Bronchoprotective Effects of Leukotriene Receptor Antagonists in Asthma*

A Meta-analysis

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**Study objective:** Cysteinyl leukotrienes are important proinflammatory mediators in the pathogenesis of asthma. Since bronchial hyperresponsiveness is a noninvasive surrogate marker of asthmatic airway inflammation, we evaluated the bronchoprotection afforded by leukotriene receptor antagonists (LTRAs).

**Design:** Systematic review of randomized, placebo-controlled trials in which LTRAs were administered for $>5$ days. Studies in which active drug was administered as a first-line or second-line therapy were used.

**Setting:** MEDLINE, BIDS, and Cochrane Library data registers.

**Measurements:** The doubling dose/dilution difference that caused a 20% fall in the FEV$_1$ between LTRA and placebo.

**Results:** Thirteen trials (353 subjects) fulfilled eligibility criteria. Combining the results the overall weighted estimated protection amounted to a 0.85 doubling dose shift (95% confidence interval, 0.69 to 1.02).

**Conclusion:** Since the estimated protection amounted to almost one doubling dose, this reinforces the role of LTRAs as anti-inflammatory therapy in asthma. *(CHEST 2002; 122:146–150)*

**Key words:** asthma; bronchial hyperreactivity; leukotriene receptor antagonist

**Abbreviations:** AMP = adenosine monophosphate; CI = confidence interval; LTRA = leukotriene receptor antagonist

Asthma is characterized by airway inflammation that manifests as reversible airflow limitation and airway hyperresponsiveness. Consequently, anti-inflammatory therapy plays a pivotal role in its management. Cysteinyl leukotrienes are important pro-inflammatory and bronchoconstrictor mediators in the pathogenesis of asthma, while leukotriene receptor antagonists (LTRAs) demonstrate hybrid anti-inflammatory and bronchodilatory properties.\(^1\) A meta-analysis found that LTRAs reduced exacerbations by 50% and reduced the requirement of additional antiasthma therapy.\(^2\) Current international guidelines\(^3\) recommend using an LTRA as first-line therapy patients with mild, persistent asthma, or as second-line therapy in conjunction with inhaled corticosteroids, as an alternative to increasing the dose of inhaled corticosteroid.

Bronchial hyperresponsiveness or hyperreactivity is a noninvasive surrogate marker of airway inflammation, and is a reproducible method of assessing the efficacy of antiasthma therapy in the laboratory. We examined the bronchoprotection afforded by commonly used LTRAs, namely montelukast, pranlukast, and zafirlukast. A meta-analysis was performed that evaluated the protection given with LTRA compared to placebo during long-term dosing when used as first-line or second-line therapy.

**Materials and Methods**

A computerized MEDLINE, BIDS, and Cochrane Library literature search was carried out from 1992 to April 2001 to identify randomized, placebo-controlled trials in which bronchoprotection was assessed using montelukast, pranlukast, and zafirlukast. The following keywords were used in the search: "leukotriene receptor..."
antagonist,” “montelukast,” “pranlukast,” “zafirlukast,” “histamine,” “methacholine,” “adenosine monophosphate,” and “bronchial hyperresponsiveness/hyperreactivity.”

Eligibility Criteria

Eligibility criteria included the following: (1) administration of LTRA (as first-line or second-line therapy) for ≥ 5 days; (2) the doubling dose/dilution difference in provocative dose/concentration to effect a 20% fall in FEV1 was given or calculable from the text, as the 95% confidence interval (CI) vs placebo; and (3) administration of the bronchial stimuli histamine, methacholine, and adenosine monophosphate (AMP). These challenge agents were included as they are commonly used for diagnostic purposes, and can be quantified in terms of doubling doses, unlike exercise and allergen.

Statistical Analysis

All data were logarithmically converted to enable the doubling dose or dilution shift for the provocative dose or dilution to be calculated. The weighted estimate of overall protection with 95% CI was calculated from the data from each of the trials.

RESULTS

The Quorum flow diagram illustrates the main reasons for trial exclusion (Fig 1). Table 1 summarizes the demographics of the 13 eligible trials. Figure 2 shows the estimated protection given by LTRAs in each of the individual trials. One study evaluated protection with AMP and methacholine (Fig 2, 9A and 9B). The overall weighted estimated protection with LTRA is shown amounting to a 0.85 doubling dose shift (95% CI, 0.69 to 1.02). A $\chi^2$ test of heterogeneity of the 13 trials (14 results) was performed, giving a $\chi^2$ value of 16.55 with 13 degrees of freedom ($p = 0.22$).

DISCUSSION

Our results have shown that use of an LTRA resulted in an overall estimated protection of almost one doubling dose. All three LTRAs conferred a consistent degree of protection, and it is worth pointing out that in all but one study, where methacholine challenge was not the primary outcome variable, the lower end of the 95% CI excluded zero, indicating a significant effect. The degree of bronchoprotection was comparable for direct acting (eg, methacholine and histamine) or indirect acting (eg, AMP) bronchoconstrictor stimuli. Furthermore, LTRA administered as first-line or second-line therapy resulted in a similar magnitude of bronchoprotection.

Bronchial hyperresponsiveness is a hallmark feature of asthma that results in episodic bronchoconstriction when exposed to an appropriate stimulus. Indirect stimuli such as AMP act on inflammatory cells, causing the release of preformed mediators such as histamine and cysteinyl leukotrienes, whereas histamine and methacholine act directly on airway smooth muscle. These tests are commonly carried out in the laboratory and provide a means of assessing the presence and severity of bronchial hyperresponsiveness, which was the rationale behind our study. Bronchial hyperresponsiveness correlates against airway eosinophils, and when used in conjunction with conventional tests of airway caliber is a useful tool in improving asthma control and reducing exacerbations. Thus, bronchial hyperresponsiveness may be regarded as a surrogate marker for airway inflammation.
We discovered 13 randomized trials that fulfilled all eligibility criteria. The length of the studies was variable, ranging from 1 to 12 weeks. However, single doses of montelukast have been shown to exhibit bronchoprotective effects in patients receiving inhaled corticosteroids.20 Furthermore, LTRAs do not show tolerance for bronchoprotective effects during long-term dosing.5,16,21

It is well recognized that suppression of the inflammatory process in asthmatics is pivotal in maintaining asthma control and prevention of long-term airway remodeling.22,23 In this respect, inhaled corticosteroids are considered as first-line anti-inflammatory therapy. Inhaled corticosteroids exhibit a relatively shallow dose-response curve for anti-inflammatory efficacy and steeper curve for systemic adverse effects.24 Treatment with corticosteroids appears to have a limited impact on airway inflammation and cysteinyl leukotriene levels.25,27 This suggests that second-line nonsteroidal antiasthma therapy with an LTRA may have a role in achieving more complete suppression of the inflammatory cascade.

Cysteinyl leukotrienes in BAL fluid and sputum are higher in subjects with more severe asthma.25,28 LTRAs are known to attenuate the early-phase and late-phase response to inhaled allergen,29 and offer protection against a variety of bronchoconstrictor stimuli.5,6,16 Various studies have demonstrated LTRAs to reduce rescue treatment requirement, improve pulmonary function, and reduce symptoms.1 This improvement has

| Table 1—Demographics of the 13 Eligible Trials |
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| Source | Reference on Figure | LRTA | No. in Study | Length of Study | Challenge | First- or Second-Line Therapy |
| Wilson et al5 | 1 | Montelukast | 20 | 2 wk | AMP | Second |
| Lipworth et al6 | 2 | Zafirlukast | 24 | 1 wk | Methacholine | Second |
| Fujimura et al7 | 3 | Zafirlukast | 11 | 1 wk | Methacholine | Second |
| Yoshida et al8 | 4 | Pranlukast | 10 | 1 wk | Methacholine | Second |
| Hamilton et al9 | 5 | Pranlukast | 10 | 5 d | Methacholine | First |
| Yoshida et al10 | 6 | Pranlukast | 32 | 4 wk | Methacholine | Second |
| Fowler et al11 | 7 | Zafirlukast | 24 | 4 wk | Methacholine | Second |
| Wilson et al12 | 8 | Montelukast | 14 | 2 wk | AMP | Second |
| Dempsey et al13 | 9A | Montelukast | 21 | 4 wk | Methacholine | First |
| | 9B | | | | | First |
| Rosenthal et al14 | 10 | Zafirlukast | 32 | 2 wk | Methacholine | First |
| Wilson et al15 | 11 | Montelukast | 12 | 2 wk | AMP | First |
| Leff et al16 | 12 | Montelukast | 107 | 12 wk | Methacholine | First |
| Westbroek and Pasma17 | 13 | Zafirlukast | 30 | 2 wk | Histamine | First |

Figure 2. Doubling dose/dilution protection of LTRA compared to placebo. *Denotes LTRA use as second-line therapy (the others being first-line therapy). Values are shown as means and 95% CI. Overall estimated protection was 0.85 (95% CI, 0.69 to 1.02). M = montelukast; P = pranlukast; Z = zafirlukast; e = estimated overall protection.

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been shown even in patients requiring high doses of inhaled corticosteroid.\textsuperscript{30}

LTRAs demonstrate disease modifying activity, as reflected by reduction in exhaled nitric oxide and airway inflammatory cells.\textsuperscript{6,31,32} Thus, the addition of a LTRA as second-line controller therapy would appear to be a reasonable option in treating patients suboptimally controlled on inhaled corticosteroids, which is supported by a further 0.85 doubling dose reduction in bronchial hyperresponsiveness from the present analysis.

It is pertinent to consider the protection conferred by the alternative option of increasing the dose of inhaled corticosteroid. In a study by Taylor et al.,\textsuperscript{33} there was a 1.4 doubling dose improvement in AMP protection comparing 400 \( \mu \text{g/d} \) vs 1,600 \( \mu \text{g/d} \) of ciclesonide; in another study using AMP by Wilson and Lipworth,\textsuperscript{34} comparing 400 \( \mu \text{g/d} \) vs 1,600 \( \mu \text{g/d} \) of budesonide, there was a 1.9 doubling dose increase in protection.

It is also evident that LTRAs exhibit less broncho-protection than low-dose inhaled corticosteroid when administered as first-line monotherapy. For example, Wilson et al.\textsuperscript{15} reported a 1.1 doubling dilution greater effect in AMP challenge with budesonide, 400 \( \mu \text{g/d} \), vs montelukast, 10 \( \mu \text{g/d} \); Westbroek and Pasma\textsuperscript{17} found a 0.8 doubling dilution difference on histamine challenge with fluticasone, 200 \( \mu \text{g/d} \), vs zafirlukast, 40 \( \mu \text{g/d} \). In conclusion, LTRAs, when used as first-line or second-line preventer therapy afforded overall protection of almost one doubling dose, reinforcing their role as anti-inflammatory therapy in asthma.

ACKNOWLEDGMENT: The authors thank Dr. S.A. Ogston (Department of Public Health and Epidemiology, University of Dundee) for statistical advice.

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