Leukotriene receptor antagonist therapy

O J Dempsey

Abstract
Leukotriene receptor antagonists (LTRA) are a new class of drugs for asthma treatment, available in tablet form. Their unique mechanism of action results in a combination of both bronchodilator and anti-inflammatory effects. While their optimal place in asthma management is still under review, LTRA represent an important advance in asthma pharmacotherapy.

Keywords: leukotriene receptor antagonist; asthma; montelukast; zafirlukast

Leukotriene receptor antagonists (LTRA) are a new class of drugs for asthma treatment, available in tablet form.1,2 Their unique mechanism of action results in a combination of both bronchodilator and anti-inflammatory effects. While their optimal place in asthma management is still under review, LTRA represent an important advance in asthma pharmacotherapy. In this article I provide a brief overview of evidence supporting their use in patients with chronic asthma, focusing on two leukotriene receptor antagonists, montelukast and zafirlukast, currently licensed for use in the United Kingdom.

Methods
Fully published papers and review articles between 1966 and January 2000 were sought using appropriate index terms and the National Library of Medicine’s computerised search service (providing access to Medline, Pre-Medline, and other related databases). Studies published only in abstract form (and thus subject to less rigorous peer review) are not discussed.

Background
The term “slow reacting substance of anaphylaxis” (SRS-A), coined by Brocklehurst in 1960, is still familiar to many physicians.3 The chemical structure of SRS-A, however, was not identified until 1979 by Samuelsson and colleagues, who discovered that it consisted of a family of biologically active fatty acids derived from arachidonic acid metabolism in many cells, including eosinophils, mast cells, and lymphocytes (fig 1).4,5 The term “leukotriene” is apt, given their synthesis in leucocytes and their chemical structure (containing three conjugated double bonds, that is, a triene). Of particular importance in the patient with asthma are leukotrienes C₄, D₄, and E₄.6,7 As these contain the amino acid residue cysteine, they are sometimes referred to collectively as the cysteinyl leukotrienes.

Cysteinyl leukotrienes are important biological mediators in asthma, interacting with at least one specific receptor in the lungs, which has now been fully identified,6,8 leading to various important biological effects (box 1). Of these, potent bronchoconstriction is well recognised, but they also have a variety of effects that are proinflammatory.9 Thus leukotrienes are capable of inducing several key features of asthma. Furthermore, studies have shown that leukotrienes are produced in excessive quantities in patients with asthma, reinforcing the view that they are important biological mediators.9

Box 1: Biological effects of cysteinyl leukotrienes
- Bronchoconstriction (100–10000 times more potent than histamine).
- Bronchial smooth muscle hyperresponsiveness, for example to allergens.
- Inflammatory cell recruitment, for example eosinophils.
- Vascular permeability (leading to tissue oedema and airflow obstruction).
- Mucus formation (leading to further airflow obstruction).

www.postgradmedj.com
Interestingly, inhaled or oral corticosteroids have not been shown to attenuate leukotriene production significantly in vivo. This led to interest in the development of specific leukotriene modifying asthma drugs, which might confer additional benefits even in patients already receiving an optimal dose of inhaled corticosteroid. Several drug classes were developed, affecting various sites in the leukotriene biosynthetic cascade, of which the most successful have been receptor antagonists.

**Leukotriene receptor antagonists**

**STRUCTURE**

Montelukast and zafirlukast are two of the most commonly prescribed LTRA available worldwide. Their structures are shown in fig 2.

**Table 1 Prescribing information**

<table>
<thead>
<tr>
<th>Indications (UK)</th>
<th>Zafirlukast&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Treatment of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy / lactation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hepatic impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult dose can be taken with food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric dose: avoid 1 h before and 2 h after meals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients on warfarin may have ⇑ prothrombin times (monitor INR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin may ⇑ zafirlukast levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafirlukast levels with erythromycin, terfenadine, theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose adjustment in the elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose adjustment in the elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablet (paediatric tablet chewable and cherry flavoured)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5mg (if aged 6–14 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg (if &gt; 14 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special instructions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid 1 h before and 2 h after meals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None with oral contraceptive pill, warfarin, digoxin, theophylline, or terfenadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coadministration with CYP 3A4 hepatic enzyme inducers (eg, phenytoin, phenobarbitone, rifampicin) may ⇑ montelukast levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL EFFICACY IN ASTHMA**

The optimal place of LTRA in asthma management is still under review. This reflects their recent introduction and the relative paucity of fully published comparative studies, particularly compared with existing asthma treatments. For simplicity, in this article I will describe as first line treatment their use in studies in conjunction with “as required” short acting β<sub>2</sub> agonists. Their use in patients already receiving inhaled corticosteroids and “as required” short acting β<sub>2</sub> agonists will be described as second line treatment.

**First line treatment studies—chronic asthma**

LTRA v PLACEBO

These studies are summarised in table 2. Most of the patients in these studies were steroid naive, and hence the description “first line treatment studies”; however, some did include a minority of patients receiving low dose inhaled corticosteroids or oral theophyllines, or both.
Table 2  First line treatment—leukotriene receptor antagonists v placebo: randomised, placebo controlled, parallel group studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age range (years)</th>
<th>Treatment duration (weeks)</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; (% predicted)</th>
<th>Inclusion criteria‡ and intercurrent treatment</th>
<th>Treatment(s)</th>
<th>Primary endpoint(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altman&lt;sup&gt;13&lt;/sup&gt;</td>
<td>343</td>
<td>18–65</td>
<td>6</td>
<td>40–80</td>
<td>β use ≥ 1 puff/day; 36% on ICS, 15% on theo</td>
<td>M 10 mg, 100 mg, or 200 mg od; P M 10 mg or 50 mg bd; P</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>M&lt;sub&gt;10mg&lt;/sub&gt;* &gt; P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No dose (or dosage interval) relation with efficacy</td>
</tr>
<tr>
<td>Knorr&lt;sup&gt;14&lt;/sup&gt;</td>
<td>336</td>
<td>6–14</td>
<td>8</td>
<td>50–85</td>
<td>36% on ICS</td>
<td>M 5 mg od; P</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>M** &gt; P</td>
</tr>
<tr>
<td>Noonan&lt;sup&gt;15&lt;/sup&gt;</td>
<td>281</td>
<td>18–65</td>
<td>3</td>
<td>40–80</td>
<td>β use ≥ 1 puff/day; 24% on ICS, 19% on theo</td>
<td>M 2 mg, 10 mg, or 50 mg od; P</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>M&lt;sub&gt;10mg&lt;/sub&gt;* &gt; P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Also significant ↑ in quality of life</td>
</tr>
<tr>
<td>Noonan&lt;sup&gt;15&lt;/sup&gt;</td>
<td>281</td>
<td>≥ 15</td>
<td>12</td>
<td>50–85</td>
<td>23% on ICS</td>
<td>M 10 mg od; P</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>M** &gt; P</td>
</tr>
<tr>
<td>Reiss&lt;sup&gt;16&lt;/sup&gt;</td>
<td>681</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improvement regardless of whether treated with inhaled steroids or oral theophyllines</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish&lt;sup&gt;11&lt;/sup&gt;</td>
<td>762</td>
<td>≥ 12</td>
<td>13</td>
<td>≥ 55</td>
<td>BHR, β reversibility</td>
<td>Z 20 mg bd; P</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Z* &gt; P</td>
</tr>
<tr>
<td>Kerop&lt;sup&gt;16&lt;/sup&gt;</td>
<td>261†</td>
<td>≥ 12 in 3 trials</td>
<td>13</td>
<td>≥ 55 in 3 trials</td>
<td></td>
<td>Z 20 mg bd; P</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, morning PEF</td>
<td>Z* &gt; P</td>
</tr>
<tr>
<td>Nathan&lt;sup&gt;18&lt;/sup&gt;</td>
<td>454</td>
<td>≥ 18 in 1 trial</td>
<td>≥ 12</td>
<td>45–80 in 1 trial</td>
<td></td>
<td>Z 20 mg bd; P</td>
<td>Morning PEF, daytime symptoms</td>
<td>Z** &gt; P</td>
</tr>
<tr>
<td>Spector&lt;sup&gt;20&lt;/sup&gt;</td>
<td>276</td>
<td>18–65</td>
<td>6</td>
<td>40–70</td>
<td>BHR; could be on theo (withdrawn during study)</td>
<td>Z 5 mg, 10 mg, or 20 mg bd; P</td>
<td>PEF, symptoms</td>
<td>Z&lt;sub&gt;symptoms&lt;/sub&gt;* &gt; P, for symptoms and evening PEF</td>
</tr>
<tr>
<td>Suissas&lt;sup&gt;21&lt;/sup&gt;</td>
<td>146</td>
<td>≥ 12</td>
<td>13</td>
<td>≥ 55</td>
<td>BHR</td>
<td>Z 20 mg bd; P</td>
<td>Clinical/economic efficacy</td>
<td>Z* &gt; P</td>
</tr>
<tr>
<td>Tashkin&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1484†</td>
<td>≥ 12 in 3 trials</td>
<td>13</td>
<td>≥ 55 in 3 trials</td>
<td>BHR</td>
<td>Z 20 mg bd; P</td>
<td>Exploratory subset analysis</td>
<td>Z* &gt; P, † benefit in those with more severe disease</td>
</tr>
</tbody>
</table>

†Retrospective analysis of four studies.
‡In addition to inclusion criteria shown, all studies required asthmatics to be symptomatic (minimum predefined symptom score) and demonstrate reversible airflow obstruction (following challenge with a short acting β<sub>2</sub> agonist).

> Significantly greater effect than placebo.

*p < 0.05; **p < 0.01.
bd, twice daily; BHR, bronchial hyperresponsiveness; FEV<sub>1</sub>, forced expiratory volume in 1 second (litres); ICS, inhaled steroid; M, montelukast; od, once daily; P, placebo; PEF, peak expiratory flow rate (l/min); theo, theophylline; Z, zafirlukast.
The primary endpoint in most of the studies was pulmonary function, usually forced expiratory volume in one second (FEV\textsubscript{1}). Improvements in mean FEV\textsubscript{1} were typically modest, for example 10%, with much interindividual variation. Commonly used secondary endpoints included symptoms and quality of life scores, other measures of pulmonary function such as peak expiratory flow rates, the need for other drugs (short acting β\textsubscript{2} agonist or inhaled/oral corticosteroid use), and effects on daily living (days off school or work). Improvement in these secondary outcomes was typically more impressive, for example 25%. The majority of these studies concluded that the use of an LTRA in patients with mild asthma was superior to placebo, using these subjective and objective measures.

Only one of these studies examined use of LTRA in patients with more severe airflow obstruction.\textsuperscript{28} In this retrospective pooled subgroup analysis, data were reviewed from four clinical trials in which zafirlukast 20 mg twice daily or placebo was given over a 13 week period to 261 steroid naive patients identified as having severe persistent asthma. Compared with placebo, patients receiving zafirlukast had significantly (p < 0.05) greater improvements in spirometry, peak expiratory flow, symptoms, and β\textsubscript{2} agonist requirement. However, these changes—although statistically significant—were small. Furthermore, given that current United Kingdom and American asthma management guidelines advise early use of an optimal dose of inhaled corticosteroids in patients with asthma of this severity,\textsuperscript{29-31} this study is of limited clinical relevance.

**LTRA vs INHALED CORTICOSTEROID**

There is only one fully published study directly comparing use of an LTRA with low dose inhaled corticosteroid in patients with mild asthma.\textsuperscript{32}

In this randomised, double bind, parallel group, multicentre study, 895 patients with mild to moderate asthma received montelukast 10 mg once daily, 200 µg of beclomethasone twice daily with a spacer, or placebo for three months. Both montelukast and beclomethasone were more effective than placebo, primary endpoints being daytime asthma symptoms and FEV\textsubscript{1}; montelukast had a faster onset of action (day 1) compared with beclomethasone (day 8). Nevertheless, patients receiving beclomethasone achieved a significantly better mean effect in terms of increased FEV\textsubscript{1} and symptom reduction. For example, the average percentage change from baseline in FEV\textsubscript{1} over three months was 13.1% with beclomethasone, 7.4% with montelukast, and 0.7% with placebo (p < 0.001 for each active treatment compared with placebo; p < 0.01 for beclomethasone compared with montelukast). It is interesting to note that both active treatment groups had a similar (normal) distribution of response, so it is incorrect to assume that patients are easily categorised into “responders” or “non-responders” to either treatment.\textsuperscript{32}

**LTRA vs OTHER ASThma TREATMENTS**

There is only one published study comparing an LTRA with sodium cromoglycate.\textsuperscript{33} This 13 week, randomised, parallel group study recruited 287 patients with mild to moderate asthma, comparing zafirlukast, sodium cromoglycate aerosol (1.6 mg four times daily), and placebo. No significant difference was detected between either of the active treatments, although both were better than placebo in terms of symptom improvement and reduced β\textsubscript{2} agonist use. Subset analysis suggested greatest improvement in patients with ≥ 10% peak flow variability.\textsuperscript{34}

**Second line treatment studies—chronic asthma**

**LTRA vs PLACEBO**

Subgroup analysis of several studies mentioned earlier (table 2) suggested that montelukast could provide additional clinical benefit for patients using concomitant inhaled corticosteroids.\textsuperscript{15-16} This has now been confirmed prospectively in an important study by Lavoilette et al.\textsuperscript{35} In that study, 642 patients with chronic asthma incompletely controlled by inhaled beclomethasone 200 µg twice daily with a spacer were randomised to one of four treatment groups: (1) montelukast 10 mg once daily + continuing beclomethasone; (2) placebo tablet + continuing beclomethasone; (3) montelukast + inhaled placebo (after blind beclomethasone removal); and (4) placebo tablet and inhaler. The use of montelukast, in conjunction with 400 µg/day beclomethasone dipropionate, provided significant additional benefit in terms of improving FEV\textsubscript{1}, daytime asthma scores, and nocturnal awakenings.

**LTRA vs LONG ACTING β\textsubscript{2} AGONISTS**

There is only one published study comparing these drug classes in chronic asthma.\textsuperscript{36} Salmeterol and zafirlukast were compared in a four week, randomised, double blind, parallel group multicentre study. Over 80% of the patients were having concomitant inhaled corticosteroid treatment, and received either inhaled salmeterol 42 µg twice daily by metered dose inhaler or oral zafirlukast 20 mg twice daily. The primary outcome measure was morning peak expiratory flow (PEF) rates. Both active treatments were associated with improvements from baseline in pulmonary function, asthma symptoms, and short acting β\textsubscript{2} agonist use. Salmeterol treatment resulted in significantly greater improvements from baseline compared with zafirlukast for most efficacy measures, including morning PEF (29.6 l/min vs 13.0 l/min; p ≤ 0.01), percentage of symptom-free days (22.4% vs 8.8%; p ≤ 0.01), and percentage of days and nights with no supplemental short acting β\textsubscript{2} agonist use (30.5% vs 11.3%; p ≤ 0.01).\textsuperscript{36}

These results, while in favour of salmeterol, are perhaps not surprising, as LTRA are recognised as being less potent bronchodilators than long acting β\textsubscript{2} agonists. The endpoint chosen in this short study is therefore very relevant when comparing these two drug classes. It may be that the presumed additional anti-
Leukotriene receptor antagonists

Inflammatory effects conferred by LTRA use (which may take several months to see) may be equally as important as improvements in spirometry.

LTRA & OTHER ASTHMA TREATMENTS

There are few fully published studies comparing the use of alternative second line treatments such as theophyllines, long acting β2 agonists, or cromones with LTRA. One study has suggested that combination treatment with montelukast and salmeterol confers additive benefits to patients who are suboptimally controlled on inhaled corticosteroids, in terms of bronchoprotection to adenosine challenge and bronchodilatation.29

LTRA AS STEROID SPARING AGENTS

Although not currently licensed for use in this way, two studies have addressed the potential role of LTRA as steroid sparing agents in patients requiring high maintenance doses of inhaled corticosteroids.30 31 This is an important issue, particularly given concerns about the potential risk of systemic adverse effects associated with prolonged use of high dose inhaled corticosteroids. In a randomised, double blind, placebo controlled study, 79 asthma patients (mean FEV1, 81% of predicted) requiring a mean daily dose of approximately 1900 μg of beclometasone dipropionate were studied.30 Following a two week run in phase, each patient's dose of beclometasone was halved for six weeks. During this time, patients received additional treatment, either as placebo or as an LTRA (pranlukast, in a standard adult dose of 450 mg twice daily). After six weeks, those receiving placebo had a significant deterioration in symptoms and lung function, combined with increased β2 agonist requirement. Furthermore, this was mirrored by a rise in non-invasive markers of airway inflammation, including exhaled breath nitric oxide and blood eosinophil cationic protein. Interestingly, in the pranlukast group this subjective and objective deterioration was not seen, suggesting that use of an LTRA may facilitate dose reduction in patients dependent on high doses of inhaled corticosteroid, but not necessarily at the cost of an increase in airway inflammation.30

In another study of different design, the use of montelukast was also shown to facilitate a significant reduction in maintenance inhaler corticosteroid dose compared with placebo, over a period of 12 weeks.31 Studies longer than 12 weeks will obviously be necessary to see whether this is indeed a true steroid sparing effect.

Exercise induced asthma

Exercise induced bronchoconstriction is common in asthmatic patients, although the mechanisms underlying this are still poorly understood.32 Leukotrienes are recognised as important mediators associated with the reduction in airway calibre. Studies in both children33 34 and adults35 36 have shown that LTRA afford substantial protection against exercise induced bronchoconstriction in many, but not all, patients with mild stable asthma. An advantage of LTRA in these patients is their duration of action. For example, protection against exercise induced bronchoconstriction is evident with montelukast even 20 to 24 hours after dosing. Furthermore, unlike long acting β2 agonists, chronic dosing with LTRA is not associated with tolerance to their effects.40 42

Aspirin induced asthma

Aspirin induced asthma affects approximately 10% of adult patients with asthma.43 In these patients, exposure to aspirin and other cyclooxygenase inhibitors, for example non-steroidal anti-inflammatory agents, is associated with excessive leukotriene release. Interestingly, bronchial biopsies from these patients show overexpression of leukotriene C4 synthesize in eosinophils and mast cells (fig 1).44 This may be secondary to a common polymorphism of the LTC4 gene.45 Intuitively therefore, LTRA are a logical treatment choice in this type of asthma patient. Clinical efficacy has been demonstrated compared with placebo, even in patients already receiving inhaled corticosteroid treatment.46 It should be emphasised, however, that patients should still avoid ingestion of aspirin and related drugs, even if taking an LTRA, as protection is not complete.46 47

Premenstrual asthma

Many women describe an increase in asthma symptoms just before and during menstruation.48 While the mechanism remains unclear, one theory is that systemic mast cell activation occurs in response to altered female hormone levels, resulting in release of potent mediators including leukotrienes. Interestingly, a recent study supports this hypothesis, suggesting that use of an LTRA may be beneficial in these patients.49

Safety

Montelukast and zafirlukast were first marketed in the United Kingdom in February and July 1998, respectively. Up to the end of April 1999, 233 000 prescriptions had been issued for montelukast and 17 000 for zafirlukast. Both drugs remain under close observation, but appear to be generally well tolerated. Most side effects are mild, for example gastrointestinal disturbance, rashes, and fatigue (box 2).50

Some isolated cases of Churg–Strauss syndrome, a rare systemic vasculitis associated with asthma, have been reported, but it seems unlikely that LTRA are directly implicated.51 A more likely explanation is that inhaled (high dose) or oral corticosteroid treatment in these patients may mask the underlying vasculitis. If steroid doses are reduced inappropriately, facilitated by use of LTRA, the underlying vasculitis may be revealed. It should be emphasised that LTRA are not currently licensed in order to allow dose reduction of either inhaled or oral corticosteroids. Clinicians should be suspicious if patients with asthma in these circumstances develop worsening asthma symp-
Box 2: Safety of leukotriene receptor antagonists
- Generally well tolerated, side effect profile similar to placebo.
- Common side effects reported include gastrointestinal disturbance, rashes, fatigue.
- Report any side effects to Committee of Safety of Medicines using yellow card scheme.
- Rare cases of Churg-Strauss syndrome (see text)—caution if reducing maintenance inhaled or oral corticosteroid.

Clinical efficacy in conditions other than asthma
Leukotriene receptor antagonists have been used successfully in a variety of other conditions, notably rhinitis, which often coexists in asthma patients.35-55 Other conditions that have included asthmatic dermatitis56 and eosinophilic gastroenteritis.57 There is no evidence that the current cysteinyl leukotriene receptor antagonists will be useful in patients with chronic obstructive pulmonary disease.

Predictors of response to LTRA
Currently, it is not possible to predict who will respond well to an LTRA and, as described earlier, this response is normally distributed, so some patients (perhaps as many as 50%) may have a disappointing response. Thus many clinicians opt for a four to eight week therapeutic trial of an LTRA, although longer trials may be necessary to detect beneficial effects in terms of attenuating airway inflammation. Recently, genetic polymorphisms of the enzymes controlling biosynthesis of leukotrienes have been described and may be important predictors of response.44 45 58

Place of LTRA in asthma management guidelines
The current British Thoracic Society asthma management guidelines, published in 1997, are in need of updating, as leukotriene receptor antagonists only became available for prescription after that date. The current American guidelines, similarly published in 1997, do mention the LTRA zafirlukast and suggest that it may be an option as monotherapy in patients in need of updating, as leukotriene receptor antagonists are potent constrictors of human bronchi. Nature 1980;288:84–6.

References
3 Brocklehurst WE. The release of histamine and the formation of a slow reacting substance (SRS-A) during anaphylactic shock. J Physiol (Lond) 1960;131:416–35.
Leukotriene receptor antagonists


