Clinical and Experimental Allergy, 2001, Volume 31, pages 1813–1821

REVIEW

Emerging role of antileukotriene therapy in allergic rhinitis

B. J. LIPWORTH

Asthma and Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Dundee, UK

Introduction

The leukotriene receptor antagonists are now familiar to most primary care doctors and to all allergists and pulmonologists, having been licensed for first- and second-line therapy in asthma for 3 years. The antagonists currently available are montelukast, zafirlukast and pranlukast whilst, in addition, the 5-lipoxygenase inhibitor, zileuton is also available in the USA but used to a much lesser degree. Given that allergic asthma and allergic rhinitis both have a similar pathophysiology, and frequently coexist, it is not surprising that allergists have become increasingly interested in the potential therapeutic role of leukotriene antagonists in allergic rhinitis [1,2]. It should however, be pointed out that none of the leukotriene antagonists are currently licensed for use in allergic rhinitis. Apart from allergen avoidance and allergen immunotherapy, the treatment options in allergic rhinitis include corticosteroids, histamine receptor antagonists, cromoglycate and α-adrenoceptor agonists.

The purpose of this article is to provide an update on clinical trials which have evaluated antileukotriene therapy in allergic rhinitis and to identify potential areas where future studies may be directed.

Pharmacology and pathophysiology of leukotrienes in allergic rhinitis

The basic pharmacology of cysteinyl leukotrienes in allergic rhinitis and asthma has been reviewed in detail elsewhere [3,4]. In brief, the cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) are produced from the arachidonic acid pathway initially via 5-lipoxygenase. Cysteinyl leukotrienes are produced by eosinophils, mast cells, monocytes and basophils. They exhibit a variety of pro-inflammatory actions including microvascular leakage, inflammatory cell chemotaxis (particularly eosinophils), mucus hypersecretion and neuronal stimulation, all of which are relevant to the pathophysiology of allergic rhinitis.

The type I cysteinyl leukotriene receptor has now been cloned and shows a rank order of potency for its natural ligands of $LTD_4 > LTC_4 > LTE_4$, and a comparable degree of *in vitro* potency for the licensed selective antagonists, namely pranlukast, zafirlukast and montelukast [5,6]. There are naturally occurring promotor polymorphisms of 5-lipoxygenase and of leukotriene C_4 synthase, which may modify the cellular capacity for leukotriene synthesis, and hence a variable contribution of cysteinyl leukotrienes may be reflected in the magnitude of response to antileukotriene drugs [7–9].

In vivo evidence for role of leukotrienes in allergic rhinitis

Specific nasal allergen challenge in atopic subjects has shown the release of cysteinyl leukotrienes in lavage fluid coinciding with the early- and late-phase response, which appear to be related to the dose of antigen [10–12]. This is supported by studies in patients with allergic rhinitis where spontaneous increases in cysteinyl leukotrienes from nasal lavage have been shown in relation to naturally occurring allergen exposure [13,14]. Nasal challenge with LTD_4 results in increased nasal blood flow and resistance, whilst having no effect on itching, sneezing and discharge, unlike challenge with antigen and histamine [15,16]. Furthermore, LTD_4 exhibited approximately 5000-fold more potency than histamine on a microgram basis for its topical activity *in vivo* [16].

Effects of antileukotriene therapy on allergen challenge

In guinea-pigs oral administration of pranlukast inhibited antigen and LTD_4 induced nasal microvascular leakage [17]. In patients with perennial or seasonal allergic rhinitis, specific allergen-induced symptoms of congestion as well as nasal lavage levels of LTD_4 were markedly reduced by a 5-lipoxygenase inhibitor, whereas histamine release and sneezing were not significantly affected [18]. In patients

Correspondence: B. J. Lipworth, Professor of Allergy and Respiratory Medicine, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Scotland, DD1 9SY, UK. E-mail: b.j.lipworth@dundee.ac.uk

© 2001 Blackwell Science Ltd

with seasonal allergic rhinitis, a 5-lipoxygenase inhibitor attenuated allergen-induced increase in nasal airway resistance, nasal secretions and plasma protein extravasation, in the absence of effects of nasal itch or sneeze [19]. The relative effects of histamine receptor antagonism (mequitazine) or leukotriene receptor antagonism (pranlukast) were evaluated in 32 patients with perennial nasal allergy to house dust mite [20]. Symptoms induced by allergen challenge showed a significant reduction in sneezing and rhinorrhoea after histamine but not leukotriene antagonism. The decrease in effective nasal cross sectional area after allergen challenge was significantly attenuated by leukotriene but not histamine antagonism, whilst diary cards showed significant effects on nasal discharge with both drugs, on nasal obstruction with leukotriene antagonist, and on sneezing with histamine antagonist.

There are also other data looking at allergen responses in other tissues which would substantiate an important role of cysteinyl leukotrienes. An *in vitro* study showed that blockade of mast cell-mediated contraction of sensitized human bronchus occurred in synergistic fashion, with the combination of a histamine antagonist (chlorpheniramine) and a leukotriene antagonist (MK-571) producing 82% inhibition, compared to 28% inhibition with MK-571 alone and 16% by chlorphenamine [21]. Allergen bronchoprovocation testing showed zafirlukast to reduce the early asthmatic response to a greater degree than loratadine, whilst each drug provided a similar degree of protection against the late asthmatic response [22]. However, the combination of zafirlukast and loratadine was significantly more effective than either drug alone during the late asthmatic response, suggesting additive antagonism. Oral fexofenadine and montelukast on their own have been shown to decrease the early and late cutaneous allergen responses, whilst the combination was not significantly more effective than fexofenadine monotherapy [23].

Clinical efficacy of antileukotriene therapy in allergic rhinitis

In a double-blind parallel-group multicentre trial of 64 patients with seasonal allergic rhinitis, 8 weeks of treatment with a 5-lipoxygenase inhibitor was more effective than a placebo on total nasal symptom and daily activity scores as well as global improvement ratings [24]. In a parallel-group double-blind placebo-controlled dose-ranging study, zafirlukast was given for 2 days in patients with seasonal allergic rhinitis and showed significant improvements in nasal congestion, sneezing and rhinorrhoea compared to a placebo, with a minimal effective dose of 20 mg and an onset of action within 2 h of dosing [25]. In abstracted data on 484 patients with seasonal allergic rhinitis, in a placebo-controlled parallel-group double-blind study, 4 weeks of treatment with oral pranlukast or loratadine produced significant reductions in total seasonal allergic rhinitis symptoms scores, although no breakdown of individual symptoms (e.g. nasal blockage) was given [26]. In another abstracted study of 1302 patients with seasonal allergic rhinitis, there were modest but highly significant improvements in all nasal symptoms and rhinoconjunctivitis quality of life scores with montelukast 10 mg or loratadine 10 mg as once daily therapy compared to a placebo over 2 weeks [27].

Pullerits *et al*. evaluated 33 patients with seasonal allergic rhinitis in double-blind, double-dummy fashion, who received oral zafirlukast, intranasal beclomethasone dipropionate or placebo for 50 days during the pollen season [28]. Beclomethasone, but not zafirlukast, significantly reduced nasal symptoms compared with a placebo. Moreover, the number of eosinophils in nasal tissue biopsy increased significantly during the pollen season in both the zafirlukast and placebo groups but not in the beclomethasone group (Fig. 1). Nonetheless, it was evident that there was a numerical trend towards attenuation of nasal eosinophils with zafirlukast compared with placebo, which raises the possibility that the study may have been underpowered to show a modest effect. The latter would appear to be consistent with the effects of pranlukast on bronchial biopsy and induced sputum where there have been consistent but relatively modest reductions in the number of eosinophils and eosinophilic cationic protein [29–31]. Taken together these studies indicate that leukotriene antagonists exhibit a variable anti-eosinophilic effect in both the upper and lower airways.

In a single-blind double-dummy placebo-controlled crossover study of 12 patients with seasonal allergic rhinitis and coexistent asthma, comparison was made of once daily oral montelukast 10 mg vs. once daily orally inhaled budesonide 400 μg plus intranasally inhaled budesonide 200 μg, with each treatment given for 2 weeks [32]. Both treatments elicited significant reductions in total seasonal allergic rhinitis symptom scores, but only the corticosteroid produced any significant reduction in nasal obstruction. Furthermore, for nasal nitric oxide and domiciliary nasal peak inspiratory flow, there were only significant differences with corticosteroid vs. placebo (Fig. 2). Both treatments produced a similar and significant fall in exhaled nitric oxide and although both drugs significantly attenuated adenosine monophosphate bronchial hyperresponsiveness, budesonide showed a 2.1-fold significantly greater shift in bronchial hyper-responsiveness than montelukast. Taken together with the findings of Pullerits, this would suggest that corticosteroid is more effective than leukotriene antagonist as monotherapy in allergic rhinitis,

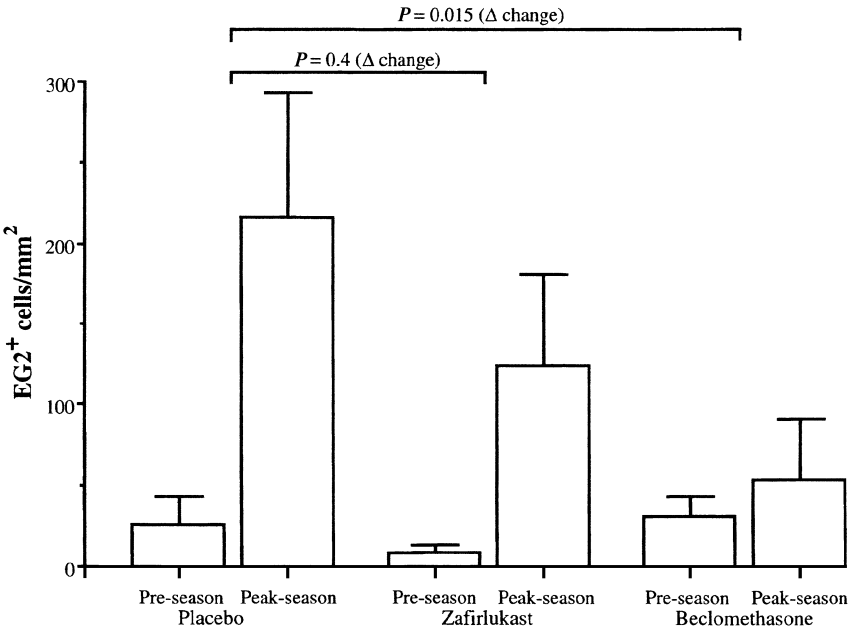


Fig. 1. Number of $EG2^+$ cells prior to and during the grass pollen season in nasal biopsies of patients with allergic rhinitis (reprinted with permission from [28]).

and that leukotriene antagonists are probably more effective in the lung than the nose.

Combined histamine/leukotriene antagonism

A general overview of combined mediator antagonism in allergic diseases was recently the subject of an editorial in this journal [33]. Indeed there are possible plans for the future to market a combined tablet containing loratadine and montelukast, depending on the results of ongoing clinical trials. On the basis of the Roquet study on allergen bronchoprovocation, one would speculate that the effects of a leukotriene antagonist in allergic rhinitis could be augmented by coadministration with a histamine antagonist, particularly as both of these agents showed additive effects on the late-phase allergen response [22]. There are a number of studies which have investigated this hypothesis, but have produced conflicting results. Wilson and coworkers evaluated 38 non-asthmatic patients with summer seasonal allergic rhinitis in a placebo-controlled single-blind, double-dummy 3 way parallel-group study, where patients received 4 weeks of once daily therapy with either cetirizine 10 mg, cetirizine with montelukast 10 mg, or cetirizine with intranasal mometasone furoate 200 μg [34]. All three treatments after 4 weeks produced significant improvements in total daily symptoms, nasal symptoms and domiciliary nasal peak inspiratory flow, but there was no significant additivity with montelukast on top of the response to cetirizine.

In a multicentre randomised double-blind parallel-group placebo-controlled 2 week trial of 460 patients with spring seasonal allergic rhinitis, for the primary endpoint of daytime nasal symptom score, there were no significant differences between placebo, loratadine 10 mg, montelukast 10 mg or montelukast 20 mg; although on secondary endpoints including day-time eye symptoms, night-time symptoms and composite score, montelukast but not loratadine as monotherapy showed significant superiority to placebo, whilst both drugs showed significant effects on rhino-conjunctivitis quality of life [35]. However when both drugs were given together, there were significant effects on all of the primary and secondary endpoints. These results were in contrast to a further study in 907 patients with fall seasonal allergic rhinitis, where there were modest but highly significant improvements in all primary and secondary endpoints including rhinoconjunctivitis quality of life scores, when comparing loratadine 10 mg or montelukast 10 mg given alone vs. placebo for 2 weeks. There were non-significant numerical trends towards further improvements when loratadine and montelukast were given together [36,37]. These apparently conflicting results may reflect the different sample size, disease severity and the varying response to loratadine, allergen load and montelukast in each study.

It is also important to consider the potency of the antihistamine used as clinical trials have shown significantly greater efficacy in seasonal allergic rhinitis with both fexofenadine and cetirizine as compared to loratadine [38–40]. It is therefore conceivable that if montelukast were given in addition to a more potent antihistamine, such as cetirizine, fexofenadine or desloratadine, that the degree of additivity might be less pronounced. This hypothesis is supported by the findings of Wilson *et al.* in seasonal allergic rhinitis where montelukast showed no additivity to cetirizine, as well as the findings of Simons *et al.* on

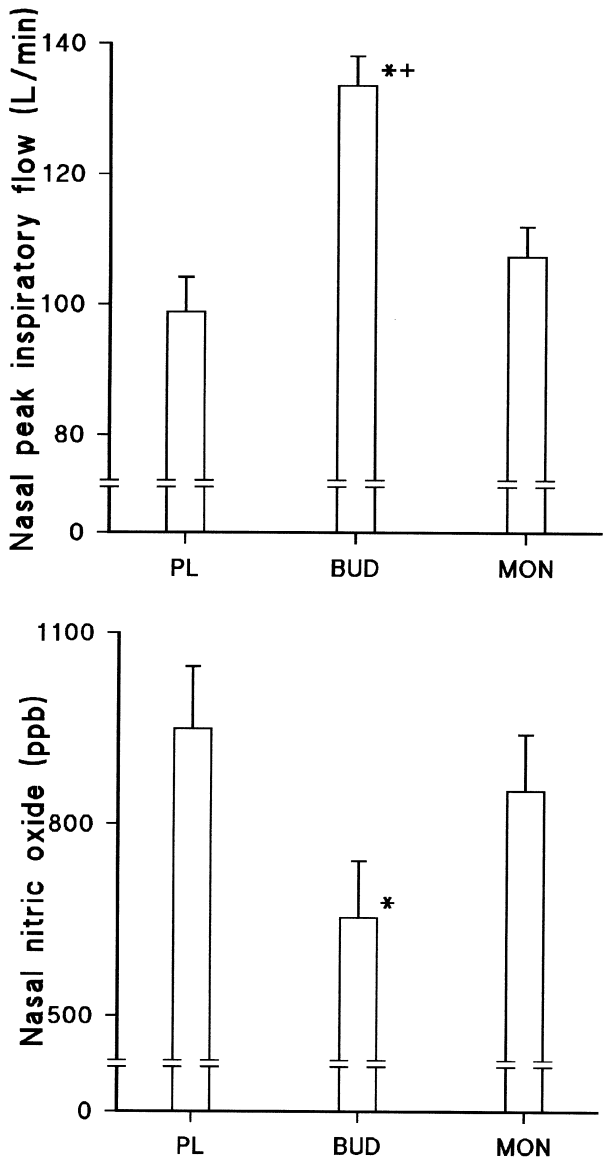


Fig. 2. Means and standard errors for domiciliary nasal peak inspiratory flow and nasal nitric oxide with placebo (PL), budesonide inhaled 400 μg plus intranasal 200 μg (BUD), or oral montelukast 10 mg (MON) in patients with seasonal allergic rhinitis and asthma. $*P < 0.05$ for each randomised crossover active treatment vs. placebo, $+P < 0.05$ for BUD vs. MON (reprinted with permission from [32]).

allergen skin prick testing where montelukast showed no additivity to fexofenadine [23,34]. In order to further investigate this question, a comparison was made in 37 patients with seasonal allergic rhinitis of once daily therapy for 2 weeks with either fexofenadine 120 mg alone vs. the combination of montelukast 10 mg with loratadine 10 mg in a randomised single-blind, double-dummy placebo-controlled cross-over study [41]. There were significant improvements in all symptom scores and domiciliary nasal peak inspiratory flow with both treatments compared to placebo, but no differences between the two treatment regimes (Fig. 3). For example, for the primary outcome variable of nasal peak inspiratory flow, the mean difference between the two treatments was 2 L/min (95% CI: – 6–10 L/min). The time profile for nasal symptoms and peak flow showed a rapid onset of action with both treatments within the first day of administration. A limitation to this study was the failure to include loratadine monotherapy as a comparator, although the brief duration of the pollen season precluded this in a cross-over design. This study raises the question as to whether there would be additivity with montelukast on top of the response to fexofenadine at a higher dose of 180 mg daily, particularly in a subgroup of patients with more severe allergic rhinitis, and in patients with perennial rather than seasonal allergic rhinitis.

Another important question to resolve regarding the use of combined mediator blockade, is how it compares to monotherapy with intranasal corticosteroid, given that it had previously been demonstrated that intranasal budesonide was superior to montelukast [32]. With this aim, 22 patients with seasonal allergic rhinitis were enrolled into a single-blind, double-dummy placebo-controlled cross-over study comparing 2 weeks of once daily therapy with either intranasal mometasone 200 μg as monotherapy or the combination of montelukast 10 mg plus cetirizine 10 mg [42]. There were significant improvements in domiciliary peak nasal inspiratory flow and in all symptom scores with both treatments compared to a placebo, whilst there were no significant differences between the two treatments (Fig. 4).

The same idea was taken one step further in terms of treating the whole airway with systemically administered combined mediator blockade (as cetirizine 10 mg plus montelukast 10 mg) or topically administered corticosteroids (as orally inhaled budesonide 400 μg plus intranasal budesonide 200 μg) both given for 2 weeks in a single-blind, double-dummy placebo-controlled cross-over study in patients with allergic rhinitis and coexistent asthma [43]. Both treatments produced significant improvements in peak expiratory flow, asthma symptom scores, daily activity score and rescue inhaler requirements. Whilst mediator blockade, but not corticosteroid, significantly improved bronchial hyper-responsiveness to adenosine monophosphate challenge, the converse was true in terms of suppression of exhaled nitric oxide. In the same patients mediator blockade and corticosteroid both produced significant improvements in all allergic rhinitis symptoms compared with a placebo, including nasal blockage, although only the corticosteroid significantly improved domiciliary peak nasal inspiratory flow rate [44]. These findings are also supported by another multicentre 2 week randomised double-blind study where the combination of

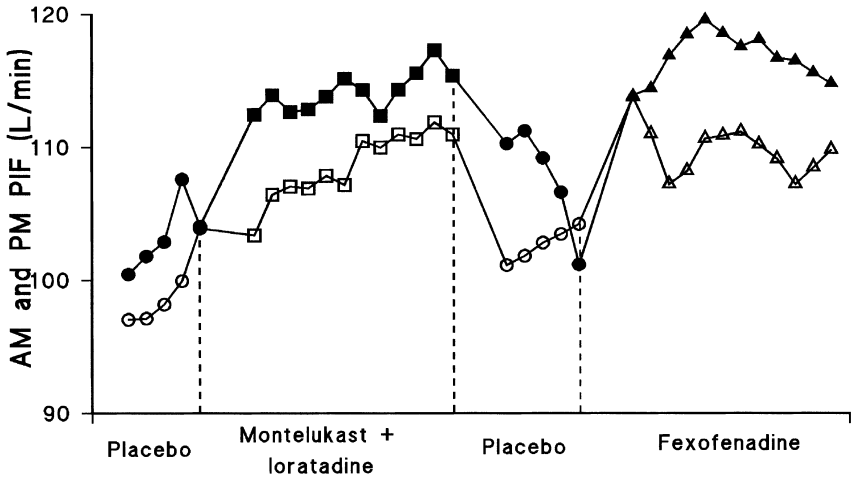


Fig. 3. Morning and evening domiciliary peak nasal inspiratory flow in patients with seasonal allergic rhinitis during placebo run-in and washout periods for 1 week (prior to each randomised cross-over active treatment) and for 2 weeks during randomised treatments with either fexofenadine 120 mg alone or montelukast 10 mg plus loratadine 10 mg. For clarity, data are represented as daily 3 day point moving averages – ○ represent placebo, □ represent montelukast and loratadine, △ represent fexofenadine, solid symbols represent evening values and open symbols represent morning values (reprinted with permission from [41]).

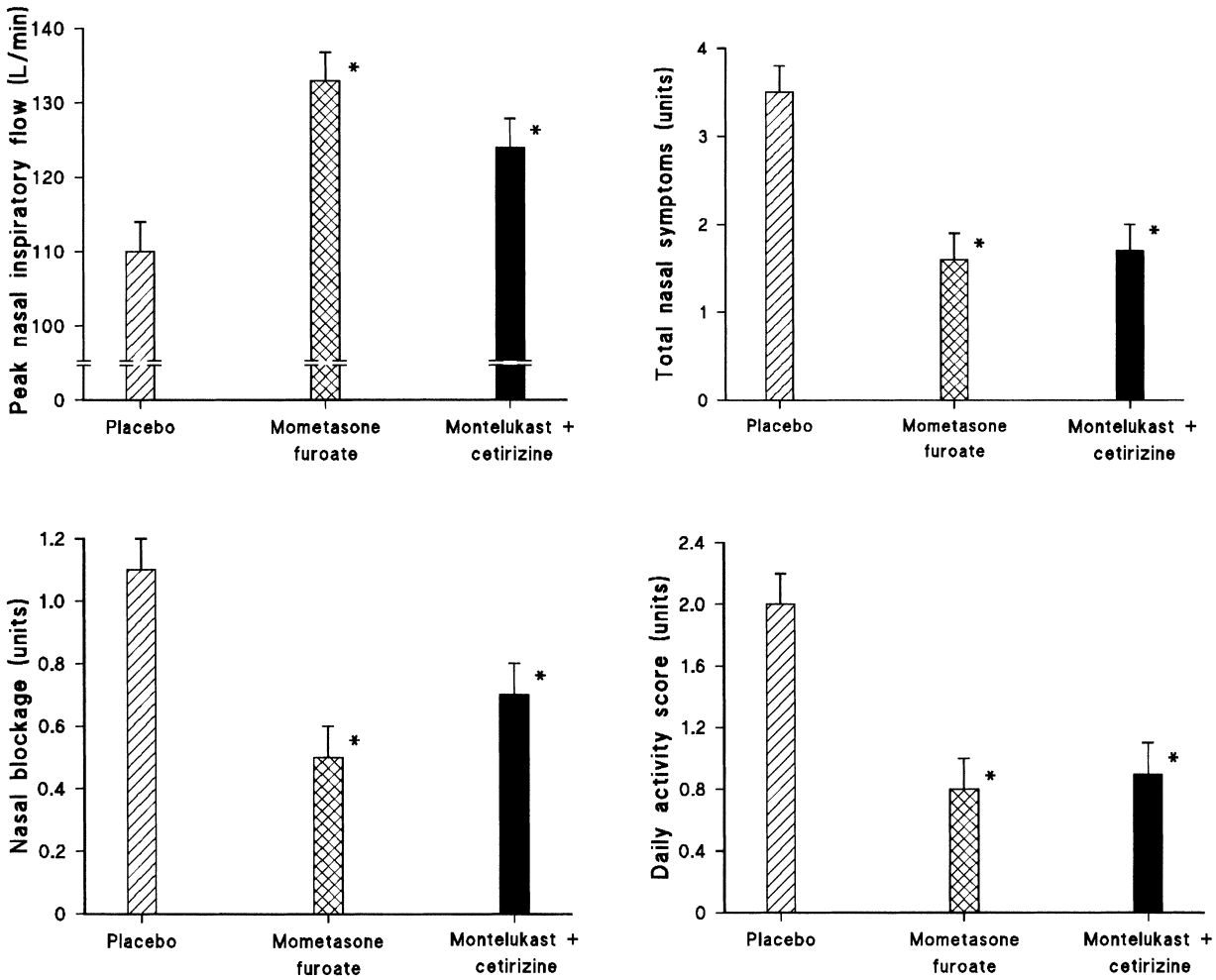


Fig. 4. Means with standard errors for domiciliary peak nasal inspiratory flow, nasal blockage, total nasal symptoms and daily activity score in patients with seasonal allergic rhinitis receiving either placebo, intranasal mometasone furoate 200 μg, or montelukast 10 mg plus cetirizine 10 mg. $*P < 0.05$ for active treatments vs. placebo (reprinted with permission from [42]).

montelukast with loratadine was significantly superior to montelukast alone on parameters of asthma control [45]. Taken together, all of these data suggest that oral therapy with combined mediator blockade is a reasonable therapeutic option for treating upper and lower allergic airway inflammation. All this data is summarised in Table 1.

It is also important to consider the relative drug costs. For example, in the UK, the current cost of 28 days treatment with the combination of cetirizine 10 mg (£8.15) and montelukast 10 mg (£25.69) is considerably more expensive than intranasal budesonide aqueous spray 200 μg (£3.28) on its own for the treatment of allergic rhinitis, or in conjunction with budesonide dry powder inhaler 400 μg (£10.36) for the treatment of allergic rhinitis and concomitant asthma. Since many patients prefer to take tablets rather than nasal sprays or oral inhalers, it is conceivable that the greater cost of combined mediator blockade might be mitigated by the effects of improved compliance on disease control, for example in

Table 1. Efficacy of leukotriene antagonists in seasonal allergic rhinitis

Reference	Design	Treatments	Endpoints	Outcomes
Donnelly *et al*. [25]	$n = 164$ SAR r, db, pg, pc	2 days: zafirlukast	SARS	Zafirlukast > placebo
Pullerits *et al*. [27]	$n = 33$ SAR r, db, pg, pc	7 weeks: zafirlukast or intranasal beclomethasone	SAR Nasal eosinophils	Beclomethasone > zafirlukast = placebo
Grossman *et al*. [26]	$n = 484$ SAR r, db, pg, pc	4 weeks: pranlukast or loratadine	SARS	Pranlukast = loratadine > placebo
Wilson *et al*. [32]	$n = 12$ SAR/Asthma r, sb, dd, co, pc	2 weeks: montelukast or inhaled + intranasal budesonide	SARS	Budesonide > montelukast > placebo
			PIF, NO	Budesonide > montelukast = placebo
Malmstrom *et al*. [27]	$n = 1302$ SAR r, db, pg, pc	2 weeks: montelukast or loratadine	SARS, QOL	Loratadine = montelukast > placebo
Wilson *et al*. [34]	$n = 38$ SAR r, sb, dd, pg, pc	4 weeks: cetirizine or cetirizine + montelukast or cetirizine + intranasal mometasone	SAR, PIF	Cetrizine = cetirizine + montelukast = cetirizine + mometasone > placebo
Meltzer *et al*. [35]	$n = 460$ SAR r, db, pg, pc	2 weeks: montelukast or loratadine, or loratadine + montelukast	SARS	Loratadine + montelukast > loratadine = montelukast > placebo
Lis *et al*. [36]	$n = 907$ SAR r, db, pg, pc	2 weeks: montelukast or loratadine, or loratadine + montelukast	SARS, QOL	Loratadine + montelukast = loratadine = montelukast > placebo
Wilson *et al*. [41]	$n = 37$ SAR r, sb, dd, co, pc	2 weeks: fexofenadine or loratadine + montelukast	SARS, PIF	Fexofenadine = montelukast + loratadine > placebo
Wilson *et al*. [42]	$n = 22$ SAR r, sb, dd, co, pc	2 weeks: intranasal mometasone or montelukast + cetrizine	SARS, PIF	Mometasone = montelukast + cetirizine > placebo
			Rhino, Acoustic, NO	Mometasone = montelukast + cetrizine = placebo
Wilson *et al*. [44]	$n = 21$ SAR/Asthma r, sb, dd, co, pc	2 weeks: inhaled + intranasal budesonide or montelukast + cetirizine	SARS	Budesonide = montelukast + cetirizine > placebo
			PIF	Budesonide > placebo = montelukast + cetirizine
			Rhino, Acoustic	Budesonide = montelukast + cetrizine = placebo

Randomised (r) controlled studies in patients with seasonal allergic rhinitis (SAR).
Design abbreviations: sb: single-blind, db: double-blind, dd: double-dummy, co: cross-over, pg: parallel-group, pc: placebo-controlled.
End points abbreviations: SARS: seasonal allergic rhinitis symptoms, QOL: quality of life, PIF: domiciliary nasal peak inspiratory flow, NO: nasal nitric oxide, Rhino: rhinomanometry, Acoustic: acoustic rhinometry (see text for more details on breakdown of SARS in each study.

patients who have both allergic rhinitis and asthma. This could be particularly relevant for atopic children where it might be easier to administer oral medication on a once daily basis. Proper pharmacoeconomic studies are therefore required to evaluate combined mediator blockade in comparison to other therapies.

Nasal polyposis and aspirin intolerance

Cysteinyl leukotrienes are involved in the aetiology of aspirin intolerance which may manifest as asthma, nasal polyposis, sinusitis and angioedema. This phenomenon may be due to a genetic over-expression of leukotriene C_4 synthase in eosinophils and mast cells, which in the presence of cyclo-oxygenase inhibition results in increased cysteinyl leukotriene production [46]. Leukotriene antagonists are a valuable treatment for aspirin-sensitive asthma, although there are no randomised controlled trials on their efficacy in associated nasal polyposis [47,48]. There is however, a study of aspirin sensitive asthmatics where the 5-lipoxygenase inhibitor zileuton blocked the increase in nasal symptoms and leukotriene levels after aspirin ingestion [49]. Our own anecdotal experience in the rhinology clinic is that leukotriene antagonists are often a valuable therapy for controlling nasal polyposis as well as asthma in aspirin-intolerant asthmatics. Further studies are indicated to evaluate the role of leukotriene antagonists in patients with nasal polyposis who are not aspirin sensitive, and are usually non-atopic to aeroallergens.

Summary

The following conclusions may be drawn from the findings of studies presented in this review:

- Leukotriene antagonists as monotherapy tend to be less effective in allergic rhinitis than in asthma.
- Leukotriene antagonists may be more effective in seasonal allergic rhinitis when given concomitantly with a histamine antagonist, although the degree of additivity may vary and depend on the potency of the histamine antagonist and the disease severity.
- Combined leukotriene/histamine antagonism may be an effective alternative to intranasal corticosteroid alone in seasonal allergic rhinitis, or as an alternative to combined intranasal/inhaled corticosteroid in patients with seasonal allergic rhinitis and coexistent asthma. However, combined mediator antagonism is considerably more expensive than intranasal ± inhaled corticosteroid.

Further studies

A number of further clinical studies in allergic rhinitis would appear to be warranted on the basis of the available evidence.

- Large multicentre studies are required in seasonal allergic rhinitis to assess whether montelukast produces additivity to more potent antihistamines than loratadine, such as fexofenadine, cetirizine or desloratadine.
- The same question with respect to montelukast additivity should be directed towards its combined use with antihistamine in perennial allergic rhinitis, using objective measures of domiciliary peak nasal inspiratory flow as well as subjective symptom scores, quality of life and long-term cost effectiveness.
- In patients with more severe allergic rhinitis, it would be relevant to compare combined mediator blockade vs. intranasal corticosteroid plus an antihistamine.
- Large studies are required to compare combined leukotriene/histamine antagonism vs. combined intranasal/inhaled corticosteroid in patients with allergic rhinitis and concomitant asthma, both for seasonal and perennial disease. Such studies should look at surrogate upper/lower airway inflammatory markers, as well as conventional measures of disease activity. It would also be of value to assess whether combined antagonism might facilitate more effective dose tapering of topical corticosteroids in patients with more severe asthma and allergic rhinitis.
- Nasal biopsy studies should be performed to evaluate putative anti-inflammatory effects of combined leukotriene/histamine antagonism in perennial/seasonal allergic rhinitis, and to compare this with intranasal corticosteroid.
- Paediatric studies are also indicated to evaluate combined antagonism, particularly to evaluate long-term effects on allergic rhinitis and its other atopic associations.
- Controlled studies need to be performed to evaluate the potential role of leukotriene-antagonists as adjunctive therapy to intranasal corticosteroids in nasal polyposis, particularly in cases of aspirin intolerance where there is already evidence for their efficacy in asthma.

References

1 Lipworth BJ. Leukotriene-receptor antagonists. Lancet 1999; 353:57–62.
2 Lipworth BJ, White PS. Allergic Inflammation in the unified airway: start with the nose. Thorax 2000; 55:878–81.
3 Naclerio RM, Baroody FM, Togias AG. The role of leukotrienes in allergic rhinitis: a review. Am Rev Respir Dis 1991; 143:S91–S95.
4 Aharony D. Pharmacology of leukotriene receptor antagonists. Am J Respir Crit Care Med 1998; 157:S214–S218.
5 Sarau HM, Ames RS, Chambers J et al. Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. Mol Pharmacol 1999; 56:657–63.
6 Lynch KR, O'Neill GP, Liv Q et al. Characterisation of the

lower cysteinyl leukotriene $CysLT_1$ receptor. Nature 1999; 399:789–93.
7 In KH, Asano K, Beier D et al. Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. J Clin Invest 1997; 99:1130–7.
8 Drazen JM, Yandava CN, Dube L et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. Nat Genet 1999; 22:168–70.
9 Sampson AP, Siddiqui S, Buchanan D et al. Variant LTC(4) synthase allele modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to zafirlukast. Thorax 2000; 55 (Suppl. 2):S28–S31.
10 Naclerio RM, Meier HL, Kagey-Sobotka A et al. Mediator release after nasal airway challenge with allergen. Am Rev Respir Dis 1983; 128:597–602.
11 Creticos PS, Peters SP, Adkinson NF Jr et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. N Engl J Med 1984; 310:1626–30.
12 Pipkorn U, Proud D, Lichtenstein LM et al. Effect of short-term systemic glucocorticoid treatment on human nasal mediator release after antigen challenge. J Clin Invest 1987; 80:957–61.
13 Knani J, Campbell A, Enander I et al. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. J Allergy Clin Immunol 1992; 90:880–9.
14 Skoner DP, Lee L, Doyle WJ, Boehm S, Fireman P. Nasal physiology and inflammatory mediators during natural pollen exposure. Ann Allergy 1990; 65:206–10.
15 Bisgaard H, Olsson P, Bende M. Effect of leukotriene D4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans. Clin Allergy 1986; 16:289–97.
16 Okuda M, Watase T, Mezawa A, Liu CM. The role of leukotriene D4 in allergic rhinitis. Ann Allergy 1988; 60:537–40.
17 Shirasaki H, Asakura K, Narita S, Kataura A. The effect of a cysteinyl leukotriene antagonist, ONO-1078 (pranlukast) on agonist and antigen induced nasal microvascular leakage in guinea pigs. Rhinology 1998; 36:62–5.
18 Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. N Engl J Med 1990; 323:1745–8.
19 Howarth PH, Harrison K, Lau L. The influence of 5-lipoxygenase inhibition in allergic rhinitis. Int Arch Allergy Immunol 1995; 107:423–4.
20 Numata T, Konno A, Yamakoshi T, Hanazawa T, Terada N, Nagata H. Comparative role of peptide leukotrienes and histamine in the development of nasal mucosal swelling in nasal allergy. Ann Otol Rhinol Laryngol 1999; 108:467–73.
21 Ruck LAM, Rizzo CA, Kreutner W, Egan RW, Hey JA. Synergistic activity of combined histamine H_1 and LTD_4-receptor blockade of mast cell medicated contraction in sensitised human bronchus. Am J Respir Crit Care Med 1999; 159:B47.
22 Roquet A, Dahlen B, Kumlin M et al. Combined antagonism of leukotrienes and histamine produces predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. Am J Respir Crit Care Med 1997; 155:1856–63.
23 Simons FER, Johnston L, Gu X, Simons GJ. Suppression of the early and late cutaneous allergic responses using fexofenadine and montelukast. Ann Allergy Asthma Immunol 2001; 86:44–50.
24 Ancill RJ, Takahashi Y, Kibune Y, Campbell R, Smith JR. Randomized double-blind, placebo-controlled clinical trial of a selective 5-lipoxygenase inhibitor (AA-861) for the prevention of seasonal allergic rhinitis. J Int Med Res 1990; 18:75–88.
25 Donnelly AL, Glass M, Minkwitz MC, Casale TB. The leukotriene D4-receptor antagonist, ICI 204, 219, relieves symptoms of acute seasonal allergic rhinitis. Am J Respir Crit Care Med 1995; 151:1734–9.
26 Grossman J, Ratner PH, Nathen R, Adelglass J, De Joung B. Pranlukast (ultair, SB205312, ONO1078), an oral leukotriene receptor antagonist relive symtpoms in patients with seasonal allergic rhinitis. J Allergy Clin Immunol 1997; 99 (2):S443.
27 Malmstrom K, Hampel FC, Philip G, Malice MP, Reiss TF. Montelukast in the treatment of spring allergic rhinitis in a large double blind randomised placebo controlled study. J Allergy Clin Immunol 2001; 107 (2):S157.
28 Pullerits T, Praks L, Skoogh BE, Ani R, Lotvall J. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. Am J Respir Crit Care Med 1999; 159:1814–8.
29 Nakamura Y, Hoshino M, Sim JJ, Ishii K, Hosaka K, Sakamoto T. Effect of the leukotriene receptor antagonist pranlukast on cellular infiltration in the bronchial mucosa of patients with asthma. Thorax 1998; 53:835–41.
30 Wada K, Minoguchi K, Kohno Y et al. Effects of a leukotriene receptor antagonist, pranlukast hydrate, on airway inflammation and airway hyperresponsiveness in patients with moderate to severe asthma. Allergol Int 2000; 49:63–8.
31 Yoshida S, Ishizaki Y, Shoji T et al. Effect of pranlukast on bronchial inflammation in patients with asthma. Clin Exp Allergy 2000; 30:1008–14.
32 Wilson M, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. Clin Exp Allergy 2001; 31:616–24.
33 Sampson AP, Rorke S. Combination therapy with anti-mediator drugs in allergic disease. Clin Exper Allergy 2001; 31:61–8.
34 Wilson A, Dempsey OJ, Sims EJ, Coutie WJ, Paterson MC, Lipworth BJ. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy 2000; 30:833–8.
35 Meltzer EO, Malmstrom K, Lu S et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol 2000; 105:917–22.
36 Lis K, Malmstrom K, Nayak A, Philip G, Malice MP, Reiss T. Treatment of fall allergic rhinitis with Montelukast alone or in

combination with loratadine in a multicenter double blind randomised placebo controlled study. J Allergy Clin Immunol 2001; 107 (2):S158.

37 Philip G, Malmstrom K, Nayak A, Malice MP, Reiss TF. Improvement in rhinoconjunctivitis quality of life outcomes in the treatment of fall allergic rhinitis by Montelukast alone or in combination with loratadine in a multicenter double blind randomised placebo controlled study. J Allergy Clin Immunol 2001; 107 (2):S158.

38 Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 2000; 30:891–9.

39 Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97:617–26.

40 Day JH, Driscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. J Allergy Clin Immunol 1998; 101:638–45.

41 Wilson AM, Orr LC, Coutie WJR, Sims EJ, Lipworth BJ. A comparison of once daily fexofenadine versus the combination of montelukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis. Clin Exp Allergy 2001; in press.

42 Wilson AM, Orr LC, Sims EJ, Lipworth BJ. Effects of monotherapy with intranasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. Clin Exp Allergy 2001; 31:61–8.

43 Wilson AM, Orr LC, Sims EJ, Dempsey OJ, Lipworth BJ. Antiasthmatic effect mediator blockade versus topical corticosteroids in allergic rhinitis and asthma. Am J Resp Crit Care Med 2000; 160:1297–301.

44 Wilson A, Sims E, Orr LC et al. Effects of topical corticosteroid and combined medicator blockade on domiciliary and laboratory measurements of nasal function in seasonal allergic rhinitis. Annals Allergy Asthma Immunol 2001; in press.

45 Reicin A, White R, Weinstein SF et al. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. Arch Intern Med 2000; 160:2481–8.

46 Cowburn AS, Sladek K, Soja R et al. Over expression of leukotriene C_4 synthase in bronchial biospies from patients with aspirin intolerant asthma. J Clin Invest 1998; 101:834–46.

47 Christie PE, Smith CM, Lee TH. The potent and selective sulfidopeptide leukotriene antagonist, SK & F 104353, inhibits aspirin-induced asthma. Am Rev Respir Dis 1991; 144:957–8.

48 Dahlen BM, Kumlin DJ, Margolskee C et al. The leukotriene receptor antagonist MK-0679 blocks airway obstruction induced by inhaled lysine aspirin in aspirin-sensitive asthmatics. Eur Respir J 1993; 6:1018–26.

49 Fischer AR, Rosenberg MA, Lilly CM et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. J Allergy Clin Immunol 1994; 94:1046–56.