Review

Therapeutic modulation of allergic airways disease with leukotriene receptor antagonists

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Summary

Although asthma is one of the most common chronic respiratory conditions, it often remains unrecognized and undertreated, while patients are often reluctant to comply with regular inhaled anti-inflammatory and bronchodilator therapy. Allergic rhinitis co-exists with asthma in as many as 40% of patients, and can be regarded as a continuum of the same inflammatory disease process. Corticosteroids are the ‘gold standard’ first-line treatment for both conditions, and have a significant impact upon underlying inflammation, symptoms and long-term outcome. Cysteinyl leukotrienes are potent airway inflammatory mediators, suggesting that treatment antagonizing their effects could play a role in disease management. In recent years, leukotriene receptor antagonists have provided a further therapeutic option in the management of allergic airways disease. These drugs are orally active, can be administered once daily, and provide a systemic approach to the management of patients with asthma and allergic rhinitis. We review the pharmacology of leukotriene receptor antagonists, their potential role in clinical practice in patients with allergic airways disease, and likely areas for further research.

Introduction

Asthma is a common chronic heterogeneous condition that displays a complex and varied phenotypic picture. It can present in early childhood as well as adulthood, and varies markedly in severity, clinical course, disability and response to treatment. Despite a greater understanding of the underlying inflammatory and bronchospastic disease process, the worldwide prevalence of asthma is increasing in both developed and developing countries.1,2 Moreover, patients with fatal and near-fatal asthma often have modifiable risk factors such as inadequate or inappropriate therapy, and poor adherence to prescribed medication.1–5

The characteristic features of asthma are bronchial hyper-responsiveness following exposure to inhaled stimuli, inflammation throughout the entire bronchial tree, and variable, mostly reversible airflow obstruction (Figure 1).6 As a consequence of these hallmark physiological features, commonly reported episodic symptoms include non-productive cough, breathlessness, wheeze and chest tightness. Oral and inhaled treatments used in the management of asthma are therefore aimed at attenuating the effects of these integral and often overlapping components. Once symptoms have developed, treatment is usually indicated and can vary from
intermittent use of short acting $\beta_2$-agonists to combinations of oral and inhaled medications.

Many asthmatics are atopic, with up to 40% demonstrating evidence of concomitant allergic rhinitis. Apart from the anatomical link between both conditions, asthma and allergic rhinitis share physiological and immunological features. This in turn has led interest into a more co-ordinated approach aimed at the treatment of the unified airway. Patients with active upper airway inflammation due to rhinitis often breathe through their mouth (usually normal only during exercise and speech), further exposing the lower airway to the adverse drying and cooling effects of repeated air flow. Furthermore, it is known that treatment of allergic rhinitis results in a commensurate improvement in parameters of asthma control.

This evidence-based review highlights the pharmacological properties of leukotriene receptor antagonists (LTRAs), their role in the management of allergic airways disease, the results of recent randomized clinical trials surrounding their use, and how they compare to other asthma treatments. It also highlights areas where further research into their use is required. We performed a comprehensive literature search using Medline, CINAHL, Clinical Evidence, Cochrane library and Embase. The following key MeSH words were used in the search: asthma, allergic rhinitis, leukotriene, leukotriene receptor antagonist, beta-agonist, corticosteroid, inflammation, lung function. We selected and extracted recent articles (almost exclusively placebo-controlled randomized trials and meta-analyses) that we felt to be of relevance or interest to practising clinicians, and chose topics that we thought were of potential importance.

**Cysteinyl leukotrienes**

Orally and nasally inhaled corticosteroids are the gold standard treatments of asthma and allergic rhinitis, respectively. Many patients, especially with both conditions, have concerns regarding the burden of corticosteroid to which they are exposed. Moreover, despite treatment with corticosteroids, suppression of inflammation is often incomplete and their effect upon cysteinyl leukotriene biosynthesis and release is limited.

Cysteinyl leukotrienes are lipid mediators produced from an arachidonic acid precursor and fall into two main classes. Leukotriene B₄ is a neutrophil chemoattractant, while the cysteinyl leukotrienes (C₄, D₄ and E₄) are eosinophil chemoattractants. The cysteinyl leukotrienes are produced from the phospholipid bilayer by a series of enzymic steps involving the rate-limiting enzyme leukotriene C₄ synthase (Figure 2). They exert their effects following activation of specific receptors located on cell membranes of pulmonary smooth muscle and macrophages. Cysteinyl leukotrienes produce an array of effects implicated in the pathogenesis of the asthmatic inflammatory process (Figure 2). Antagonizing their actions could thus play an important role in attenuating integral features of asthma pathophysiology. Pharmacologically, this can be achieved by drugs preventing their synthesis using a 5-lipoxygenase inhibitor (zileuton), or blocking specific cysteinyl leukotriene receptors using a leukotriene receptor antagonist (LTRA).

**Leukotriene receptor antagonists: pharmacology and prescribing**

Two LTRAs are licensed for clinical use: montelukast and zafirlukast (Figure 3). Both are orally active, with the former used at a daily dose of 10 mg and the latter given as 20 mg twice daily (in adults); pranlukast, another LTRA, has not been licensed for use in the UK. Montelukast and zafirlukast share some pharmacokinetic properties including rapid oral absorption (3 h to peak plasma concentrations), near maximal plasma protein binding and after extensive hepatic biotransformation, excretion principally in bile. Their terminal half-lifes are 5 h and 10 h, respectively. Montelukast can be used in children from the age of 2 years and has been formulated as a chewable, pink, cherry flavoured tablet. Oral efficacy has the obvious advantages
of avoiding the technical difficulties associated with, and dislike of, inhaled medication, especially in children, adolescents and the elderly.

These drugs are unique in that they demonstrate both bronchodilator and anti-inflammatory properties (albeit less than long-acting $\beta_2$-agonists and corticosteroids, respectively), suggesting that they may have an important dual action in the treatment of allergic airways disease (Figure 4). A further therapeutic benefit is that LTRAs are clinically active following single doses. Moreover, unlike long-acting $\beta_2$-agonists, tolerance to their broncho-protective effects has not been demonstrated.

As a class of drug, they are generally well tolerated, although adverse effects such as abdominal pain, rashes, headaches, angioedema, pulmonary eosinophilia and arthralgia have been reported. Due to lack of data, their use in pregnancy is not advised. Concerns have been raised regarding

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**Figure 2.** Cysteinyl leukotriene synthesis pathway and their effects in the airway. FLAP, 5-lipoxygenase-activating protein, HPETE, 5-hydroxyperoxyeicosatetraenoic acid.

**Figure 3.** Chemical structures of zafirlukast and montelukast.
the development of Churg-Strauss syndrome (CSS) and administration of LTRAs. Many, although not all, of the documented cases of CSS have been in patients in whom concomitant LTRA treatment has permitted a reduction in dose of inhaled corticosteroid. This in turn suggests that latent CSS may have been unmasked by a reduction in anti-inflammatory therapy delivered to the lungs.\textsuperscript{18} However, LTRAs do in general demonstrate a favourable adverse effect profile in comparison to inhaled corticosteroids, as the latter demonstrates such effects in a dose-dependent fashion. For example, it is generally accepted that at orally inhaled beclomethasone doses (or equivalent) \(>800\) \(\mu\)g/day, the dose-response curve for beneficial effects becomes flat, while that for systemic adverse effects becomes steep.\textsuperscript{19,20} Typical dose-dependent adverse sequelae include adrenal and growth suppression, and skin thinning and bruising, especially at high doses.\textsuperscript{19} The systemic bioactivity of intranasal corticosteroids at standard doses in terms of effects upon the hypothalamic-pituitary-adrenal axis is negligible.\textsuperscript{21} Troublesome local effects of orally inhaled corticosteroids include candidiasis and dysphonia, while nasally administered drug can cause dryness, irritation and occasionally septal perforation.

The exact positioning of LTRAs in the management of asthma has been the source of considerable debate over the past few years, often as a result of paucity of data. The following sections of this review article present an evidence-based update of different areas where LTRAs have had an expanding role in the management of allergic airways disease, and identify potential areas of future research.

**Leukotriene receptor antagonists as monotherapy**

Accumulating evidence suggests that LTRAs are clinically inferior when used as monotherapy compared to a low dose of inhaled corticosteroid, and as a consequence, are not generally advocated for use in this manner. This comparison has been rigorously reviewed and evaluated elsewhere.\textsuperscript{22,23} For example, Ducharme performed a systematic review of randomized controlled trials examining the effects of LTRAs as monotherapy vs. daily doses of \(<450\) \(\mu\)g beclomethasone or equivalent.\textsuperscript{23} Thirteen trials were examined that incorporated mild-to-moderate asthmatics. Patients treated with a LTRA alone were 60\% more likely to have an exacerbation than those using an inhaled corticosteroid. The latter treatment also conferred significantly greater improvements upon measure of lung calibre. However, a role does exist for LTRAs as monotherapy in mild asthmatics with exercise-induced symptoms alone.\textsuperscript{24}
**Inhaled corticosteroids plus leukotriene receptor antagonists as second-line therapy**

Inhaled corticosteroids exert their effects by binding to cytoplasmic receptors, concentrated in airway epithelial and endothelial cells. Once bound, they act by increasing and decreasing transcription of a variety of anti-inflammatory and pro-inflammatory mediators, respectively. Although corticosteroids are potent anti-inflammatory agents, they have little or no impact on cysteinyl leukotriene synthesis or release, suggesting that add-on therapy with a LTRA may provide a more complete and complimentary role in asthma control. Many studies have evaluated the effects of concomitant treatment with LTRA plus inhaled corticosteroids. Indeed, beneficial effects have been observed with add-on LTRA on a multitude of outcome measures, including reduced rescue treatment requirement, symptoms, improved pulmonary function, fewer exacerbations and effects on surrogate inflammatory markers. For example, in a randomized double-blind, double-dummy study, Laviolette evaluated 642 symptomatic asthmatics with impaired lung function where montelukast 10 mg/day was added to 400 µg/day beclomethasone. Active treatment compared to placebo provided significant (p < 0.05) clinical benefit in terms of improving FEV₁, asthma symptom scores and nocturnal awakenings.

Additive effects have also been demonstrated in patients receiving high-dose inhaled corticosteroids. Tamaoko evaluated 79 asthmatics who required at least 1500 µg/day of beclomethasone. Addition of zafirlukast 20 mg twice daily permitted a reduction in beclomethasone dose while maintaining asthma control. This in turn highlights the fact that LTRAs can exert a steroid-sparing effect, which is of particular importance when patients have concerns regarding potential effects of high inhaled corticosteroid doses. Another study examined the effects of montelukast 10 mg/day when added to a constant dose of budesonide (400–1600 µg/day) over a 16-week period. This multi-centre, double-blind, parallel group trial randomized 326 patients to receive montelukast and 313 to receive identical placebo; subjects were symptomatic despite inhaled corticosteroid treatment, and the mean FEV₁ was 81% predicted in both groups. Individuals receiving active treatment experienced 35% fewer asthma exacerbation days with a 56% increase in asthma-free days compared to placebo. Thus, concomitant treatment with a LTRA plus inhaled corticosteroid confers benefit in patient orientated end-points such as fewer nocturnal awakenings and short-acting β₂-agonist use, in addition to a reduction in asthma exacerbations.

**Leukotriene receptor antagonists versus long-acting β₂-agonists**

In symptomatic patients using low-to-moderate doses of inhaled corticosteroids (step 3), British Thoracic Society (BTS) guidelines suggest adding a long-acting β₂-agonist, after checking compliance, inhaler technique and addressing trigger factors. However, several large studies have been published since the guidelines were disseminated, which have shown that in inhaled-corticosteroid-treated patients, concomitant therapy with a LTRA can provide similar efficacy in terms of exacerbation reduction to that for an add-on long-acting β₂-agonist. For example, 1490 chronic asthmatics uncontrolled on inhaled fluticasone 200 µg/day were randomized to receive add-on montelukast 10 mg/day or salmeterol 50 µg twice daily. After a year of treatment, 20.1% of patients in the montelukast group, compared with 19.1% in the salmeterol group, experienced an exacerbation of asthma, with a non-significant confidence interval between groups. However, salmeterol-treated patients had a significantly greater FEV₁ and morning PEF (p ≤ 0.001), while the combination of fluticasone plus montelukast conferred greater reduction (p = 0.011) upon blood eosinophils than add-on salmeterol. Previous in vitro data have demonstrated that long-acting β₂-agonists can potentiate the anti-inflammatory effects of inhaled corticosteroids, although in the present study, no additional effect upon blood eosinophils was observed with salmeterol. This is in keeping with other studies in which no further beneficial effects upon surrogate inflammatory markers (i.e. in vivo) occurred with add-on long-acting β₂-agonist.

In contrast, in a multicentre trial by Fish et al., the addition of salmeterol 50 µg twice daily was superior to that of add-on montelukast 10 mg/day in uncontrolled asthmatics using inhaled corticosteroids. This was in terms of measures of lung calibre (the primary endpoint) and symptom scores. Similarly, in the multi-centre trial of Nelson et al., adding salmeterol to fluticasone was superior to concomitant treatment with zafirlukast 20 mg/day. Indeed, the former treatment provided significantly greater improvement in pulmonary function, significantly greater relief of both daytime and nighttime asthma symptoms and a significantly greater...
improvement in the Asthma Quality of Life Questionnaire, compared with oral zafirlukast.

When evaluating the results of clinical trials, it is important to consider whether the primary endpoint includes a 'bronchodilator-sensitive' parameter such as PEF or FEV1. This is especially important when head-to-head comparisons are made between LTRAs and long-acting β2-agonists. Long-acting β2-agonists are potent bronchodilators and exert an 'airway-stabilizing' effect on acute exposure to a bronchoconstrictor stimulus.37 As a consequence, it is of little surprise that when the primary outcome in a study is based on effects on relaxing bronchial smooth muscle, long-acting β2-agonists fare significantly better than LTRAs (which are only weak bronchodilators). As demonstrated by studies by Bjørmer29 and Ilowite,30 in patients using inhaled corticosteroids, add-on montelukast provides similar asthma control to that of add-on salmeterol when outcome measures such as exacerbations are evaluated, with montelukast conferring superiority in terms of effects upon surrogate inflammatory markers. Whether future updated guidelines will suggest that LTRAs should be given a more equal place with long-acting β2-agonists at step 3 remains to be seen.

'Triple therapy' with leukotriene receptor antagonists, inhaled corticosteroids plus long-acting β2-agonists

Despite treatment with an inhaled corticosteroid plus long-acting β2-agonist, many asthmatic patients remain symptomatic. Since inhaled corticosteroids have limited effects upon biosynthesis of cysteinyl leukotrienes,14–16 add-on therapy with a LTRA could therefore confer additional benefit in terms of attenuating endobronchial inflammation. However, very few trials have evaluated the effects of LTRAs along with combinations of inhaled and oral pharmacotherapy.

Robinson et al.38 evaluated whether LTRAs confer additional benefit in symptomatic asthmatics, despite inhaled corticosteroids plus additional second-line controller therapy. In a study evaluating 72 moderate-to-severe asthmatics maintained on inhaled corticosteroids and mostly taking long-acting β2-agonists, the addition of montelukast 10 mg daily for 2 weeks conferred no significant improvement in terms of peak expiratory flow (PEF) and symptom scores. However, several limitations of this study were observed,39 in turn raising questions with regard to their negative findings. For example, no assessment was made of effects upon bronchial hyper-responsiveness or surrogate inflammatory biomarkers such as airway eosinophils. Moreover, no meaningful data upon exacerbations could be obtained, due to the relatively short duration of treatment. Since patients in the study were maximally bronchodilated (due to the effects of the long-acting β2-agonist) no room for improvement in PEF (the primary endpoint in the study) could reasonably be expected from adding in montelukast.

In an attempt to address some of these concerns, another randomized placebo controlled crossover study evaluated the effects of add-on montelukast 10 mg/day in patients taking inhaled fluticasone 500 μg/day in combination with salmeterol. The addition of montelukast conferred additional beneficial effects upon several surrogate inflammatory biomarkers, in addition to attenuating bronchial hyper-responsiveness. Similar to the study by Robinson et al.,38 montelukast conferred no additional bronchodilator benefit in terms of PEF or FEV1. In other words, the long-acting β2-agonist moiety would have sufficiently relaxed the airway smooth muscle, allowing no further improvement in airway calibre.

Thus, serial monitoring of PEF or FEV1 often allows no evaluation of the potential benefits of non-steroidal anti-inflammatory therapy such as LTRAs when patients are using regular long-acting β2-agonists. This problem of determining clinical efficacy not only exists in clinical trials, but also in everyday life. Further prospective studies are therefore required to evaluate the effects of LTRAs in patients using combination inhalers in terms of more long-term outcome parameters such as exacerbations, markers of airway remodelling and quality of life, as well as inflammatory biomarkers, lung function and bronchial hyper-responsiveness.

Aspirin-sensitive asthma

Aspirin-sensitive asthma has an uncertain prevalence, although it may exist in as many as 20% of all asthmatics.40 It is characterized by profound bronchoconstriction following aspirin ingestion, and is associated with rhinosinusitis, nasal polyposis and sometimes abdominal cramps. It is caused by aspirin and non-steroidal anti-inflammatory drugs that selectively inhibit cyclo-oxygenase-1. This in turn shunts arachidonic acid down the 5-lipoxygenase-activating protein pathway, causing the overproduction of cysteinyl leukotrienes. As a consequence, elevated levels of cysteinyl leukotrienes can be found in bronchial and nasal
aspirates, and in urine following aspirin challenge.\textsuperscript{41,42} Moreover, the rate-limiting enzyme, leukotriene C\textsubscript{4} synthase, is found to a greater extent in eosinophils and mast cells in patients with aspirin-sensitive asthma.\textsuperscript{43}

Thus, LTRAs might play an important role in ameliorating the clinical symptoms of aspirin-sensitive asthma. Montelukast was effective in aspirin-sensitive patients who were receiving inhaled corticosteroids.\textsuperscript{44} This study evaluated 80 patients with aspirin-sensitive asthma, who were randomized to receive placebo or montelukast 10 mg/day for 4 weeks. Pulmonary function and symptoms were improved in the latter group, in turn suggesting that LTRAs such as montelukast improve asthma control in aspirin-sensitive patients over and above that achieved by inhaled corticosteroids. Other studies using both LTRAs and zileuton have blocked the response following ingestion of aspirin.\textsuperscript{45–47} These results demonstrate that LTRAs play a complimentary role in attenuating the effects of aspirin in predisposed individuals.

**Exercise-induced asthma**

Many patients with asthma develop symptoms in relation to exercise. This is thought to be due to drying and cooling effects occurring in the airway, with the subsequent release of pro-inflammatory mediators such as cysteinyl leukotrienes and histamine.\textsuperscript{48} LTRAs and inhibitors of the cysteinyl leukotriene pathway have protected against exercise-induced bronchoconstriction in a number of studies in both adults and children.\textsuperscript{49–52} For example, in 100 corticosteroid-naive asthmatics with a mean FEV\textsubscript{1} of 83\% predicted, the effects of montelukast 10 mg/day were evaluated over a 12-week period.\textsuperscript{24} Compared to placebo, montelukast was significantly superior in protecting against exercise-induced bronchoconstriction, with patients experiencing better asthma control during active treatment. Moreover, tolerance to its effects was not observed, which is often the case with long-acting $\beta_2$-agonists.\textsuperscript{53} This suggests that treatment with a LTRA is an effective option in patients with troublesome exercise-induced symptoms, either alone, or in combination with inhaled corticosteroids.

**Allergic rhinitis**

Allergic rhinitis is a complex inflammatory disease of the upper airway characterized by sneezing, nasal pruritus, rhinorrhoea and nasal obstruction.\textsuperscript{54} In addition to sharing the same epithelial lining, exaggerated airway responsiveness and underlying inflammation can be demonstrated in both conditions with the subsequent appearance of symptoms.\textsuperscript{7} Uncontrolled allergic rhinitis is known to precipitate and exacerbate asthma, suggesting that clinicians should positively search for typical nasal and ocular symptoms, especially in those with difficult-to-control asthma.\textsuperscript{55} Cysteinyl leukotrienes are inflammatory mediators common to both the upper and lower airways,\textsuperscript{56,57} which has prompted investigators to evaluate their therapeutic potential in allergic rhinitis.\textsuperscript{58,59}

The pioneering work on LTRAs in the upper airway began a decade ago,\textsuperscript{60} with the exciting possibility of oral therapy with few adverse effects, avoiding the discomfort of nasal sprays.\textsuperscript{61} In *in vitro* studies, montelukast and pranlukast reduced levels of nasal pro-inflammatory mediators and inhibited antigen-induced microvascular leakage.\textsuperscript{62–65}

The effects of cysteinyl leukotrienes and LTRAs on nasal symptoms of allergic rhinitis have been evaluated by examining the response following antigen provocation. Sneezing and rhinorrhoea are thought to represent the early-phase response, whereas oedema and eosinophilic infiltration predominate the late-phase response.\textsuperscript{66,67} Cysteinyl leukotrienes mediate both early- and late-phase responses.\textsuperscript{67} Pranlukast suppressed the increase in nasal airway resistance, but was ineffective in suppressing sneezing and rhinorrhoea.\textsuperscript{67} Cysteinyl leukotrienes are therefore important mediators in allergic rhinitis,\textsuperscript{68} especially with regard to nasal obstruction.\textsuperscript{69,70} Moreover, cysteinyl leukotrienes have a greater role in the development of mucosal swelling in nasal allergy than that of histamine.\textsuperscript{71}

The mechanism by which nasal blockage develops in allergic rhinitis is thought to be due to activation of the CysLT\textsubscript{1}-receptor\textsuperscript{66} and overproduction of nitric oxide, leading to dilatation of nasal blood vessels and congestion of the nasal mucosa.\textsuperscript{72} Montelukast as monotherapy is effective in the treatment of allergic rhinitis. For example, in a study of 1302 patients with allergic rhinitis, montelukast 10 mg/day improved day- and night-time nasal symptoms, as well as quality of life parameters.\textsuperscript{73} Similar results were obtained in two other large studies,\textsuperscript{74,75} where the treatment effects of montelukast were found to be more persistent than those of loratadine.\textsuperscript{75} A study of 1862 symptomatic patients with allergic rhinitis, which showed superiority of montelukast over placebo in improving nasal symptoms, also evaluated the interaction between treatment effects and timing. A greater response to montelukast was seen in patients who were exposed to a higher pollen count. Similarly, zafirlukast has also been shown to improve nasal
symptoms in allergic rhinitis with reduction in nasal resistance and lavage eosinophil count.\textsuperscript{76}

Data relating to the combined effects of LTRAs and histamine H\textsubscript{1}-receptor antagonists on nasal symptoms in allergic rhinitis offer conflicting results. In one study of 460 patients with allergic rhinitis, the combination of montelukast and loratadine improved day-time nasal symptoms, while less benefit was observed with either drug alone.\textsuperscript{77} In contrast, in another larger study of 907 patients with allergic rhinitis, both drugs alone improved day-time nasal symptoms with no further additional benefit from the combination.\textsuperscript{78} In a study of 62 patients, the combination of montelukast and loratadine was no more effective than montelukast alone on day-or night-time nasal symptoms,\textsuperscript{79} while the combination of montelukast and cetirizine was more effective than cetirizine as monotherapy in another study.\textsuperscript{80} The lack of superiority with combination therapy compared to monotherapy with either LTRA or histamine H\textsubscript{1}-receptor antagonist has been replicated in one study using nasal adenosine monophosphate provocation,\textsuperscript{81} while non-inferiority of LTRA compared to histamine H\textsubscript{1}-receptor antagonist has been demonstrated in another study using nasal mannitol provocation.\textsuperscript{82} In comparison to intranasal corticosteroids, the use of oral combined LTRA and histamine H\textsubscript{1}-receptor antagonist was similar in two studies\textsuperscript{83,84} and less effective in three other studies\textsuperscript{79,85,86} in terms of nasal symptoms.

In summary, LTRAs can provide an effective treatment option for patients with allergic rhinitis. Moreover, in patients with concomitant asthma, the combination of a LTRA plus histamine H\textsubscript{1}-receptor antagonist may provide similar asthma control to that of orally and nasally inhaled corticosteroids, although further large scale studies are required to confirm this finding.\textsuperscript{87} Montelukast has recently gained approval from the Food and Drug Administration in the US for use in allergic rhinitis alone, although this is not the case currently in the UK.

Polymorphisms of leukotriene C\textsubscript{4} synthase

An interesting ‘real life’ property of LTRAs is their propensity for greater therapeutic effects in subgroups of asthmatics. Polymorphisms of leukotriene C\textsubscript{4} synthase, the terminal enzyme in leukotriene synthesis, have been discovered, and are postulated to be important in determining this differential response to treatment. They are characterized by adenine (A) to cytosine (C) translocation at the -444 nucleotide. Moreover, in aspirin-sensitive asthmatics, overactive transcription of variant C polymorphism is associated with enhanced expression of leukotriene C\textsubscript{4} synthase in peripheral blood eosinophils.\textsuperscript{88}

In a study by Sampson \textit{et al.}\textsuperscript{89} of 23 asthmatics, zafirlukast 20 mg twice daily for 2 weeks resulted in a numerically greater (although statistically non-significant) response in FEV\textsubscript{1}, comparing genotypes AA vs. AC or CC. Furthermore, Asano \textit{et al.}\textsuperscript{90} evaluated the effects of pranlukast for 4 weeks in 48 patients with moderate-to-severe persistent asthma. Patients with AC/CC had a significantly greater bronchodilator response with LTRA in FEV\textsubscript{1}, compared to patients with AA. In a retrospective analysis,\textsuperscript{91} polymorphisms of leukotriene C\textsubscript{4} synthase were not associated with clinical response to LTRAs in terms of surrogate inflammatory markers and measures of airway calibre. However, it may not be surprising to discover that a single allelic variation does not determine the response to LTRAs, since cysteinyl leukotrienes are synthesized via a cascade of enzymes. Indeed, whether a combination of polymorphisms is implicated in the interindividual variability in response to LTRAs requires further evaluation.

\textbf{Conclusions}

As a consequence of greater insight into the underlying inflammatory process synonymous with asthma, LTRAs have emerged as a distinct class of drug over the past decade. It is evident that there is a role for LTRAs across a broad spectrum of asthma severities and manifestations, ranging from beneficial effects as add-on second-line therapy in patients using low through to high doses of inhaled corticosteroids, and those with mild through to marked impairment in lung calibre. LTRAs also have an impact in patients with activity-related and aspirin-sensitive asthma. With the emergence of new data, and greater emphasis placed on more holistic outcome measures such as quality of life, patient satisfaction and exacerbation frequency, it is likely that over the next few years LTRAs will more comfortably fit into updated asthma guidelines. Indeed, when compared to add on long-acting \( \beta \textsubscript{2} \)-agonists in patients using inhaled corticosteroids, it is important for the prescribing physician to be aware that adding in a LTRA (instead of a long-acting \( \beta \textsubscript{2} \)-agonist) confers similar effects upon reductions in exacerbation frequency, despite less dramatic improvements in lung function.

Current British Thoracic Society guidelines suggest that a LTRA should be considered at step 4,
Indeed, the use of a long-acting 
2-agonist fails to adequately control symptoms. Alternatively, they may be given to patients maintained on inhaled corticosteroids after a failed therapeutic trial of long-acting 
2-agonist. In patients with persistent symptoms despite a low-to-moderate dose of inhaled corticosteroid, compliance and inhaler technique should obviously be assessed, along with trigger factors such as aeroallergens, concomitant allergic rhinosinusitis and gastro-oesophageal reflux disease. Many patients using inhaled corticosteroids have preserved lung function, with underlying inflammation and bronchial hyper-responsiveness being the driving forces behind episodic airflow obstruction and persistent symptoms. In these patients, add-on therapy with a LTRA would appear to be the most logical therapeutic option, in view of its dual actions of attenuating bronchial hyper-responsiveness and suppressing inflammation, in turn reducing exacerbation frequency. Indeed, the use of a long-acting 
2-agonist, with no intrinsic anti-inflammatory properties,92,93 would do little to deal with these underlying problems. In patients with persistent symptoms and impaired lung function (FEV1 <80% predicted), adding in a long-acting 
2-agonist as a combination inhaler (such as fluticasone propionate/salmeterol), while keeping the inhaled corticosteroid dose the same would appear to be the most reasonable step. Further increases in anti-inflammatory therapy (either with a LTRA or increased inhaled corticosteroid dose) would be unlikely to improve lung function to any great extent,94 and a combined inhaled corticosteroid/long acting 
2-agonist inhaler would ensure maximal bronchodilatation.

While not licensed for use in patients with allergic rhinitis per se,LTRAs have consistently demonstrated efficacy in asthmatics with concomitant upper airway inflammation, especially when combined with an anti-histamine. Thus, therapy directed towards the nose would offer the added advantage of attenuating lower airway inflammation and perhaps reducing corticosteroid requirement in patients with concomitant asthma. Moreover, their favourable adverse effect profile, for example compared to patients using both inhaled and nasal corticosteroids, is certainly advantageous. Patient compliance tends also to be greater with oral treatment than compared to inhaled,95 and patient acceptance, adherence and ease of administration plays a part in the effectiveness of any therapeutic regime.

In conclusion,LTRAs are one of the first asthma drugs to be developed as an attempt to antagonize the effects of a specific inflammatory pathway. They not only provide a further therapeutic tool in which to control inflammation, bronchial hyper-responsiveness and symptoms, but facilitate an orally active means by which to reduce the burden of asthma in both primary and secondary care settings.

Acknowledgements

Conflicts of interest: GPC and OJD have received funding from MSD and GSK for attending postgraduate educational meetings. PS has received funding from GSK for attending postgraduate educational meetings.

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