	**2**	**5**	**164**	**13**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
				Incidence – Etanercept		**1%**	**2%**	**0%**	**0%**	**9%**	**1%**
IVIG	Aggarwal et al., 2004 [51]	Series	214	IVIG	1	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Prieur et al., 1990[53]	Series	16	IVIG	16	-	-	-	-	-	-
	Silverman et al., 1994 [54]	RCT	31	IVIG	14	2	-	-	-	1	-
	Uziel et al., 1996 [55]	Series	27	IVIG	27	-	-	-	-	-	-
				Total	**60**	**2**	-	-	-	**1**	**-**
Infliximab	Armbrust et al., 2004[56]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Becker et al., 2004[57]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Billiau et al., 2002[59]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Corona et al., 2004[58]	Series	9	Infliximab	9	-	-	-	-	-	-
	Katsicas et al., 2005 [60]	Series	6	Infliximab	6	-	-	-	-	-	4
	Lahdenne et al., 2003 [61]	Series	24	Infliximab	14	-	-	-	-	-	-
	Mangge et al., 2003 [62]	Case report	1	Infliximab	1	-	-	-	1	1	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Morishita et al., 2010[30]	Case reports	2	Infliximab	2	-	-	-	-	-	-
	Pipitone et al., 2005 [63]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Simonini et al., 2008[64]	Series	15	Infliximab	15	-	-	-	-	-	-
	Tutar et al., 2004[65]	Case reports	2	Infliximab	2	2	-	-	-	-	-
	Tyler et al., 2007[66]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[41]	Series	45	Infliximab	21	-	-	-	-	-	-
	Ruperto et al., 2007[67]	RCT	122	Infliximab + MTX	60	-	-	-	-	-	-
	Ruperto et al., 2010[68]	Post-RCT open-label trial	78	Infliximab + MTX	78	18	17	-	-	19	-
	Yildirim-Toruner et al., 2008[50]	Case reports	2	Infliximab	2	-	-	-	-	-	-
				Total	**219**	**20**	**17**	**-**	**1**	**20**	**4**
Leflunomide	Foeldvari and Wierk, 2010[69]	Series	58	Leflunomide	58	-	-	-	7	-	-
	Silverman et al., 2005[70]	RCT	94	Leflunomide	47	4	13	-	7	32	-
	Silverman et al., 2005[71]	Series	27	Leflunomide	27	-	8	-	7	24	-
				Total	**132**	**4**	**21**		**21**	**56**	

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
Tocilizumab	Woo et al., 2005[72]	RCT	18	Tocilizumab	18	-	-	-	-	-	1
	Yokota et al., 2008[73]	RCT	56	Tocilizumab	56	-	-	-	-	-	-
				Total	**74**	-	-	-	-	-	**1**
				Total – Biologics	**3097**	**78**	**116**	**2**	**44**	**370**	**48**
				Incidence – Biologics		**3%**	**4%**	**0%**	**2%**	**12%**	**2%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[51]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[74]	RCT	32	Azathioprine	17	1	1	-	-	1	-
	Lin et al., 2000[75]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[76]	Series	129	Azathioprine	129	-	1	-	-	9	1
	de Castro et al., 2003[52]	Case reports	5	Azathioprine + MTX	5	-	1	-	-	-	-
				Total	**182**	**1**	**3**			**10**	**1**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
Cyclosporine A	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[77]	Case reports	50 35 w/ JRA	Cyclosporine A	50	-	-	-	-	-	-
	Gerloni et al., 2001[78]	Series	41	Cyclosporine A	41	-	-	-	-	1	-
	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[79]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Mateicka et al., 1994[80]	Series	3	Cyclosporine A	3	-	-	-	-	-	-
	Murphy et al., 1993[81]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[82]	Series	14	Cyclosporine A	14	-	-	-	-	-	-
	Pistoia et al., 1993[83]	Series	9	Cyclosporine A	9	-	-	-	-	-	-
	Ruperto et al., 2006[84]	Series	329	Cyclosporine A	329	-	-	-	-	-	-
	Ravelli et al., 2002[85]	Series	17	Cyclosporine A + MTX	17	-	-	-	-	-	-
				Total	**468**	-	-	-	-	**1**	**-**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
Penicillamine	Aggarwal et al., 2004[51]	Series	214	Penicillamine	23	-	-	-	-	-	-
	Kvien et al., 1985[86]	RCT	77	Penicillamine	38	-	-	-	-	1	-
	Prieur et al., 1985[87]	RCT	74	Penicillamine	74	-	-	-	-	-	-
	Sahn et al., 1989[88]	Case report	1	Penicillamine	1	-	-	-	-	-	-
	Brewer et al., 1986[89]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[90]	RCT	72	Penicillamine	24	-	-	-	-	-	-
	Swartz et al., 1984[91]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	-	-	-	-	**1**	**-**
Methotrexate	Aggarwal et al., 2004[51]	Series	214	Methotrexate	118	-	-	-	-	-	-
	Arakawa et al., 2003[92]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Becker et al., 2010[93]	Series	220	Methotrexate	220	-	-	-	-	-	-
	Chedeville et al., 2005[94]	Series	27	Methotrexate	27	-	4	-	-	-	-
	Cleary et al., 2002[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Corona et al., 1993[96]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	de Castro et al., 2003[52]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Douglas Graham et al., 1992[98]	Series	62	Methotrexate	62	-	14	-	-	-	-
	Falcini et al., 1997[99]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[100]	RCT	127	Methotrexate	86	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	197	Methotrexate	197	-	-	-	-	-	-
	Gottlieb et al., 1997[101]	Series	25	Methotrexate	25	-	-	-	-	-	-
	Graham et al., 1992[102]	Series	62	Methotrexate	62	-	14	-	-	-	-
	Halle et al., 1991[103]	Series	30	Methotrexate	30	-	6	-	-	-	-
	Huang et al., 1996[104]	Series	26	Methotrexate	26	-	-	-	-	-	-
	Hunstad et al., 2007[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[106]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2006[107]	Series	84	Methotrexate	46	-	15	-	-	-	-
	Lee et al., 2009[108]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[109]	Series	52	Methotrexate	52	-	11	-	11	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Londino et al., 1998[110]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[111]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[112]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[113]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[114]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1996[115]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[116]	Series	256	Methotrexate	256	-	-	-	-	-	-
	Ravelli et al., 2001[117]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[118]	Series	57	Methotrexate	20	-	9	3	2	3	
	Rose et al., 1990[119]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Ruperto et al., 2004[120]	RCT	595	Methotrexate	595	-	26	6	-	-	-
	Russo et al., 2000[121]	Series	20	Methotrexate	20	-	1	2	-	1	-
	Savolainen et al., 2001[122]	Case reports	2	Methotrexate	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Schmeling et al., 2005[123]	Series	58	Methotrexate	58	-	-	-	-	-	-
	Silverman et al., 2005[70]	RCT	94	Methotrexate	47	1	16	-	8	22	-
	Speckmaier et al., 1989[124]	Series	12	Methotrexate	12	-	-	-	-	-	-
	Takeyama et al., 2006[125]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Truckenbrodt et al., 1986[126]	Series	19	Methotrexate	12	-	-	-	-	-	-
	van der Meer et al., 2007[127]	Series	29	Methotrexate	29	-	20	-	-	-	-
	Wallace et al., 1992[128]	Series	13	Methotrexate	13	-	2	-	-	-	-
	Yildirim et al., 2000[129]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Kocharla et al., 2009[130]	Series	588	Methotrexate + folic acid	198	-	-	-	-	-	-
				Total	**2411**	**1**	**138**	**11**	**21**	**26**	**-**
				Incidence – Methotrexate		**0%**	**6%**	**1%**	**2%**	**2%**	**-**
Sulfasalazine	Balci et al., 2009[131]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[132]	RCT	33	Sulfasalazine	17	-	-	-	-	4	-
	Chen et al., 2002[133]	Series	24	Sulfasalazine	24	-	2	-	-	2	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	de Castro et al., 2003[52]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzbergerten Cate et al., 1991[134]	Series	3	Sulfasalazine	3	3	2	-	-	-	-
	Imundo et al., 1996[135]	Series	139	Sulfasalazine	139	5	-	-	-	3	-
	Joos et al., 1991[136]	Series	41	Sulfasalazine	41	-	-	-	-	-	-
	van Rossum et al., 1998[137]	RCT	69	Sulfasalazine	35	-	10	10	5	26	1
	van Rossum et al., 2007[138]	Series	61	Sulfasalazine	32	1	-	-	-	-	-
	Aggarwal et al., 2004[51]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[139]	Series	51	Sulfasalazine	51	1	1	-	2	1	
	Gedalia et al., 1993[140]	Series	10	Sulfasalazine	10	-	-	-	-	-	-
	Gunnarson et al., 1997[141]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[142]	Series	15	Sulfasalazine	15	-	1	-	2	1	-
	Huang et al., 1998[143]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 2 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Kummerle-Deschner et al., 1995[144]	Case report	1	Sulfasalazine	1	-	-	-	-	-	1
	Ozdogan et al., 1986[145]	Series	18	Sulfasalazine	18	-	1	-	2	1	-
	Pinana et al., 2010[146]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Settas et al., 1991[147]	Series	18	Sulfasalazine	18	-	8	4	-	6	-
	Varbanova et al., 1999[148]	Series	32	Sulfasalazine	32	-	1	-	-	1	-
				Total	**476**	**10**	**26**	**14**	**11**	**45**	**1**
				Incidence – Sulfasalazine		**2%**	**5%**	**3%**	**2%**	**9%**	**0%**
OTHER											
	Flato et al., 1998[149]	Series	117	DMARDs	28	-	2	-	2	3	2
	Lomater et al., 1994[150]	Series	7	Plaquenil + MTX + gold salts	7	-	1	-	-	-	-
	Barash et al., 199[151]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	-	-	-	-	17	-
				Total	**191**	-	-	-	-	**17**	-
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Cimaz et al., 2010[4]	Case report	1	Adalimumab	1	-	-	-	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab	85	-	-	1	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab + MTX	86	-	-	-	-	-	-
				Total	**343**	-	-	**1**	-	-	-
Anakinra	Canna et al., 2009[6]	Case reports	3	Anakinra	3	-	-	-	-	-	-
	Ilowite et al., 2009[7]	RCT	86	Anakinra	86	9	-	-	-	5	-
	Kone-Paut et al., 2007[8]	Case report	1	Anakinra	1	-	-	-	-	-	-
	Lequerre et al., 2008[9]	Series	20	Anakinra	20	-	-	-	-	-	-
	Ohlsson et al., 2008[10]	Series	7	Anakinra	7	-	-	-	-	1	-
	Zeft et al., 2009[11]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**149**	**9**	-	-	-	**6**	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
Etanercept	Bloom, 2000[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Bout-Tabaku et al., 2007[13]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Dallocchio et al., 2010[14]	Case reports	8	Etanercept	8	-	-	-	-	-	-
	Elwood et al., 2003[15]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[16]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	103	Etanercept	103	-	-	-	-	-	-
	Horneff et al., 2009[18]	Series	20	Etanercept	20	-	-	-	-	-	-
	Horneff et al., 2009[19]	Series	604	Etanercept	100	-	-	-	-	-	-
	Hung et al., 2005[20]	Case reports	3	Etanercept	3	-	-	-	-	1	-
	Kimura et al., 2005[21]	Series	82	Etanercept	82	-	-	-	-	-	-
	Kunzmann et al., 2005[22]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[23]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[25]	Series	69	Etanercept	69	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Lovell et al., 2003[26]	Series	58	Etanercept	58	-	-	-	-	-	-
	Mangge et al., 2003[27]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mene et al., 2010[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mori et al., 2005[29]	Series	22	Etanercept	22	-	-	-	-	-	-
	Morishita et al., 2010[30]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Peek et al., 2006[31]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[32]	Series	146	Etanercept	146	-	2	-	-	2	-
	Quartier et al., 2003[33]	Series	61	Etanercept	61	-	-	-	-	1	-
	Ramanan et al., 2003[34]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Robinson et al., 2003[35]	Series	21	Etanercept	21	-	-	-	-	-	-
	Skytta et al., 2000[36]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[37]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[38]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[39]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[40]	Case reports	2	Etanercept	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Tynjala et al., 2007[41]	Series	45	Etanercept	24	-	-	-	-	-	-
	Tzaribachev et al., 2008[42]	Series	25	Etanercept	25	-	-	-	-	-	-
	Wiegering et al., 2010[43]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Aikawa et al., 2009[44]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Billiau et al., 2010[45]	Series	16	Etanercept + MTX	16	-	-	-	-	-	-
	Fitch et al., 2006[46]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	294	Etanercept + MTX	294	-	-	-	-	-	-
	Holl-Wieden et al., 2008[47]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2004[48]	Series	322	Etanercept + MTX	322		4	2			1
	Horneff et al., 2009[19]	Series	604	Etanercept + MTX	504	-	1	-	-	-	2
	Kuemmerle-Deschner et al., 2007[49]	Series	12	Etanercept + MTX	12	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Yildirim-Toruner et al., 2008[50]	Correspondence	1	Etanercept + MTX	1	-	-	-	-	-	1
				Total	**1929**	**-**	**7**	**2**	**-**	**4**	**4**
				Incidence – Etanercept		**-**	**0%**	**0%**	**-**	**0%**	**0%**
IVIG	Aggarwal et al., 2004 [51]	Series	214	IVIG	1	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Prieur et al., 1990[53]	Series	16	IVIG	16	-	-	-	-	-	-
	Silverman et al., 1994 [54]	RCT	31	IVIG	14	-	-	-	-	-	-
	Uziel et al., 1996 [55]	Series	27	IVIG	27	-	-	-	-	-	-
				Total	**60**	-	-	-	-	-	-
Infliximab	Armbrust et al., 2004[56]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Becker et al., 2004[57]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Billiau et al., 2002[59]	Case reports	3	Infliximab	3	**-**	**-**	**-**	**-**	**-**	**-**
	Corona et al., 2004[58]	Series	9	Infliximab	9	-	-	-	-	-	-
	Katsicas et al., 2005 [60]	Series	6	Infliximab	6	3	**-**	**-**	**-**	**-**	**-**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Lahdenne et al., 2003 [61]	Series	24	Infliximab	14	-	1	-	-	-	-
	Mangge et al., 2003 [62]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Morishita et al., 2010[30]	Case reports	2	Infliximab	2	-	-	-	-	-	-
	Pipitone et al., 2005 [63]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Simonini et al., 2008[64]	Series	15	Infliximab	15	-	-	-	-	-	-
	Tutar et al., 2004[65]	Case reports	2	Infliximab	2	-	-	-	-	-	-
	Tyler et al., 2007[66]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[41]	Series	45	Infliximab	21	-	3	-	-	-	-
	Ruperto et al., 2007[67]	RCT	122	Infliximab + MTX	60	-	-	-	-	-	-
	Ruperto et al., 2010[68]	Post-RCT open-label trial	78	Infliximab + MTX	78	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Case reports	2	Infliximab + MTX + etanercept	2	-	-	-	-	-	2
				Total	**219**	**3**	**4**	-	-	-	**2**
Leflunomide	Foeldvari and Wierk, 2010[69]	Series	58	Leflunomide	58	-	-	-	-	-	-
	Silverman et al., 2005[70]	RCT	94	Leflunomide	47	-	7	3	-	5	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Silverman et al., 2005[71]	Series	27	Leflunomide	27	-	8	6	-	5	-
				Total	**132**	**-**	**15**	**9**	**-**	**10**	**-**
Tocilizumab	Woo et al., 2005[72]	RCT	18	Tocilizumab	18	-	-	-	-	-	-
	Yokota et al., 2008[73]	RCT	56	Tocilizumab	56	-	-	-	-	-	-
				Total	**74**	-	-	-	-	-	-
				Total – Biologics	**3097**	**12**	**26**	**12**	**0**	**37**	**6**
				Incidence – Biologics		**0%**	**1%**	**0%**	**0%**	**1%**	**0%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[51]	Series	214	Azathioprine	5	**-**	**-**	**-**	**-**	**-**	**-**
	de Castro et al., 2003[52]	Case reports	5	Azathioprine	2	**-**	**-**	**-**	**-**	**-**	**-**
	Kvien et al., 1986[74]	RCT	32	Azathioprine	17	-	1	**-**	**-**	**-**	**-**
	Lin et al., 2000[75]	Series	24	Azathioprine	24	**-**	**-**	**-**	**-**	**-**	**-**
	Savolainen et al., 1997[76]	Series	129	Azathioprine	129	**-**	**-**	**-**	**-**	**-**	**-**
	de Castro et al., 2003[52]	Case reports	5	Azathioprine + MTX	5	**-**	**-**	**-**	**-**	**-**	**-**
				Total	**182**	**-**	**1**	**-**	**-**	**-**	**-**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
Cyclosporine A	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[77]	Case reports	50 35 w/ JRA	Cyclosporine A	50	-	9	-	-	-	-
	Gerloni et al., 2001[78]	Series	41	Cyclosporine A	41	-	12	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[79]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	1
	Mateicka et al., 1994[80]	Series	3	Cyclosporine A	3	-	1	-	-	-	-
	Murphy et al., 1993[81]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[82]	Series	14	Cyclosporine A	14	-	14	-	-	-	-
	Pistoia et al., 1993[83]	Series	9	Cyclosporine A	9	1	2	-	-	-	-
	Ruperto et al., 2006[84]	Series	329	Cyclosporine A	329	-	7	-	-	-	-
	Ravelli et al., 2002[85]	Series	17	Cyclosporine A + MTX	17	-	-	-	-	-	-
				Total	**468**	**-**	**45**	**-**	**-**	**-**	**1**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
Penicillamine	Aggarwal et al., 2004[51]	Series	214	Penicillamine	23	**-**	**-**	**-**	**-**	**-**	**-**
	Kvien et al., 1985[86]	RCT	77	Penicillamine	38	**-**	**-**	2			
	Prieur et al., 1985[87]	RCT	74	Penicillamine	74	**-**	**-**	**-**	**-**	**-**	**-**
	Sahn et al., 1989[88]	Case report	1	Penicillamine	1	**-**	**-**	**-**	**-**	**-**	**-**
	Brewer et al., 1986[89]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[90]	RCT	72	Penicillamine	24	-	-	-	-	-	-
	Swartz et al., 1984[91]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	**-**	**-**	**2**	**-**	**-**	**-**
Methotrexate	Aggarwal et al., 2004[51]	Series	214	Methotrexate	118	-	-	-	-	-	-
	Arakawa et al., 2003[92]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Becker et al., 2010[93]	Series	220	Methotrexate	220	-	-	-	-	-	-
	Chedeville et al., 2005[94]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Cleary et al., 2002[95]	Case report	1	Methotrexate	1	-	-	-	-	-	1
	Corona et al., 1993[96]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	de Castro et al., 2003[52]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Douglas Graham et al., 1992[98]	Series	62	Methotrexate	62	-	2	-	-	-	-
	Falcini et al., 1997[99]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[100]	RCT	127	Methotrexate	86	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	197	Methotrexate	197	-	-	-	-	-	-
	Gottlieb et al., 1997[101]	Series	25	Methotrexate	25	-	-	-	-	1	-
	Graham et al., 1992[102]	Series	62	Methotrexate	62	-	2	-	-	-	-
	Halle et al., 1991[103]	Series	30	Methotrexate	30	-	-	-	-	-	-
	Huang et al., 1996[104]	Series	26	Methotrexate	26	-	-	-	-	-	-
	Hunstad et al., 2007[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[106]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2006[107]	Series	84	Methotrexate	46	-	-	2	-	-	-
	Lee et al., 2009[108]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[109]	Series	52	Methotrexate	52	-	-	1	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Londino et al., 1998[110]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[111]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[112]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[113]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[114]	Case report	1	Methotrexate	1	-	-	-	-	-	1
	Ravelli et al., 1996[115]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[116]	Series	256	Methotrexate	256	-	2	-	-	-	-
	Ravelli et al., 2001[117]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[118]	Series	57	Methotrexate	20	-	-	-	-	-	-
	Rose et al., 1990[119]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Ruperto et al., 2004[120]	RCT	595	Methotrexate	595	-	4	-	-	-	-
	Russo et al., 2000[121]	Series	20	Methotrexate	20	-	-	-	-	-	-
	Savolainen et al., 2001[122]	Case reports	2	Methotrexate	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Schmeling et al., 2005[123]	Series	58	Methotrexate	58	-	3	-	-	-	-
	Silverman et al., 2005[70]	RCT	94	Methotrexate	47	-	3	2	-	-	-
	Speckmaier et al., 1989[124]	Series	12	Methotrexate	12	-	-	-	-	-	-
	Takeyama et al., 2006[125]	Case report	1	Methotrexate	1	-	-	-	-	-	1
	Truckenbrodt et al., 1986[126]	Series	19	Methotrexate	12	-	-	-	-	-	-
	van der Meer et al., 2007[127]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Wallace et al., 1992[128]	Series	13	Methotrexate	13	-	-	-	-	-	-
	Yildirim et al., 2000[129]	Case report	1	Methotrexate	1	-	-	-	-	-	1
	Kocharla et al., 2009[130]	Series	588	Methotrexate + folic acid	198	-	-	-	-	-	-
				Total	**2411**	-	**16**	**4**	-	-	**4**
				Incidence – Methotrexate		-	**1%**	**0%**	-	-	**0%**
Sulfasalazine	Balci et al., 2009[131]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[132]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[133]	Series	24	Sulfasalazine	24	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	de Castro et al., 2003[52]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzbergerten Cate et al., 1991[134]	Series	3	Sulfasalazine	3	1	-	-	-	-	-
	Imundo et al., 1996[135]	Series	139	Sulfasalazine	139	-	-	-	-	-	-
	Joos et al., 1991[136]	Series	41	Sulfasalazine	41	-	-	-	-	-	-
	van Rossum et al., 1998[137]	RCT	69	Sulfasalazine	35	-	-	-	-	-	-
	van Rossum et al., 2007[138]	Series	61	Sulfasalazine	32	-	-	-	-	-	-
	Aggarwal et al., 2004[51]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[139]	Series	51	Sulfasalazine	51	-	-	-	-	-	-
	Gedalia et al., 1993[140]	Series	10	Sulfasalazine	10	-	-	-	-	-	-
	Gunnarson et al., 1997[141]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[142]	Series	15	Sulfasalazine	15	-	-	1	-	-	-
	Huang et al., 1998[143]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 3 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Kummerle-Deschner et al., 1995[144]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Ozdogan et al., 1986[145]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Pinana et al., 2010[146]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Settas et al., 1991[147]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Varbanova et al., 1999[148]	Series	32	Sulfasalazine	32	-	-	-	-	-	-
				Total	**476**	**1**	-	**1**	-	-	-
				Incidence – Sulfasalazine		**0%**	-	**0%**	-	-	-
OTHER											
	Flato et al., 1998[149]	Series	117	DMARDs	28	1	3	-	-	-	-
	Lomater et al., 1994[150]	Series	7	Plaquenil + MTX + gold salts	7	-	-	-	-	-	-
	Barash et al., 199[151]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	79	-	-	-	-	-
				Total	**191**	**79**	-	-	-	-	-
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	5	-	-	-	-	-
	Cimaz et al., 2010[4]	Case report	1	Adalimumab	1	-	-	-	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab	85	11	-	-	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab + MTX	86	18	-	-	-	-	-
				Total	**343**	**34**	-	-	-	-	-
Anakinra	Canna et al., 2009[6]	Case reports	3	Anakinra	3	-	-	-	-	-	-
	Ilowite et al., 2009[7]	RCT	86	Anakinra	86	25	-	-	-	-	-
	Kone-Paut et al., 2007[8]	Case report	1	Anakinra	1	1	-	-	-	-	-
	Lequerre et al., 2008[9]	Series	20	Anakinra	20	5	-	-	-	-	-
	Ohlsson et al., 2008[10]	Series	7	Anakinra	7	1	-	-	-	-	-
	Zeft et al., 2009[11]	Series	32	Anakinra	32	1	-	-	-	-	-
				Total	**149**	**33**	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
Etanercept	Bloom, 2000[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Bout-Tabaku et al., 2007[13]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Dallocchio et al., 2010[14]	Case reports	8	Etanercept	8	-	-	-	-	-	-
	Elwood et al., 2003[15]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Fathalla et al., 2008[16]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	103	Etanercept	103	2	13	-	2	-	-
	Horneff et al., 2009[18]	Series	20	Etanercept	20	11	-	-	-	-	-
	Horneff et al., 2009[19]	Series	604	Etanercept	100	10	-	-	-	-	-
	Hung et al., 2005[20]	Case reports	3	Etanercept	3	-	-	-	-	-	-
	Kimura et al., 2005[21]	Series	82	Etanercept	82	9	-	-	-	-	-
	Kunzmann et al., 2005[22]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[23]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Livermore et al., 2002[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[25]	Series	69	Etanercept	69		1	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Lovell et al., 2003[26]	Series	58	Etanercept	58	9	-	-	-	-	-
	Mangge et al., 2003[27]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mene et al., 2010[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mori et al., 2005[29]	Series	22	Etanercept	22	16	-	-	-	-	-
	Morishita et al., 2010[30]	Case reports	2	Etanercept	2	2	-	-	-	-	-
	Peek et al., 2006[31]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[32]	Series	146	Etanercept	146	8	3	-	-	-	-
	Quartier et al., 2003[33]	Series	61	Etanercept	61	-	8	-	-	-	-
	Ramanan et al., 2003[34]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Robinson et al., 2003[35]	Series	21	Etanercept	21	1	-	-	-	-	-
	Skytta et al., 2000[36]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[37]	RCT	12	Etanercept	7	21	-	-	-	-	-
	Takei et al., 2001[38]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[39]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[40]	Case reports	2	Etanercept	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Tynjala et al., 2007[41]	Series	45	Etanercept	24	2	-	-	-	-	-
	Tzaribachev et al., 2008[42]	Series	25	Etanercept	25	1	-	-	-	-	-
	Wiegering et al., 2010[43]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Aikawa et al., 2009[44]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Billiau et al., 2010[45]	Series	16	Etanercept + MTX	16	2	-	-	-	-	-
	Fitch et al., 2006[46]	Case report	1	Etanercept + MTX	1	1	-	-	-	-	-
	Giannini et al., 2009[17]	Series	294	Etanercept + MTX	294	-	33	-	1	-	-
	Holl-Wieden et al., 2008[47]	Case report	1	Etanercept + MTX	1	1	-	-	-	-	-
	Horneff et al., 2004[48]	Series	322	Etanercept + MTX	322	10	-	-	-	-	-
	Horneff et al., 2009[19]	Series	604	Etanercept + MTX	504	63	-	-	-	-	1
	Kuemmerle-Deschner et al., 2007[49]	Series	12	Etanercept + MTX	12	1	-	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Correspondence	1	Etanercept + MTX	1	-	-	-	-	-	-
				Total	**1929**	**171**	**58**	**-**	**3**	**2**	**1**
				Incidence – Etanercept		**9%**	**3%**	**-**	**0%**	**0%**	**0%**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
IVIG	Aggarwal et al., 2004 [51]	Series	214	IVIG	1	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Prieur et al., 1990[53]	Series	16	IVIG	16	-	-	-	-	-	-
	Silverman et al., 1994 [54]	RCT	31	IVIG	14	-	-	-	-	-	-
	Uziel et al., 1996 [55]	Series	27	IVIG	27	-	-	-	-	1	-
				Total	**60**	**-**	-	-	-	**1**	-
Infliximab	Armbrust et al., 2004[56]	Case report	1	Infliximab	1	1	-	-	-	-	-
	Becker et al., 2004[57]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Billiau et al., 2002[59]	Case reports	3	Infliximab	3	2	-	-	-	-	-
	Corona et al., 2004[58]	Series	9	Infliximab	9	-	-	-	-	-	-
	Katsicas et al., 2005 [60]	Series	6	Infliximab	6	-	-	-	-	-	-
	Lahdenne et al., 2003 [61]	Series	24	Infliximab	14	-	-	-	-	-	-
	Mangge et al., 2003 [62]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Morishita et al., 2010[30]	Case reports	2	Infliximab	2	2	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Pipitone et al., 2005 [63]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Simonini et al., 2008[64]	Series	15	Infliximab	15	-	-	-	-	-	-
	Tutar et al., 2004[65]	Case reports	2	Infliximab	2	1	-	-	-	-	-
	Tyler et al., 2007[66]	Case report	1	Infliximab	1	-	-	-	1	-	-
	Tynjala et al., 2007[41]	Series	45	Infliximab	21	-	-	-	-	-	-
	Ruperto et al., 2007[67]	RCT	122	Infliximab + MTX	60	46	-	-		-	-
	Ruperto et al., 2010[68]	Post-RCT open-label trial	78	Infliximab + MTX	78	57	-	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Case reports	2	Infliximab	2	-	-	-	-	-	-
				Total	**219**	**109**	-	-	**1**	-	-
Leflunomide	Foeldvari and Wierk, 2010[69]	Series	58	Leflunomide	58	-	-	1	-	-	-
	Silverman et al., 2005[70]	RCT	94	Leflunomide	47	6	-	-		-	-
	Silverman et al., 2005[71]	Series	27	Leflunomide	27	12	-	-	4	-	-
				Total	**74132**	**18**	-	**1**	**4**	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
Tocilizumab	Woo et al., 2005[72]	RCT	18	Tocilizumab	18	2	-	-	-	-	-
	Yokota et al., 2008[73]	RCT	56	Tocilizumab	56	1	-	-	-	-	-
				Total	**74**	**3**	-	-	-	-	-
				Total – Biologics	**3097**	**447**	**58**	**1**	**8**	**3**	**1**
				Incidence – Biologics		**14%**	**2%**	**0%**	**0%**	**0%**	**0%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[51]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[74]	RCT	32	Azathioprine	17	3	-	-	-	-	-
	Lin et al., 2000[75]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[76]	Series	129	Azathioprine	129	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	**3**	-	-	-	-	-
Cyclosporine A	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[77]	Case reports	50 35 w/ JRA	Cyclosporine A	50	8	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Gerloni et al., 2001[78]	Series	41	Cyclosporine A	41	3	-	6	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A + MTX	1	-	-	1	-	-	-
	Krugmann et al., 2000[79]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Mateicka et al., 1994[80]	Series	3	Cyclosporine A	3	-	-	1	-	-	-
	Murphy et al., 1993[81]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[82]	Series	14	Cyclosporine A	14	-	-	1	-	-	-
	Pistoia et al., 1993[83]	Series	9	Cyclosporine A	9	-	-	2	-	-	-
	Ruperto et al., 2006[84]	Series	329	Cyclosporine A	329	-	-	6	-	-	-
	Ravelli et al., 2002[85]	Series	17	Cyclosporine A + MTX	17	-	-	-	-	-	-
				Total	**468**	**11**	-	**17**	-	-	-
Penicillamine	Aggarwal et al., 2004[51]	Series	214	Penicillamine	23	-	-	-	-	-	-
	Kvien et al., 1985[86]	RCT	77	Penicillamine	38	-	-	-	-	-	-
	Prieur et al., 1985[87]	RCT	74	Penicillamine	74	2	-	-	-	-	-
	Sahn et al., 1989[88]	Case report	1	Penicillamine	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Brewer et al., 1986[89]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[90]	RCT	72	Penicillamine	24	-	-	-	-	-	-
	Swartz et al., 1984[91]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	**2**	-	-	-	-	-
Methotrexate	Aggarwal et al., 2004[51]	Series	214	Methotrexate	118	2	-	-	4	-	-
	Arakawa et al., 2003[92]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Becker et al., 2010[93]	Series	220	Methotrexate	220	-	-	-	-	-	-
	Chedeville et al., 2005[94]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Cleary et al., 2002[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Corona et al., 1993[96]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Douglas Graham et al., 1992[98]	Series	62	Methotrexate	62	12	-	-	1	-	-
	Falcini et al., 1997[99]	Case report	1	Methotrexate	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Giannini et al., 1992[100]	RCT	127	Methotrexate	86	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	197	Methotrexate	197	-	15	-	1	-	-
	Gottlieb et al., 1997[101]	Series	25	Methotrexate	25	1	-	-	-	-	-
	Graham et al., 1992[102]	Series	62	Methotrexate	62	12	-	-	1	-	-
	Halle et al., 1991[103]	Series	30	Methotrexate	30	1	-	-	-	-	-
	Huang et al., 1996[104]	Series	26	Methotrexate	26	-	-	-	-	-	-
	Hunstad et al., 2007[105]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Keim et al., 1990[106]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2006[107]	Series	84	Methotrexate	46	-	-	-	-	-	-
	Lee et al., 2009[108]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[109]	Series	52	Methotrexate	52	1	-	-	-	-	-
	Londino et al., 1998[110]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[111]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[112]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[113]	Series	89	Methotrexate	89	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Padeh et al., 1997[114]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1996[115]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[116]	Series	256	Methotrexate	256	-	-	-	-	-	-
	Ravelli et al., 2001[117]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[118]	Series	57	Methotrexate	20	-	-	-	-	-	-
	Rose et al., 1990[119]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Ruperto et al., 2004[120]	RCT	595	Methotrexate	595	-	-	-	-	-	-
	Russo et al., 2000[121]	Series	20	Methotrexate	20	-	-	-	-	-	-
	Savolainen et al., 2001[122]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Schmeling et al., 2005[123]	Series	58	Methotrexate	58	-	-	-	-	-	-
	Silverman et al., 2005[70]	RCT	94	Methotrexate	47	2	-	-	-	-	-
	Speckmaier et al., 1989[124]	Series	12	Methotrexate	12	-	1	-	-	-	-
	Takeyama et al., 2006[125]	Case report	1	Methotrexate	1	1	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Truckenbrodt et al., 1986[126]	Series	19	Methotrexate	12	1	-	-	-	-	-
	van der Meer et al., 2007[127]	Series	29	Methotrexate	29	-	17	-	-	-	-
	Wallace et al., 1992[128]	Series	13	Methotrexate	13	-	-	-	-	-	-
	Yildirim et al., 2000[129]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Kocharla et al., 2009[130]	Series	588	Methotrexate + folic acid	198	-	-	-	-	-	-
				Total	**2411**	**34**	**33**	-	**1**	-	-
				Incidence – Methotrexate		**1%**	**1%**	-	**0%**	-	-
Sulfasalazine	Balci et al., 2009[131]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[132]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[133]	Series	24	Sulfasalazine	24	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzbergerten Cate et al., 1991[134]	Series	3	Sulfasalazine	3	-	-	-	-	-	-
	Imundo et al., 1996[135]	Series	139	Sulfasalazine	139	-	-	-	-	-	-
	Joos et al., 1991[136]	Series	41	Sulfasalazine	41	-	1	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	van Rossum et al., 1998[137]	RCT	69	Sulfasalazine	35	-	-	-	-	-	-
	van Rossum et al., 2007[138]	Series	61	Sulfasalazine	32	-	-	-	-	-	-
	Aggarwal et al., 2004[51]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[139]	Series	51	Sulfasalazine	51	-	-	-	-	-	-
	Gedalia et al., 1993[140]	Series	10	Sulfasalazine	10	-	-	-	-	-	-
	Gunnarson et al., 1997[141]	Series	8	Sulfasalazine	8	-	-	-	-	8	-
	Huang et al., 1998[142]	Series	15	Sulfasalazine	15	-	-	-	-	-	-
	Huang et al., 1998[143]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Kummerle-Deschner et al., 1995[144]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Ozdogan et al., 1986[145]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Pinana et al., 2010[146]	Case report	1	Sulfasalazine	1	1	-	-	-	-	-
	Settas et al., 1991[147]	Series	18	Sulfasalazine	18	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 4 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Varbanova et al., 1999[148]	Series	32	Sulfasalazine	32	-	-	-	-	-	-
				Total	**476**	**1**	**1**	**-**	**-**	**-**	**0**
				Incidence – Sulfasalazine		**0%**	**0%**	**-**	**-**	**-**	**0%**
OTHER											
	Flato et al., 1998[149]	Series	117	DMARDs	28	-	-	-	-	-	-
	Lomater et al., 1994[150]	Series	7	Plaquenil + MTX + gold salts	7	-	-	-	-	-	-
	Barash et al., 199[151]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	1	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	-	-	-	-	26	-
				Total	**191**	-	-	-	-	**27**	**-**
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Cimaz et al., 2010[4]	Case report	1	Adalimumab	1	-	-	-	-	-	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab	85	-	-	-	-	8	-
	Lovell et al., 2008[5]	RCT	171	Adalimumab + MTX	86	-	-	4	2	14	-
				Total	**343**	-	-	**4**	**2**	**22**	-
Anakinra	Canna et al., 2009[6]	Case reports	3	Anakinra	3	-	-	-	3	-	-
	Ilowite et al., 2009[7]	RCT	86	Anakinra	86	-	-	-	-	12	-
	Kone-Paut et al., 2007[8]	Case report	1	Anakinra	1	-	-	-	-	1	-
	Lequerre et al., 2008[9]	Series	20	Anakinra	20	-	-	-	-	-	-
	Ohlsson et al., 2008[10]	Series	7	Anakinra	7	-	-	-	-	-	-
	Zeft et al., 2009[11]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**149**	-	-	-	-	**13**	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
Etanercept	Bloom, 2000[12]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Bout-Tabaku et al., 2007[13]	Case report	1	Etanercept	1	-	3	-	-	-	-
	Dallocchio et al., 2010[14]	Case reports	8	Etanercept	8	-	-	-	-	-	-
	Elwood et al., 2003[15]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[16]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Giannini et al., 2009[17]	Series	103	Etanercept	103	-	-	-	-	1	-
	Horneff et al., 2009[18]	Series	20	Etanercept	20	-	-	-	1	2	-
	Horneff et al., 2009[19]	Series	604	Etanercept	100	-	-	-	-	1	-
	Hung et al., 2005[20]	Case reports	3	Etanercept	3	-	-	-	-	-	-
	Kimura et al., 2005[21]	Series	82	Etanercept	82	-	-	-	-	6	-
	Kunzmann et al., 2005[22]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[23]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[25]	Series	69	Etanercept	69	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Lovell et al., 2003[26]	Series	58	Etanercept	58	-	-	-	-	13	-
	Mangge et al., 2003[27]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mene et al., 2010[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Mori et al., 2005[29]	Series	22	Etanercept	22	-	-	-	-	19	-
	Morishita et al., 2010[30]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Peek et al., 2006[31]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[32]	Series	146	Etanercept	146	-	-	-	-	10	-
	Quartier et al., 2003[33]	Series	61	Etanercept	61	-	-	2	-	6	-
	Ramanan et al., 2003[34]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Robinson et al., 2003[35]	Series	21	Etanercept	21	-	-	-	1	-	-
	Skytta et al., 2000[36]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[37]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[38]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[39]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[40]	Case reports	2	Etanercept	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Tynjala et al., 2007[41]	Series	45	Etanercept	24	-	-	-	-	-	-
	Tzaribachev et al., 2008[42]	Series	25	Etanercept	25	-	-	-	-	-	-
	Wiegering et al., 2010[43]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Aikawa et al., 2009[44]	Case report	1	Etanercept + MTX	1	1	-	-	-	-	-
	Billiau et al., 2010[45]	Series	16	Etanercept + MTX	16	-	-	-	-	-	-
	Fitch et al., 2006[46]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[17]	Series	294	Etanercept + MTX	294	-	1	4	1	5	-
	Holl-Wieden et al., 2008[47]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2004[48]	Series	322	Etanercept + MTX	322	-	-	4	7	4	-
	Horneff et al., 2009[19]	Series	604	Etanercept + MTX	504	-	-	-	-	5	-
	Kuemmerle-Deschner et al., 2007[49]	Series	12	Etanercept + MTX	12	-	-	-	1		-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Yildirim-Toruner et al., 2008[50]	Correspondence	1	Etanercept + MTX	1	-	-	-	-	-	-
				Total	**1929**	**2**	**4**	**10**	**11**	**74**	**-**
				Incidence – Etanercept		**0%**	**0%**	**1%**	**1%**	**4%**	**-**
IVIG	Aggarwal et al., 2004 [51]	Series	214	IVIG	1	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Prieur et al., 1990[53]	Series	16	IVIG	16	-	-	-	-	-	-
	Silverman et al., 1994 [54]	RCT	31	IVIG	14	-	-	-	-	1	-
	Uziel et al., 1996 [55]	Series	27	IVIG	27	-	-	-	-	1	-
				Total	**60**	-	-	-	-	**2**	-
Infliximab	Armbrust et al., 2004[56]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Becker et al., 2004[57]	Case reports	3	Infliximab	3	-	-	-	-	3	-
	Billiau et al., 2002[59]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Corona et al., 2004[58]	Series	9	Infliximab	9	-	-	-	-	-	-
	Katsicas et al., 2005 [60]	Series	6	Infliximab	6	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Lahdenne et al., 2003 [61]	Series	24	Infliximab	14	1	1	-	-	-	-
	Mangge et al., 2003 [62]	Case report	1	Infliximab	1	-	-	-	-	2	-
	Morishita et al., 2010[30]	Case reports	2	Infliximab	2	-	-	-	-	-	-
	Pipitone et al., 2005 [63]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Simonini et al., 2008[64]	Series	15	Infliximab	15	-	-	1	1	1	-
	Tutar et al., 2004[65]	Case reports	2	Infliximab	2	-	-	-	-	1	-
	Tyler et al., 2007[66]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[41]	Series	45	Infliximab	21	-	-	-	3	-	-
	Ruperto et al., 2007[67]	RCT	122	Infliximab + MTX	60		35	-	-	-	-
	Ruperto et al., 2010[68]	Post-RCT open-label trial	78	Infliximab + MTX	78	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[50]	Case reports	2	Infliximab + MTX + etanercept	2	-	-	-	-	-	-
				Total	**219**	**1**	**36**	**1**	**4**	**7**	-
Leflunomide	Foeldvari and Wierk, 2010[69]	Series	58	Leflunomide	58	-	-	-	9	1	-
	Silverman et al., 2005[70]	RCT	94	Leflunomide	47	-	-	-	4	5	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Silverman et al., 2005[71]	Series	27	Leflunomide	27	-	-	-	3	14	-
				Total	**132**	-	-	-	**16**	**20**	-
Tocilizumab	Woo et al., 2005[72]	RCT	18	Tocilizumab	18	-	-	13	3	-	-
	Yokota et al., 2008[73]	RCT	56	Tocilizumab	56	-	-	1	12	1	-
				Total	**74**	-	-	**14**	**15**	**1**	-
				Total – Biologics	**3097**	**2**	**40**	**28**	**37**	**144**	**0**
				Incidence – Biologics		**0%**	**1%**	**1%**	**1%**	**5%**	**0%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[51]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[74]	RCT	32	Azathioprine	17	-	-	2	-	2	-
	Lin et al., 2000[75]	Series	24	Azathioprine	24	-	-	2	-	-	-
	Savolainen et al., 1997[76]	Series	129	Azathioprine	129	-	-	3	7	-	-
	de Castro et al., 2003[52]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	-	-	**7**	**7**	**2**	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
Cyclosporine A	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[77]	Case reports	50 35 w/ JRA	Cyclosporine A	50	-	-	1	2	5	-
	Gerloni et al., 2001[78]	Series	41	Cyclosporine A	41	-	-	1	3	6	-
	de Castro et al., 2003[52]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[79]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	1
	Mateicka et al., 1994[80]	Series	3	Cyclosporine A	3	-	-	-	-	3	-
	Murphy et al., 1993[81]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[82]	Series	14	Cyclosporine A	14	-	-	13	-	-	-
	Pistoia et al., 1993[83]	Series	9	Cyclosporine A	9	-	1	-	-	1	-
	Ruperto et al., 2006[84]	Series	329	Cyclosporine A	329	-	-	2	-	10	-
	Ravelli et al., 2002[85]	Series	17	Cyclosporine A + MTX	17	-	-	-	1	-	-
				Total	**468**	-	-	**17**	**6**	**25**	**1**

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
Penicillamine	Aggarwal et al., 2004[51]	Series	214	Penicillamine	23	-	-		-	1	-
	Kvien et al., 1985[86]	RCT	77	Penicillamine	38	-	-	3	-	3	-
	Prieur et al., 1985[87]	RCT	74	Penicillamine	74	-	-	1	-	-	-
	Sahn et al., 1989[88]	Case report	1	Penicillamine	1	-	-	-	-	1	-
	Brewer et al., 1986[89]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[90]	RCT	72	Penicillamine	24	-	1	3	-	2	-
	Swartz et al., 1984[91]	Case report	1	Penicillamine	1	-	-	-	-	1	-
				Total	**215**	-	**1**	**7**	-	**8**	-
Methotrexate	Aggarwal et al., 2004[51]	Series	214	Methotrexate	118	-	-	2	-	-	-
	Arakawa et al., 2003[92]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Becker et al., 2010[93]	Series	220	Methotrexate	220	-	-	-	142	-	-
	Chedeville et al., 2005[94]	Series	27	Methotrexate	27	-	9	1	9	1	-
	Cleary et al., 2002[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Corona et al., 1993[96]	Series	34	Methotrexate	34	-	-	-	6	-	-
	Cron et al., 1998[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	de Castro et al., 2003[52]	Case reports	5	Methotrexate	4	-	-	-	1	-	-
	Douglas Graham et al., 1992[98]	Series	62	Methotrexate	62	-	-	-	9	-	-
	Falcini et al., 1997[99]	Case report	1	Methotrexate	1	-	-	-	-	1	-
	Giannini et al., 1992[100]	RCT	127	Methotrexate	86	-	-	-	1	-	-
	Giannini et al., 2009[17]	Series	197	Methotrexate	197	-	8	1	11	6	-
	Gottlieb et al., 1997[101]	Series	25	Methotrexate	25	-	-	-	-	-	-
	Graham et al., 1992[102]	Series	62	Methotrexate	62	-	-	-	9		-
	Halle et al., 1991[103]	Series	30	Methotrexate	30	-	-	1	3	2	-
	Huang et al., 1996[104]	Series	26	Methotrexate	26	-	-	-	4	2	-
	Hunstad et al., 2007[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[106]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2006[107]	Series	84	Methotrexate	46	-	-	-	-	-	-
	Lee et al., 2009[108]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[109]	Series	52	Methotrexate	52	-	-	2	6	1	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Londino et al., 1998[110]	Case report	1	Methotrexate	1	-	-	-	-	1	-
	Martini et al., 1991[111]	Series	27	Methotrexate	27	-	-	-	1		-
	Muzaffer et al., 1996[112]	Case reports	2	Methotrexate	2	-	-	-	-	2	-
	Ortiz-Alvarez et al., 2004[113]	Series	89	Methotrexate	89	-	-	24	13		-
	Padeh et al., 1997[114]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1996[115]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Ravelli et al., 1998[116]	Series	256	Methotrexate	256	-	-	-	53	4	-
	Ravelli et al., 2001[117]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Riddle et al., 2006[118]	Series	57	Methotrexate	20	-	-	-	-	5	-
	Rose et al., 1990[119]	Series	29	Methotrexate	29	-	-	-	1	1	-
	Ruperto et al., 2004[120]	RCT	595	Methotrexate	595	-	-	-		12	-
	Russo et al., 2000[121]	Series	20	Methotrexate	20	-	-	-	5	-	-
	Savolainen et al., 2001[122]	Case reports	2	Methotrexate	2	-	-	2	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Schmeling et al., 2005[123]	Series	58	Methotrexate	58	-	-	-	19	-	-
	Silverman et al., 2005[70]	RCT	94	Methotrexate	47	-	-	-	4	6	-
	Speckmaier et al., 1989[124]	Series	12	Methotrexate	12	-	-	-	1	1	-
	Takeyama et al., 2006[125]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Truckenbrodt et al., 1986[126]	Series	19	Methotrexate	12	-	-	-	3	-	-
	van der Meer et al., 2007[127]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Wallace et al., 1992[128]	Series	13	Methotrexate	13	-	-	-	1	-	-
	Yildirim et al., 2000[129]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Kocharla et al., 2009[130]	Series	588	Methotrexate + folic acid	198	-	-	-	30	-	-
				Total	**2411**	**2**	**-**	**33**	**332**	**45**	**-**
				Incidence – Methotrexate		**0%**	**-**	**1%**	**14%**	**2%**	**-**
Sulfasalazine	Balci et al., 2009[131]	Case report	1	Sulfasalazine	1	-	-	-	-	1	-
	Burgos-Vargas et al., 2002[132]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[133]	Series	24	Sulfasalazine	24	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	de Castro et al., 2003[52]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzbergerten Cate et al., 1991[134]	Series	3	Sulfasalazine	3	-	-	-	-	1	-
	Imundo et al., 1996[135]	Series	139	Sulfasalazine	139	-	-	7	3	-	-
	Joos et al., 1991[136]	Series	41	Sulfasalazine	41	-	-	1	-	-	-
	van Rossum et al., 1998[137]	RCT	69	Sulfasalazine	35	-	4	2	2	2	-
	van Rossum et al., 2007[138]	Series	61	Sulfasalazine	32	-	1	1		1	-
	Aggarwal et al., 2004[51]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[139]	Series	51	Sulfasalazine	51	-	-	2	3	-	-
	Gedalia et al., 1993[140]	Series	10	Sulfasalazine	10	-	-	-	1	-	-
	Gunnarson et al., 1997[141]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[142]	Series	15	Sulfasalazine	15	-	-	-	-	-	-
	Huang et al., 1998[143]	Case report	1	Sulfasalazine	1	-	-	1	-	1	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA—main search and horizon scan—part 5 (continued)

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Kummerle-Deschner et al., 1995[144]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Ozdogan et al., 1986[145]	Series	18	Sulfasalazine	18	-	-	1	-	-	-
	Pinana et al., 2010[146]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Settas et al., 1991[147]	Series	18	Sulfasalazine	18	-	-	1	-	-	-
	Varbanova et al., 1999[148]	Series	32	Sulfasalazine	32	-	-	2	-	-	-
				Total	**476**	**-**	**5**	**18**	**9**	**6**	-
				Incidence – Sulfasalazine		**-**	**1%**	**4%**	**2%**	**1%**	-
OTHER											
	Flato et al., 1998[149]	Series	117	DMARDs	28	-	-	4	5	-	-
	Lomater et al., 1994[150]	Series	7	Plaquenil + MTX + gold salts	7	-	-	1	-	-	-
	Barash et al., 199[151]	Case reports	2	Penicillamine + gold	2	-	-	-	-	2	-

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Appendix F. Excluded Studies

All studies listed below were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Abinun M, Flood TJ, Cant AJ, et al. Autologous T cell depleted haematopoietic stem cell transplantation in children with severe juvenile idiopathic arthritis in the UK (2000-2007). Mol Immunol 2009;47(1):46-51. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention*

Agarwal V, Aggarwal A, Misra R. Methotrexate induced accelerated nodulosis. J Assoc Physicians India 2004;52:538-40. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Aggarwal A, Agarwal V, Danda D, et al. Outcome in juvenile rheumatoid arthritis in India. Indian Pediatr 2004;41(2):180-4. *Q1, 2, 4 - Exclude study not prospective*

Aggarwal R, Manadan AM, Poliyedath A, et al. Safety of etanercept in patients at high risk for mycobacterial tuberculosis infections. J Rheumatol 2009;36(5):914-7. *Q1, 2, 4 - Exclude population not JIA/JRA/JCA; Q3 - Exclude population not JIA/JRA*

Aikawa NE, Carvalho JF, Bonfa E, et al. Macrophage activation syndrome associated with etanercept in a child with systemic onset juvenile idiopathic arthritis. Israel Medical Association Journal 2009;11(10):635-636. *Q1, 2, 4 - Exclude no acceptable comparator*

Alarcon GS, Morgan SL. Folinic acid to prevent side effects of methotrexate in juvenile rheumatoid arthritis. J Rheumatol 1996;23(12):2184-5. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

al-Sewairy W, al-Mazyed A, al D, et al. Methotrexate therapy in systemic-onset juvenile rheumatoid arthritis in Saudi Arabia: a retrospective analysis. Clin Rheumatol 1998;17(1):52-7. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Andre M, Hagelberg S, Stenstrom CH. The juvenile arthritis foot disability index: development and evaluation of measurement properties. J Rheumatol 2004;31(12):2488-93. *Q5 - Exclude not priority instrument*

Angeles-Han S, Flynn T, Lehman T. Abatacept for refractory juvenile idiopathic arthritis-associated uveitis- a case report. J Rheumatol 2008;35(9):1897-8. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

Angevaren M, Aufdemkampe G, Verhaar HJ, et al. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database of Systematic Reviews 2008(3):CD005381. *Exclude - population not JIA/JRA/JCA*

Anonymous. Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. *Exclude - computer program*

Anonymous. Efficacy of etanercept in the treatment of children with polyarticular juvenile rheumatoid arthritis. Eur J Pediatr 2000;159(10):785. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

Ansell BM. Cyclosporin A in paediatric rheumatology. Clin Exp Rheumatol 1993;11(2):113-5. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

Ansell BM, Hall MA. Penicillamine in chronic arthritis of childhood. J Rheumatol Suppl 1981;7:112-5. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Ansell BM, Hall MA, Loftus JK, et al. A multicentre pilot study of sulphasalazine in juvenile chronic arthritis. Clin Exp Rheumatol 1991;9(2):201-3. *Q1, 2, 4 - Exclude no acceptable comparator*

Ansell BM, Moran H, Arden GP. Penicillamine and wound healing in rheumatoid arthritis. Proc R Soc Med 1977;70 Suppl 3:75-7. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Ansell BM, Simpson C. The effect of penicillamine on growth as height in juvenile chronic polyarthritis. Proc R Soc Med 1977;70 Suppl 3:123-5. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

April KT, Feldman DE, Platt RW, et al. Comparison between children with Juvenile Idiopathic Arthritis (JIA) and their parents concerning perceived quality of life. Research 2006;15(4):655-661. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude not priority measure*

Arakawa H, Yamasaki M, Kurihara Y, et al. Methotrexate-induced pulmonary injury: serial CT findings. J Thorac Imaging 2003;18(4):231-6. *Q1, 2, 4 - Exclude population > 18*

Arguedas O, Fasth A, Andersson-Gare B. A prospective population based study on outcome of juvenile chronic arthritis in Costa Rica. J Rheumatol 2002;29(1):174-83. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no AE data reported*

Armbrust W, Kamphuis SS, Wolfs TW, et al. Tuberculosis in a nine-year-old girl treated with infliximab for systemic juvenile idiopathic arthritis. Rheumatology (Oxford) 2004;43(4):527-9. *Q1, 2, 4 - Exclude not peer-reviewed*

Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490. *Exclude - methods paper*

Bacon BR, Treuhaft WH, Goodman AM. Azathioprine-induced pancytopenia. Occurrence in two patients with connective-tissue diseases. Arch Intern Med 1981;141(2):223-6. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Balci DD, Peker E, Duran N, et al. Sulfasalazine-induced hypersensitivity syndrome in a 15-year-old boy associated with human herpesvirus-6 reactivation. Cutan Ocul Toxicol 2009;28(1):45-7. *Q1, 2, 4 - Exclude no acceptable comparator*

Bandeira M, Falcone A, Pistorio A, et al. Weighting improves the information provided by joint counts on the severity of arthritis and its impact on patients' well-being in juvenile idiopathic arthritis. Rheumatology (Oxford) 2006;45(3):343-347. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude not priority measure*

Barash J, Cooper M, Tauber Z. Hepatic, cutaneous and hematologic manifestations in juvenile chronic arthritis. Clin Exp Rheumatol 1991;9(5):541-3. *Q1, 2, 4 - Exclude no acceptable comparator*

Barlow JH, Shaw KL, Wright CC. Development and preliminary validation of a self-efficacy measure for use among parents of children with juvenile idiopathic arthritis. Arthritis Care Res 2000;13(4):227-36. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude not priority instrument*

Barlow JH, Shaw KL, Wright CC. Development and preliminary validation of a children's arthritis self-efficacy scale. Arthritis Care Res 2001;45(2):159-166. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention*

Barron KS, Sher MR, Silverman ED. Intravenous immunoglobulin therapy: magic or black magic. J Rheumatol Suppl 1992;33:94-7. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Bass JC, Giannini EH, Brewer EJ, et al. Pirprofen (Rengasil) in the treatment of juvenile rheumatoid arthritis. A segment I study. J Rheumatol 1982;9(1):140-3. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention*

Becker M, Rose CD, McIlvain-Simpson G. Niacin-like reaction to infliximab infusion in systemic juvenile rheumatoid arthritis. J Rheumatol 2004;31(12):2529-30. *Q1, 2, 4 - Exclude not peer-reviewed*

Becker ML, Rose CD, Cron RQ, et al. Effectiveness and toxicity of methotrexate in juvenile idiopathic arthritis: Comparison of 2 initial dosing regimens. J Rheumatol 2010;37(4):870-875. *Q1, 2, 4 - Exclude no acceptable comparator*

Benestad B, Vinje O, Veierod MB, et al. Quantitative and qualitative assessments of pain in children with juvenile chronic arthritis based on the Norwegian version of the Pediatric Pain Questionnaire. Scand J Rheumatol 1996;25(5):293-299. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention*

Bertamino M, Rossi F, Pistorio A, et al. Development and initial validation of a radiographic scoring system for the hip in juvenile idiopathic arthritis. J Rheumatol 2010;37(2):432-439. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention*

Bertamino M, Rossi F, Pistorio A, et al. Development and initial validation of a radiographic scoring system for the hip in juvenile idiopathic arthritis. J Rheumatol 2010;37(2):432-9. *Exclude - no clinical outcomes measure*

Berthelot JM, De Bandt M, Goupille P, et al. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. Joint Bone Spine 2009;76(1):28-34. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Bianchi ML, Cimaz R, Galbiati E, et al. Bone mass change during methotrexate treatment in patients with juvenile rheumatoid arthritis. Osteoporos Int 1999;10(1):20-5. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 2007;91(3):319-24. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Billiau AD, Cornillie F, Wouters C. Infliximab for systemic onset juvenile idiopathic arthritis: experience in 3 children. J Rheumatol 2002;29(5):1111-4. *Q1, 2, 4 - Exclude not peer-reviewed*

Billiau AD, Loop M, Le PQ, et al. Etanercept improves linear growth and bone mass acquisition in MTX-resistant polyarticular-course juvenile idiopathic arthritis. Rheumatology (Oxford) 2010;49(8):1550-1558. *Exclude Q1, 2, 4 - no acceptable comparator*

Bjerkhoel F, Forre O. Cyclosporin treatment of a patient with severe systemic juvenile rheumatoid arthritis. Scand J Rheumatol 1988;17(6):483-6. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Bloom BJ. Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 2000;43(11):2606-2608. *Q1, 2, 4 - Exclude no acceptable comparator*

Bongartz T. Tocilizumab for rheumatoid and juvenile idiopathic arthritis. Lancet 2008;371(9617):961-3. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

Bout-Tabaku S, Rivas-Chacon R, Restrepo R. Systemic lupus erythematosus in a patient treated with etanercept for polyarticular juvenile rheumatoid arthritis. J Rheumatol 2007;34(12):2503-4. *Q1, 2, 4 - Exclude not peer-reviewed*

Bowyer SL, Roettcher PA, Higgins GC, et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003;30(2):394-400. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Braun-Moscovici Y, Markovits D, Rozin A, et al. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. Isr Med Assoc J 2008;10(4):277-81. *Q1, 2, 4 - Exclude population >18; Q3 - Exclude population >18 background*

Bresnihan FP, Ansell BM. Effect of penicillamine treatment on immune complexes in two cases of seropositive juvenile rheumatoid arthritis. Ann Rheum Dis 1975;35(5):463-5. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Brik R, Berkowitz D, Berant M. Duration of methotrexate treatment until partial and total remission of refractory juvenile rheumatoid arthritis. Ann Rheum Dis 1998;57(3):174-5. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

Brik R, Gepstein V, Berkovitz D. Low-dose methotrexate treatment for oligoarticular juvenile idiopathic arthritis nonresponsive to intra-articular corticosteroids. Clin Rheumatol 2005;24(6):612-4. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Brunner HI, Silverman ED, To T, et al. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. Arthritis Rheum 2002;46(2):436-44. *Q5 - Exclude population not JIA/JRA/JCA*

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Press J, Neumann L, Uziel Y, et al. Assessment of quality of life of parents of children with juvenile chronic arthritis. Clin Rheumatol 2002;21(4):280-283. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention*

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Ravelli A, Viola S, Migliavacca D, et al. Discordance between proxy-reported and observed assessment of functional ability of children with juvenile idiopathic arthritis. Rheumatology (Oxford) 2001;40(8):914-919. *Q1, 2, 4 - Exclude noa cceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude unclear if differences in CHAQ are related to true perceived differences in function or different definitions of "some" and "much" difficulty*

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Remesal A, De Inocencio J, Merino R, et al. Discontinuation of etanercept after successful treatment in patients with juvenile idiopathic arthritis. J Rheumatol 2010;37(9):1970-1971. *Exclude Q1, 2, 4 - publication not peer-reviewed Exclude; Q3 - no AE data reported*

Ringold S, Bittner R, Neogi T, et al. Performance of rheumatoid arthritis disease activity measures and juvenile arthritis disease activity scores in polyarticular-course juvenile idiopathic arthritis: Analysis of their ability to classify the american college of rheumatology pediatric measures of response and the preliminary criteria for flare and inactive disease. Arthritis Care Res 2010;62(8):1095-1102. *Exclude - no clinical outcomes measure*

Ringold S, Chon Y, Singer NG. Associations between the American College of Rheumatology pediatric response measures and the continuous measures of disease activity used in adult rheumatoid arthritis: a secondary analysis of clinical trial data from children with polyarticular-course juvenile idiopathic arthritis. Arthritis Rheum 2009;60(12):3776-83. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude not on TEP priority list*

Ringold S, Wallace CA. Measuring clinical response and remission in juvenile idiopathic arthritis. Curr Opin Rheumatol 2007;19(5):471-6. *Exclude - methods paper*

Ringold S, Wallace CA, Rivara FP. Health-related quality of life, physical function, fatigue, and disease activity in children with established polyarticular juvenile idiopathic arthritis. J Rheumatol 2009;36(6):1330-6. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude not on TEP priority list*

Robinson RF, Nahata MC, Hayes JR, et al. Quality-of-life measurements in juvenile rheumatoid arthritis patients treated with etanercept. Clinical Drug Investigation 2003;23(8):511-518. *Q1, 2, 4 - Exclude no acceptable comparator*

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Rossi F, Di Dia F, Galipo O, et al. Use of the Sharp and Larsen scoring methods in the assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 2006;55(5):717-23. *Q5 - Exclude instrument not on TEP priority list*

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Ruemmele FM, Prieur AM, Talbotec C, et al. Development of Crohn disease during anti-TNF-alpha therapy in a child with juvenile idiopathic arthritis. J Pediatr Gastroenterol Nutr 2004;39(2):203-6. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Ruperto N, Giannini EH. Redundancy of conventional articular response variables used in juvenile chronic arthritis clinical trials. Ann Rheum Dis 1996;55(1):73-5. *Q5 - Exclude no test performance data reported*

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Ruperto N, Ravelli A, Falcini F, et al. Responsiveness of outcome measures in juvenile chronic arthritis. Italian Pediatric Rheumatology Study Group. Rheumatology (Oxford) 1999;38(2):176-80. *Q5 - Exclude no test performance data reported*

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Russo RA, Katsicas MM. Tolerance of parenteral, higher dose methotrexate in children with juvenile chronic arthritis. Clin Exp Rheumatol 2000;18(3):425. *Q1, 2, 4 - Exclude not peer-reviewed*

Russo RA, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. J Rheumatol 2009;36(5):1078-82. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Russo RA, Katsicas MM, Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. Clin Exp Rheumatol 2002;20(5):723-6. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Rybar I, Rozborilova E, Zanova E, et al. The effectiveness for prevention of tuberculosis in patients with inflammatory rheumatic diseases treated with TNF inhibitors. Bratisl Lek Listy 2008;109(4):164-7. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Saba NS, Kosseifi SG, Charaf EA, et al. Adalimumab-induced acute myelogenic leukemia. South Med J 2008;101(12):1261-2. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Sahn EE, Maize JC, Garen PD, et al. D-penicillamine-induced elastosis perforans serpiginosa in a child with juvenile rheumatoid arthritis. Report of a case and review of the literature. J Am Acad Dermatol 1989;20(5 Pt 2):979-88. *Q1, 2, 4 - Exclude no acceptable comparator*

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Saougou I, Papagoras C, Markatseli TE, et al. A case report of a psoriatic arthritis patient on hemodialysis treated with tumor necrosis factor blocking agent and a literature review. Clin Rheumatol 2010;29(12):1455-1459. *Exclude Q124 - population not < 18; Q3 - population not < 18*

Sari I, Binicier O, Birlik M, et al. Thymic enlargement in a patient with juvenile idiopathic arthritis during etanercept therapy. Rheumatol Int 2009;29(5):591-3. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Saurenmann RK, Levin AV, Feldman BM, et al. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. J Pediatr 2006;149(6):833-6. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Savolainen HA, Kautiainen H, Isomaki H, et al. Azathioprine in patients with juvenile chronic arthritis: a longterm followup study. J Rheumatol 1997;24(12):2444-50. *Q1, 2, 4 - Exclude no acceptable comparator*

Savolainen HA, Leirisalo-Repo M. Eosinophilia as a side-effect of methotrexate in patients with chronic arthritis. Clin Rheumatol 2001;20(6):432-4. *Q1, 2, 4 - Exclude no acceptable comparator*

Sawar H, Espinoza LR, Gedalia A. Macrophage activation syndrome and etanercept in children with systemic juvenile rheumatoid arthritis. J Rheumatol 2004;31(3):623; author reply 623-4. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude no AE data reported*

Schmeling H, Biber D, Heins S, et al. Influence of methylenetetrahydrofolate reductase polymorphisms on efficacy and toxicity of methotrexate in patients with juvenile idiopathic arthritis. J Rheumatol 2005;32(9):1832-6. *Q1, 2, 4 - Exclude no acceptable comparator*

Schmeling H, Mathony K, John V, et al. A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study. Ann Rheum Dis 2001;60(4):410-2. *Q1, 2, 4 - Exclude no acceptable no comparator; Q3 - Exclude no AE data reported*

Schmeling H, Stephan V, Burdach S, et al. Pulmonary function in children with juvenile idiopathic arthritis and effects of methotrexate therapy. Z Rheumatol 2002;61(2):168-72. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Seid M, Opipari L, Huang B, et al. Disease control and health-related quality of life in juvenile idiopathic arthritis. Arthritis Rheum 2009;61(3):393-9. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARD intervention Q5 - Exclude not on TEP priority list*

Settas L, Alexiou P, Dimitriadis G, et al. Effect of sulphasalazine in patients with juvenile chronic arthritis (JCA). Acta Univ Carol Med (Praha) 1991;37(1-2):76-9. *Q1, 2, 4 - Exclude no acceptable comparator*

Shaikov AV, Maximov AA, Speransky AI, et al. Repetitive use of pulse therapy with methylprednisolone and cyclophosphamide in addition to oral methotrexate in children with systemic juvenile rheumatoid arthritis--preliminary results of a longterm study. J Rheumatol 1992;19(4):612-6. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Shanmugavel C, Sodhi KS, Sandhu MS, et al. Role of power Doppler sonography in evaluation of therapeutic response of the knee in juvenile rheumatoid arthritis. Rheumatol Int 2008;28(6):573-8. *Q5 - Exclude no test performance data reported*

Sharma SM, Ramanan AV, Riley P, et al. Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease. Ann Rheum Dis 2007;66(6):840-1. *Q1, 2, 4 - Exclude not peer-reviewed; Q3 - Exclude population not JIA/JRA*

Shaw KL, Southwood TR, Duffy CM, et al. Health-related quality of life in adolescents with juvenile idiopathic arthritis. Arthritis Rheum 2006;55(2):199-207. *Q5 - Exclude not TEP priority measure*

Shetty AK, Zganjar BE, Ellis GS, Jr., et al. Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. J Pediatr Ophthalmol Strabismus 1999;36(3):125-8. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Sicotte NL, Voskuhl RR. Onset of multiple sclerosis associated with anti-TNF therapy. Neurology 2001;57(10):1885-8. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Sijssens KM, Rothova A, Van De Vijver DA, et al. Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol 2007;144(4):574-9. *Q1, 2, 4 - Exclude study not prospective; Q3 - Exclude no AE data reported*

Silverman E, Spiegel L, Hawkins D, et al. Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2005;52(2):554-62. *Q1, 2, 4 - Exclude no acceptable comparator*

Silverman ED, Laxer RM, Greenwald M, et al. Intravenous gamma globulin therapy in systemic juvenile rheumatoid arthritis. Arthritis Rheum 1990;33(7):1015-22. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Simard JF, Neovius M, Hagelberg S, et al. Juvenile idiopathic arthritis and risk of cancer: A nationwide cohort study. Arthritis Rheum 2010;62(12):3776-3782. *Exclude Q124 - no acceptable comparator*

Simon D, Prieur AM, Quartier P, et al. Early recombinant human growth hormone treatment in glucocorticoid-treated children with juvenile idiopathic arthritis: a 3-year randomized study. J Clin Endocrinol Metab 2007;92(7):2567-73. *Q1, 2, 4 - Exclude no acceptable DMARD intervention; Q3 - Exclude no acceptable DMARDintervention*

Simonini G, Zannin ME, Caputo R, et al. Loss of efficacy during long-term infliximab therapy for sight-threatening childhood uveitis. Rheumatology (Oxford) 2008;47(10):1510-1514. *Q1, 2, 4 - Exclude no acceptable comparator*

Skoglund RR, Schanberger JE, Kaplan JM. Cyclophosphamide therapy for severe juvenile rheumatoid arthritis. Am J Dis Child 1971;121(6):531-3. *Q1, 2, 4 - Exclude no acceptable comparator; Q3 - Exclude no AE data reported*

Skytta E, Pohjankoski H, Savolainen A. Etanercept and urticaria in patients with juvenile idiopathic arthritis. Clin Exp Rheumatol 2000;18(4):533-4. *Q1, 2, 4 - Exclude no acceptable comparator*

Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum 2003;48(2):319-24. *Q1, 2, 4 - Exclude population not JIA/JRA/JCA; Q3 - Exclude population not JIA/JRA*

Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Rheum 2001;45(3):252-7. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population >18*

Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology 2008;115(8):1416-21, 1421 e1. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Somerville MF, Scott DG. Neoral--new cyclosporin for old? Br J Rheumatol 1997;36(10):1113-5. *Q1, 2, 4 - Exclude population > 18; Q3 - Exclude population > 18*

Speckmaier M, Findeisen J, Woo P, et al. Low-dose methotrexate in systemic onset juvenile chronic arthritis. Clin Exp Rheumatol 1989;7(6):647-50. *Q1, 2, 4 - Exclude no acceptable comparator*

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Stinson JN, Stevens BJ, Feldman BM, et al. Construct validity of a multidimensional electronic pain diary for adolescents with arthritis. Pain 2008;136(3):281-92. *Q5 - Exclude not priority instrument*

Sukal SA, Nadiminti L, Granstein RD. Etanercept and demyelinating disease in a patient with psoriasis. J Am Acad Dermatol 2006;54(1):160-4. *Q1, 2, 4 - Exclude population not JIA/JRA/JCA; Q3 - Exclude population not JIA/JRA*

Sulpice M, Deslandre CJ, Quartier P. Efficacy and safety of TNFalpha antagonist therapy in patients with juvenile spondyloarthropathies. Joint, Bone, Spine: Revue du Rhumatisme 2009;76(1):24-7. *Q1, 2, 4 - Exclude no acceptabl comparator; Q3 - Exclude no AE data reported*

Swale VJ, Perrett CM, Denton CP, et al. Etanercept-induced systemic lupus erythematosus. Clin Exp Dermatol 2003;28(6):604-7. *Q1, 2, 4 - Exclude population not JIA/JRA/JCA; Q3 - Exclude population not JIA/JRA*

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