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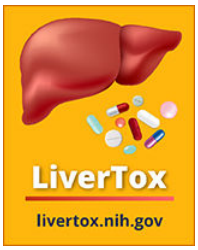


Telithromycin

Updated: August 10, 2017.

OVERVIEW

Introduction

Telithromycin is a ketolide, a novel form of macrolide antibiotic that is recommended for treatment of community acquired pneumonia. Telithromycin was approved for use in the United States in 2004 and subsequently linked to several cases of severe drug induced liver injury.

Background

Telithromycin (tel ith" roe mye' sin) is a ketolide antibiotic, a novel form of macrolide antibiotic that is used to treated community acquired pneumonia. Telithromycin differs from erythromycin by several substitutions that render it less susceptible to erythromycin-resistant strains of bacteria. Telithromycin is active against staphylococci, streptococci, S. pneumoniae, Haemophilus spp., Moraxella catarrhalis, mycoplasma, chlamydia and Legionella. Telithromycin was first approved for use in the United States in 2004 and initially had several clinical indications including sinusitis and bronchitis. Currently, because of the potential of serious side effects, the only approved indication for telithromycin is moderate-to-severe community acquired pneumonia due to sensitive organisms. Telithromycin is available in oral forms under the trade name Ketek in tablets of 300 mg (for reduced dosing in patients with renal disease) and 400 mg. The recommended dosage is 800 mg once daily for 7 to 10 days. Telithromycin is generally well tolerated, but side effects can include nausea, abdominal pain, diarrhea, dyspepsia, headache, dizziness and rash.

Hepatotoxicity

As with other macrolide antibiotics, telithromycin has been associated with a low rate (1% to 2%) of transient serum enzyme elevations during therapy. These elevations, however, are usually transient and resolve even with drug continuation and a similar rate of serum enzyme elevations can occur with comparator agents. More importantly, telithromycin has been linked to severe forms of acute, clinically apparent hepatotoxicity, first reported within a short time of its general approval for use in the United States. The typical latency to onset of liver injury is rapid, some cases presenting within a day or two of initiation of therapy, the average latency being 1 week. The liver injury is often abrupt in onset with fatigue, weakness, jaundice and fever. The pattern of enzyme elevations is typically hepatocellular and serum aminotransferase levels can be quite high (>1000 U/L). Mild and anicteric cases of liver injury attributed to telithromycin have been reported, but some cases are very severe and associated with rapid development of hepatic failure with ascites and hepatic encephalopathy. Eosinophilia and rash can occur, but are not common. Recurrence of injury with reexposure has been described.

Likelihood score: A (well known cause of clinically apparent liver injury).

Mechanism of Injury

The cause of hepatotoxicity from telithromycin is unknown, but the short latency period and abrupt onset of injury suggests hypersensitivity as the cause. Only a proportion of cases have been associated with eosinophilia, and rash, fever, adenopathy and facial edema are rarely described.

Outcome and Management

Severe cases of liver injury appearing within days of starting telithromycin have been described some of which have been associated with acute and rapid onset of ascites and liver failure requiring liver transplantation. Milder cases of injury and cases without jaundice have generally resolved rapidly over 4 to 6 weeks. Persons with a history of allergy or liver injury due to telithromycin or any macrolide antibiotic such as erythromycin, azithromycin or clarithromycin should not be reexposed to macrolide antibiotics.

Drug Class: Antiinfective Agents, Macrolide Antibiotics

CASE REPORT

Case 1. Mild hepatitis after telithromycin therapy.

[Modified from a case in the database of the Drug-Induced Liver Injury Network.]

A 31 year old man was treated with two 5-day courses of telithromycin for sinusitis. Five days after finishing the second course, he developed fever and chills and was found to have abnormal liver tests. On hospital admission, his ALT was 589 U/L but bilirubin was normal (Table). He had no previous history of liver disease or jaundice and drank little alcohol. He took antihistamines and used a nasal spray for his sinusitis, but took no medications chronically and had no drug allergies. Tests for hepatitis A, B and C were negative. Tests for anti-smooth muscle and antinuclear antibodies were weakly positive (1:80). A computed tomography scan of the abdomen showed no evidence of gallstone disease or obstruction. His serum aminotransferases fluctuated and peaked at levels of 15-25 times the upper limit of the normal range, but then gradually declined. Six weeks after admission, he was without symptoms and laboratory tests were completely normal.

Key Points

Medication:	Telithromycin (800 mg daily for 5 days)
Pattern:	Hepatocellular (R=43)
Severity:	1+ (no jaundice)
Latency:	2 weeks after starting second course
Recovery:	Complete in 6 weeks
Other medications:	Brompheniramine tannate, mometasone nasal spray, rarely acetaminophen

Laboratory Values

Time After Starting	Days After Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin *(mg/dL)	Other
Second 5-day course of telithromycin (800 mg daily) – 1 week after the first					
10 days	5 days	589	43	0.7	Admission
12 days	7 days	1091	35	1.2	INR 1.5
15 days	10 days	553	35	0.8	INR 1.3
19 days	14 days	768	47	1.1	

Table continued from previous page.

Time After Starting	Days After Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin *(mg/dL)	Other
24 days	19 days	359	59	1.1	Discharge
31 days	26 days	151	65	0.4	
2 months	7 weeks	36	40	0.7	INR 1.0
Normal Values		**<42**	**<110**	**<1.2**	

Comment

This patient developed anicteric but symptomatic hepatitis within 10 days of starting a second course of oral telithromycin. Worrisome was a slight increase in prothrombin time, but this reversed with time and after vitamin K injections. Serum aminotransferases remained elevated for several weeks, but recovery was complete. The finding of low levels of autoantibodies should lead to further follow up to exclude the possibility of autoimmune hepatitis with an onset marked by episodes of activity, but this is unlikely. The first course of telithromycin may have sensitized this patient; a history of previous exposure to macrolide antibiotics is not uncommon in patients presenting with liver injury. This patient should be strongly warned against future use of telithromycin, the indications for which have now been restricted to community acquired pneumonia. Recommendations regarding other macrolide antibiotics are not as clearly made, but use of a single test dose might be appropriate if these agents are considered necessary.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Telithromycin — Ketek®

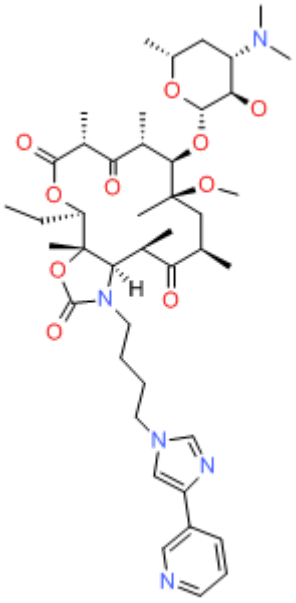
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Telithromycin	173838-31-8	C43-H65-N5-O10	

ANNOTATED BIBLIOGRAPHY

References updated: 10 August 2017

Moseley RH. Macrolide antibiotics. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced Liver Disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 466-7.

(Expert review of macrolide antibiotic induced liver injury; telithromycin was impicated in at least 42 cases of clinically apparent liver injury with four deaths and one liver transplant; clinical features were short latency, abrupt onset and jaundice).

MacDougall C, Chambers HF. Macrolides and ketolides. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1529-34.

(Textbook of pharmacology and therapeutics).

Zhanel GG, Walters M, Noreddin A, Vercaigne LM, Wierzbowski A, Embil JM, Gin AS, et al. The ketolides: a critical review. Drugs 2002; 62: 1771-804. PubMed PMID: 12149046.

(Extensive review of ketolides, macrolides designed to overcome the usual pattern of bacterial resistance to macrolide antibiotics; telithromycin is first member of this class and others are in development; it hs excellent pharmacokinetic properties, but metabolized in liver, interacting with CYP 3A4; clinical trials support efficacy with similar safety profiles as other newer macrolides: diarrhea in 13%, nausea 8%, vomiting 3%, rates of termination 4.8%, no treatment related deaths, ALT elevations in <1% in non-pneumonia cases, <2% with pneumonia and similar rates of elevations as with comparable antibiotics).

Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in

patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother 2004; 54: 515-23. PubMed PMID: 15269191.

(Clinical trial in 388 patients with community acquired pneumonia found similar rates of efficacy [~90%] and adverse events [~22% mild-to-moderate, possibly related and ~3% severe] with telithromycin as with clarithromycin; no mention of ALT monitoring, hepatitis or liver injury).

Ciervo CA, Shi J. Pharmacokinetics of telithromycin: application to dosing in the treatment of community-acquired respiratory tract infections. Curr Med Res Opin 2005; 21: 1641-50. PubMed PMID: 16238904.

(Review of pharmacokinetics of telithromycin, hepatic metabolism 50% largely by CYP 3A4, no discussion of hepatotoxicity).

Shi J, Montay G, Bhargava VO. Clinical pharmacokinetics of telithromycin, the first ketolide antibacterial. Clin Pharmacokinet 2005; 44: 915-34. PubMed PMID: 16122280.

(Review of pharmacokinetics of telithromycin; no dose adjustment needed with liver disease, inactions with CYP 3A4, but little effect of grapefruit juice or ketoconazole; rifampin increases plasma levels).

Clay KD, Hanson JS, Pope SD, Rissmiller RW, Purdum PP 3rd, Banks PM. Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. Ann Intern Med 2006; 144: 415-20. Summary for patients in: Ann Intern Med 2006; 144: I42. PubMed PMID: 16481451.

(Three initial case reports of serious liver injury arising within a few days of starting 5 day courses of telithromycin; 2 men and 1 woman, ages 26-51 years [initial ALT 948, 730 and 2200 U/L, Alk P 291, 188 and 575 U/L and bilirubin 3.8, 9.5 and 13.6 mg/dL] 1 died, 1 underwent liver transplantation and one recovered; histology in two showed massive necrosis; review of published prelicensure trials comparing telithromycin to other antibiotics showed similar rates of ALT elevations during therapy).

Summaries for patients. Telithromycin: a possible cause of severe liver damage? Ann Intern Med 2006; 144: I42. PubMed PMID: 16481450.

(Summary of recommendations on telithromycin based upon report of Clay et al [2006]).

Turner M, Corey GR, Abrutyn E. Telithromycin. Ann Intern Med 2006; 144: 447-8. PubMed PMID: 16549859.

(Editorial accompanying article by Clay et al [2006] advising caution in using telithromycin).

Telithromycin: severe hepatitis. Prescrire Int 2006; 15: 139. PubMed PMID: 16991219.

(Summary of report of Clay et al [2006]).

Barie PS. A fine pile of paté: the cautionary tale of telithromycin, hepatic failure, and study 3014. Surg Infect (Larchmt) 2006; 7: 247-9. PubMed PMID: 16875457.

(Editorial summarizing Wall Street Journal investigation on FDA's handling of telithromycin approval).

Bertino JS. Severe hepatotoxicity of telithromycin. Ann Intern Med 2006; 145: 472; author reply 472. PubMed PMID: 16983140.

(Letter regarding report of Clay et al. [2006] without new information or data).

Graham DJ. Telithromycin and acute liver failure. N Engl J Med 2006; 355: 2260-1. PubMed PMID: 17124030.

(History of FDA approval of telithromycin recounting use of postmarketing databases and European spontaneous reporting of adverse events; estimated from subsequent reporting rates that telithromycin may cause 167 cases of acute liver failure per 1 million person years of use, which is greater than for troglitazone and trovafloxacin, two other agents withdrawn from use because of hepatotoxicity).

Dore DD, DiBello JR, Lapane KL. Telithromycin use and spontaneous reports of hepatotoxicity. Drug Saf 2007; 30: 697-703. PubMed PMID: 17696582.

(Analysis of the FDA Adverse Event Reporting System estimating the increased risk of liver injury from telithromycin compared to other medications, demonstrating an 1.82 relative risk of hepatotoxicity compared to other agents, subject to the usual reporting biases).

Gleason PP, Walters C, Heaton AH, Schafer JA. Telithromycin: the perils of hasty adoption and persistence of off-label prescribing. J Manag Care Pharm 2007; 13: 420-5. PubMed PMID: 17605513.

(Analysis of data from commercial insurers on secular trends and indications for use of telithromycin; its use increased and overtook clarithromycin within 2 years of its approval, but use fell markedly after FDA warning; only 52% of prescriptions were for listed indications, 4% for pneumonia).

Curtiss FR. Effective integration of medical and pharmacy claims to better protect patient safety--a long road yet to travel. J Manag Care Pharm 2007; 13: 429-30. PubMed PMID: 17605515.

(Editorial in response to report by Gleason et al. [2007]).

Onur O, Guneysel O, Denizbasi A, Celikel C. Acute hepatitis attack after exposure to telithromycin. Clin Ther 2007; 29: 1725-9. PubMed PMID: 17919553.

(Turkish patient had two episodes of cholestatic jaundice after two exposures to telithromycin one year apart, latency to onset of only 2-3 days, second episode worse, recovery in 4-8 weeks).

Ross DB. The FDA and the case of Ketek. N Engl J Med 2007; 356: 1601-4. PubMed PMID: 17442902.

(Editorial on the history of FDA approval of telithromycin describing irregularities that arose in prelicensure studies, controversial reliance on non-inferiority studies, and use of foreign safety data of uncertain reliability).

Soreth J, Cox E, Kweder S, Jenkins J, Galson S. Ketek--the FDA perspective. N Engl J Med 2007; 356: 1675-6. PubMed PMID: 17442912.

(FDA response to editorial by Ross [2007] providing history of review of safety concerns, warnings and changes in recommended indications for telithromycin and statement that "..we believe that the potential benefits of Ketek outweigh its risks when it is used according to current approved label…").

Brown SD. Benefit-risk assessment of telithromycin in the treatment of community-acquired pneumonia. Drug Saf 2008; 31: 561-75. PubMed PMID: 18558790.

(Review of benefits and risks of telithromycin concluding that it offers an "acceptable risk ratio in treatment of mild to moderate CAP" [community acquired pneumonia]).

Shlaes DM, Moellering RC. Telithromycin and the FDA: implications for the future. Lancet Infect Dis 2008; 8: 83-5. PubMed PMID: 18222155.

(Editorial on decision by FDA to require placebo controlled [rather than comparative agent controlled] trials of new antibiotics for approval of use for acute bacterial sinusitis and acute exacerbation of chronic bronchitis in view of the experience with telithromycin; analyses of the Adverse Event Reporting System showed no excess of reports of hepatitis or cholestasis for telithromycin in comparison to azithromycin, clarithromycin, trovafloxacin or nitrofurantoin; estimated frequency of severe hepatotoxicity to be 1:100,000 to 1:200,000 patients treated).

Chen Y, Guo JJ, Healy DP, Lin X, Patel NC. Risk of hepatotoxicity associated with the use of telithromycin: a signal detection using data mining algorithms. Ann Pharmacother 2008; 42: 1791-6. PubMed PMID: 19033479.

(Using a data mining algorithm an excess of reports of hepatotoxicity to the FDA's Adverse Event Reporting System [AERS] was detected between release of telithromycin in early 2004 and the first quarter of 2005; assessed number of reports of hepatotoxicity of all drugs and number reported for telithromycin compared to total numbers of adverse events reported for each).

Bolesta S, Roslund BP. Elevated hepatic transaminases associated with telithromycin therapy: a case report and literature review. Am J Health Syst Pharm 2008; 65: 37-41. PubMed PMID: 18159037.

(44 year old man developed mild serum enzyme elevations 3 days after taking telithromycin [800 mg/day] for 3 days [ALT 155 U/L, AST 68 U/L, but normal bilirubin and Alk P]; improved over time, but little follow up given; authors provide a review of the literature on telithromycin).

Brinker AD, Wassel RT, Lyndly J, Serrano J, Avigan M, Lee WM, Seeff LB. Telithromycin-associated hepatotoxicity: Clinical spectrum and causality assessment of 42 cases. Hepatology 2009; 49: 250-7. PubMed PMID: 19085949.

(Analysis of 42 cases of hepatotoxicity attributed to telithromycin reported to FDA between 2004-6; 26 were considered probable or highly likely and 16 as only possibly related to telithromycin, many cases were severe including 4 deaths and one liver transplant; onset in 2-43 days [median=10 days] with abrupt onset of symptoms or jaundice, usually hepatocellular with very high ALT, some developing ascites early, resolving with recovery; fever in 29% and eosinophilia in 19%).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, 5 cases were attributed to telithromycin and 3 to azithromycin as single agents, but none to erythromycin or clarithromycin).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including 66 due to antimicrobial agents, but only one due to macrolides [clarithromycin] and none to telithromycin).

Leitner JM, Graninger W, Thalhammer F. Hepatotoxicity of antibacterials: pathomechanisms and clinical data. Infection 2010; 38: 3-11. PubMed PMID: 20107858.

(Review; the macrolide antibiotics may cause cholestatic hepatitis with jaundice at an estimated rate of 3.6 per 100,000 prescriptions for erythromycin, 3.8 for clarithromycin, and 5.5 cases for telithromycin, compared to 10 for sulfonamides and 2000 for isoniazid).

Gagne JJ, Glynn RJ, Rassen JA, Walker AM, Daniel GW, Sridhar G, Schneeweiss S. Active safety monitoring of newly marketed medications in a distributed data network: application of a semi-automated monitoring system. Clin Pharmacol Ther 2012; 92: 80-6. PubMed PMID: 22588606.

(Description of results of a semiautomated, sequential propensity score with a matched cohort approach for drug safety monitoring based upon electronic databases; among 106,658 new users of telithromycin and a similar number of users of azithromycin identified over a 5 year period, 41 cases of hepatitis were found, 23 due to telithromycin for a risk rate of 2 per 10,000 users, not appreciably greater than with azithromycin).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 114: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, of which none were attributable to telithromycin or other macrolide antibiotics).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, one of which was attributed to clarithromycin [acute liver failure], but none were attributed to other macrolide antibiotics).

Ferrajolo C, Coloma PM, Verhamme KM, Schuemie MJ, de Bie S, Gini R, Herings R, et al.; EU-ADR consortium. Signal detection of potentially drug-induced acute liver injury in children using a multi-country healthcare database network. Drug Saf 2014; 37: 99-108. PubMed PMID: 24446276.

(Analyses of large spontaneous reporting databases from 3 European countries between 1995 and 2010 identified 125 drugs with at least one exposed case of unexplained acute liver injury in children, 20 of which had a statistically significant association, including clarithromycin [5 cases] and erythromycin [4 cases], but no cases were attributed to telithromycin).

Kaye JA, Castellsague J, Bui CL, Calingaert B, McQuay LJ, Riera-Guardia N, Saltus CW, et al. Risk of acute liver injury associated with the use of moxifloxacin and other oral antimicrobials: a retrospective, population-based cohort study. Pharmacotherapy 2014; 34: 336-49. PubMed PMID: 24865821.

(In a nested case control analysis of a health care network database of persons between 2001 and 2009, 8 selected antibiotics were assessed for association with risk of hospitalization for liver injury, adjusted relative risks being significantly elevated for levofloxacin [3.2], moxifloxacin [2.3], doxycycline [2.5], amoxicllin/clavulanate [2.5] and amoxicillin [2.3], but not for clarithromycin [1.8], telithromycin [1.7] or cefuroxime [0.9]).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 323 [36%] were attributed to antibiotics including 29 [3.2%] due to marolides of which 18 were linked to azithromycin, 2 to clarithromycin, 2 erythromycin and 7 telithromycin).

Ferrajolo C, Verhamme KM, Trifirò G, 't Jong GW, Picelli G, Giaquinto C, Mazzaglia G, et al. Antibiotic-induced liver injury in paediatric outpatients: a case-control study in primary care databases. Drug Saf 2017; 40: 305-15. PubMed PMID: 28025733.

(In a health care database of 429,772 children in Italy and the Netherlands followed between 2008 and 2010, 938 cases of liver injury of uncertain cause were identified, the rate being higher in those with current use of antibiotics [12% vs 3.6%] for an adjusted odds rate ratio [aOR] of 3.2; specific antibiotics most commonly implicated were fluoroquinolones [19.0], cephalosporins [4.5], macrolides [3.5] and penicillins [2.6], but no cases were attributed to telithromycin).

Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, Fontana RJ, et al.; U.S. Drug Induced Liver Injury Network Investigators. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology 2017; 65: 1267-77. PubMed PMID: 27981596.

(Among 363 patients with drug induced liver injury who underwent liver biopsy, 26 [7%] had bile duct loss, including 2 cases attributed to azithromycin, but none to clarithromycin or other macrolides).