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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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LEUKOTRIENE ANTAGONISTS: What is their role in the management of ASTHMA?

Management options for chronic asthma were reviewed in Therapeutics Letter #12 (Jan/Feb 1996). In 1998 Canada licensed two members of a new class of drugs for asthma, leukotriene antagonists, **zafirlukast (Accolate®)** and **montelukast (Singulair®).** The goal of this Letter is to assess the published randomised controlled trial evidence to determine the role of these drugs in the management of asthma.

What is the rationale for leukotriene receptor antagonists (LTRAs)?

LTRAs inhibit the effects of the cysteinyl leukotrienes, which represent 3 of a large number of chemical mediators of asthma. Leukotrienes are released by several types of cells and can cause bronchoconstriction and inflammation[1,2]. The cysteinyl leukotrienes are particularly important mediators in patients with aspirin-sensitive asthma (characterized by chronic severe asthma symptoms, nasal polyps, and aspirin-induced bronchospasm)[3]. LTRAs competitively block leukotriene receptors on bronchial smooth muscle and elsewhere[1,2].

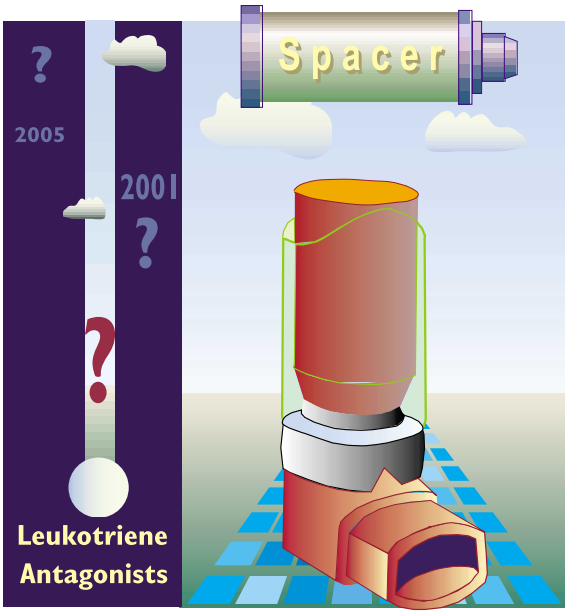
How are LTRAs handled in the body?

Both drugs are rapidly absorbed after oral administration. Zafirlukast absorption is decreased in the presence of food. Both drugs are highly bound to plasma albumin and are eliminated by liver metabolism. The half-life of montelukast is 3 to 6 hours and that for zafirlukast is 10 hours.

What is the evidence for their effectiveness?

Zafirlukast administered twice daily has been compared with placebo in two published short-term trials[4,5] of patients > age 11 (*see Table*). There have been no published trials comparing zafirlukast with inhaled corticosteroids.

Montelukast has been compared with placebo in 11 published RCTs. Most of these trials were designed to ascertain the dose and dose regimen, and showed that 10 mg of montelukast once daily at bedtime produces maximum effects in adults. At the recommended doses montelukast has been compared with placebo in one large trial in adults[6] and one large trial in children[7], *(see Table*). In one trial of 110 patients with exercise induced asthma the maximal decrease in FEV_1 associated with exercise was 32.4% with placebo as compared to 22.2% with montelukast[8]. A recently published trial compared montelukast to inhaled glucocorticoid and placebo in adults with chronic asthma. **Montelukast was better than placebo but not as effective as low-dose inhaled beclomethasone** [9] *(see Table)*.



The average effects in the trials, though statistically significant, are small and of questionable clinical significance. The effects on home peak expiratory flow rate are marginal, increase of 20L/min (6%), the day after the first dose.[10]

Safety

In the short-term clinical trials, adverse effects did not differ between the leukotriene antagonists, placebo or inhaled glucocorticoids. Rare cases of Churg-Strauss syndrome (allergic angiitis and granulomatosis) have been reported with both drugs[10]. Some of these cases may have been unmasked by steroid withdrawal, however, not all cases have coincided with steroid withdrawal. Zafirlukast inhibits liver microsomal enzymes, P450 CYP3A4 and CYP2C9, and has been shown to increase the effects of warfarin. Other clinically important drug interactions are likely, but unknown at present. Montelukast has been shown to **not** interact with human P450s *in vitro* and **not** to interact with theophylline, prednisone, prednisolone, ethinyl estradiol, terfenadine, digoxin and warfarin in clinical studies.

TABLE: Evidence of effectiveness of leukotriene antagonists.

Drug and dose	N	Outcomes Δ FEV_1 *	Outcomes ↓ B_2 agonist♦	Trial details
Zafirlukast [4] (20 mg BID)	57	+11%	- 31%	Chronic asthma
Placebo	56	+ 1%	- 15%	Age: 18-65 years 6 weeks
Zafirlukast [5] (20 mg BID)	514	+ 5.6%	- 22.3%	Chronic asthma
Placebo	248	+ 1%	+ 7%	Age: > 11 years 13 weeks
Montelukast [6] (10 mg HS)	408	+ 13%	- 25%	Chronic asthma
Placebo	273	+ 4.2%	0%	Age: > 14 years 12 weeks
Montelukast [7] (5 mg HS)	201	+ 8.2%	- 12%	Chronic asthma
Placebo	135	+ 3.6%	+ 6%	Age: 6-14 years 8 weeks
Beclomethasone[9] (200 µg BID)	251	+13.1%	- 40%	Chronic asthma
Montelukast (10 mg HS)	387	+ 7.4%	- 24%	Age: 15-85 years
Placebo	257	+ 0.7%	0%	12 weeks

* Forced expiratory volume in one second

♦ Inhalers (e.g. salbutamol)

Dose and daily cost

	Dose	Daily cost
zafirlukast	20 mg tablet BID on an empty stomach (age > 11 years)	$1.50
montelukast	10 mg tablet at HS (age >14 years)	$2.20
	5 mg chewable tablet at HS (age 6 to14 years)	$1.50

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to March15,1999. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 110 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.

Conclusions:

LEUKOTRIENE ANTAGONISTS IN ASTHMA

- **Cause statistically significant effects on measures of airway obstruction and symptoms as compared to placebo in short-term trials.**
  –– effects are detectable on the first day and do not change appreciably over 6 to 13 weeks.
  –– average clinical effects are small and would unlikely be detectable by individual patients.
- **Cause average clinical benefits that are less than low-dose inhaled glucocorticoids.**
- **Cause few adverse effects in short-term use, but long-term risks are unknown.**
- **Are not appropriate for treatment of acute asthma exacerbations.**
- **May be useful as add-on or an alternative to inhaled glucocorticoids in problematic patients with inadequate response or intolerance, respectively**

References:

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