

EDITORIAL

Leukotriene receptor antagonists for the treatment of allergic rhinitis

Seasonal allergic rhinitis (SAR) is characterized by symptoms of nasal itch, sneezing, rhinorrhoea and congestion. Early symptoms occur as the result of mast cell degranulation which in turn release mediators like leukotrienes, histamine, prostaglandins and proteases such as tryptase. These have both local and systemic effects. The nasal mucosa becomes infiltrated with basophils, eosinophils, neutrophils and mononuclear cells which also release mediators such as leukotrienes and histamine, but not kinin or prostaglandins [1]. This response is known to occur either spontaneously, with further allergen challenge, or in response to irritants such as tobacco smoke [2]. Cysteinyl-leukotrienes and histamine are thought to be quantitatively the most important mediators in the final pathways of allergic rhinitis [3]. Effective therapy needs to abolish both the early and late responses and therefore needs to target one or more of the mediators inducing this response. Antihistamines have been part of the therapeutic armamentarium for SAR for years, in contrast to leukotriene receptor antagonists (LTRA) which are a relatively new treatment strategy.

Leukotrienes are derived from arachidonic acid, which is cleaved from intracellular membrane phospholipids and then catalysed by 5-lipoxygenase to produce leukotriene A₄. This is rapidly converted to leukotriene C₄ in most inflammatory cells and to leukotriene B₄ in the neutrophil. Leukotrienes C₄ and B₄ are transported to the extracellular space and are further catalysed to form leukotrienes D₄ and E₄. Since leukotrienes C₄, D₄ and E₄ contain the amino acid cysteine, they are known as cysteinyl-leukotrienes (cysLT). The cysLTs bind to specific receptors cysLT₁ and cysLT₂, with leukotrienes C₄, D₄ and E₄ acting mainly via the cysLT₁ receptors [4]. The cysLTs are known to cause inflammation, constriction of human airway smooth muscle, chemotaxis and an increase in microvascular permeability [5]. Leukotrienes C₄ and D₄ have been shown to be 1000 times more potent than histamine in inducing bronchial smooth muscle constriction and proliferation, and conceivably could also be more potent in inducing other responses [6].

The mechanism of allergic inflammation is common to both upper and lower respiratory tracts, however, most studies of leukotrienes and LTRAs have taken place in the lower airways. Before extrapolating from this information it is important to recognize how the upper and lower airways respond to allergens. Pseudostratified columnar epithelium lines both respiratory tracts, with an abundance of richly vascularized submucosal glands being present in the upper tract. Airway narrowing within the lower airway is determined by smooth muscle tone, whereas in the upper airways airflow is altered by changes in turbinate size resulting from changes in venous capacitance of the submucosa. The late-phase response to allergen challenge may be more important in the lower airways occurring in more than 50% of allergic responses compared to only 5–50% of cases in the upper airway [7].

The role for leukotrienes in SAR is supported by nasal provocation studies performed in the 1980s. One study showed increased production of leukotrienes C₄, D₄ and E₄ within 10 min of allergen challenge in allergic subjects but not in normal subjects [8]. Another study looking at the late nasal response showed low levels of leukotrienes, but with a relatively higher proportion of leukotriene E₄ than in the early-phase, possibly suggesting increased metabolism of leukotrienes C₄ and D₄ during the late-phase [9]. None of these experiments individually mimic natural disease, which is likely to consist of a combination of early- and late-phase responses. However, there is less good published evidence for increased leukotriene production following natural exposure to allergen [10,11].

Histamine challenge is known to induce short-lived nasal blockage as well as itch, sneeze and rhinorrhoea, suggesting direct activity of histamine on neural reflexes [12,13]. In contrast, the primary symptom induced with cysLTs is nasal congestion. Nasal insufflation of leukotriene D₄ has been shown to increase blood flow, increase nasal resistance but not increase secretions, nor cause pruritus or sneezing [12,13]. Antihistamines have been much less effective at treating nasal blockage compared to other symptoms of SAR [14], however, some of the newer antihistamines appear to improve nasal congestion [15].

Few studies have looked at LTRAs in the treatment of allergic rhinitis as opposed to asthma. The best evidence for the role of leukotrienes in the pathogenesis of asthma comes from clinical studies showing benefit from leukotriene modifiers. Up to 25% of asthmatics have concurrent allergic rhinitis [7] and there is anecdotal evidence from those taking LTRAs for bronchospasm to suggest a reduction in rhinitis symptoms.

The evidence favouring the use of LTRAs in SAR amounts to three studies showing modest benefit. A small study showed that Zileuton, a 5-lipoxygenase inhibitor reduces leukotrienes in nasal lavage and reduces nasal congestion following nasal allergen challenge [16]. Following this, a double-blind, placebo-controlled study in 159 patients with ragweed-induced rhinitis demonstrated that 20 or 40 mg, but not 100 mg, of zafirlukast resulted in less nasal congestion than placebo within 2 h of treatment [17]. Surprisingly, sneeze and rhinorrhoea were also reduced in the treatment group [17]. A third study suggested that 4 weeks of treatment with LTRA pranlukast improved nasal symptoms by 24% compared with placebo on week 4 of treatment [18]. However two studies have shown no benefit. L649,923, the LTD₄ antagonist, had no effect on early response to nasal antigen challenge [19]. This is likely to be due to the low affinity of this agent for the leukotriene receptor. A further study in 33 patients comparing oral zafirlukast with topical nasal beclomethasone in a double-blind, double-dummy randomized design showed no significant benefit of zafirlukast in terms of symptoms, assessed compositely, nor a reduction in the number of activated eosinophils present in the nasal mucosa [20].

Symptoms of SAR result from the direct effects of a complex network of mediators and from the development of inflammation. It seems likely that antagonizing more than one of these mediators would be more effective in suppressing the disease process than antagonizing one alone. Antagonists used in combination can achieve their effects by working either additively or synergistically. A study by Reicin et al. has shown that combination therapy with an antihistamine and LTRA is beneficial in the treatment of chronic asthma [21]. However, there are no further stronger studies to support a role for the combination therapy in asthma. The benefit of simultaneously blocking both mediators in rhinitis was demonstrated by Meltzer et al. in a multi-centre, double-blind, placebo-controlled, parallel-group trial of 460 patients comparing the use of montelukast, with loratadine and with montelukast and loratadine cotherapy [22]. This trial showed significant improvement in primary outcome, namely nasal symptom score (blockage, itch, sneeze and rhinorrhea) within just 1 day with the combination therapy compared to both placebo and the individual drugs used alone. Additionally, when compared to placebo, there was a significant improvement in secondary outcome, night-time symptoms, eye symptoms, global evaluation and rhinoconjunctivitis quality-of-life scores (QOL). Interestingly, neither the antihistamine or leukotriene receptor antagonist alone resulted in a significant improvement in the primary end-point compared to placebo. However, secondary end-points such as daytime eye, night-time and composite (daytime nasal and night-time symptoms) were significantly improved by 10 mg but not 20 mg of montelukast. Monotherapy with montelukast of either dosage, or loratadine, was shown to improve rhinoconjunctivitis QOL scores, but again the combination therapy was found to be the most effective. Although this trial supports the use of combination therapy in the treatment of SAR, the clinical relevance of a 20–40% reduction in nasal symptoms from baseline in a non-trial setting is unclear.

A further study by Wilson et al. investigated the effect of combination, LTRA and antihistamine therapy, with topical nasal corticosteroids in SAR [23]. This was clearly an important trial since previous studies had shown that intranasal corticosteroids were superior to either antihistamines or LTRA alone [20,24]. The authors undertook a single-blind, double-dummy, cross-over trial, comparing 2 weeks of 10 mg montelukast plus cetirizine with the effects of intranasal corticosteroid, mometasone furoate (200 µg) in 22 patients with SAR during the pollen season. This study showed improvement in domiciliary peak flow and all nasal and eye symptom scores compared to placebo but with no differences between the two active groups. Both symptom scores and scores of interference with daily activity fell by about 50% with both treatment regimens. Laboratory measures, including exhaled nitric oxide (NO), acoustic rhinometry and rhinomanometry showed no significant improvement compared to placebo. This study suggests that combination therapy with an oral LTRA and an antihistamine can be as effective as intranasal corticosteroids in SAR and demonstrates the efficacy of the combination therapy against nasal blockage. However this was a small study and was conducted over a short period only.

In this issue of *Clinical and Experimental Allergy*, a study by the same authors undertook a single-blind, double-dummy, cross-over study comparing the effects of 2 weeks of once daily fexofenadine (120 mg) with the effects of co-therapy of

montelukast (10 mg) plus loratadine (10 mg), in patients with SAR in the pollen season with a 7–10 day run-in period (25). This study was modelled on previous studies performed by this group with a few modifications to the end-points selected. The primary end-point was domiciliary nasal peak inspiratory flow, previously shown by this group to be a good objective physiological measure correlating well with subjective measures of disease severity and drug activity [23]. The secondary outcome was symptoms, analysed on an individual symptom and a composite score basis.

Both treatment groups were shown to significantly improve both nasal peak inspiratory flow and all symptoms, including nasal blockage, compared to placebo. There was no significant difference in outcomes between treatments, however, there was a trend towards superior outcome in both primary and secondary end-points with the combination therapy. This study has a small sample size with only 37 patients took part. It is possible that larger patient numbers would demonstrate a difference in efficacy between these two treatment modalities. It is somewhat unclear why a different antihistamine was used in each arm of the trial. The evidence demonstrating the superiority of one antihistamine over another in the treatment of SAR is conflicting. Fexofenadine has been shown to be better than loratadine in a study comparing the effect on eye symptoms, nasal blockage and QOL [26] and weal and flare reactions [27]. In contrast, another study has demonstrated reduced symptoms with loratadine and more non-responders with fexofenadine [28]. Assuming that fexofenadine is superior, one could argue that the authors have followed directly on from the Meltzer study in the investigation of the optimal treatment strategy for SAR. It would perhaps seem more logical to compare combination treatment using fexofenadine in both the co-therapy and monotherapy arms. This, after all, is the conclusion reached by this research group.

This study is generally well designed with the run-in and washout periods being shown to be adequate, however, not all points were charted for these run-in periods. The fact that grass pollen count was used as a co-variable was very important, particularly with the rapidly falling counts at the end of July. It would also be interesting to see the distribution of those with mixed allergies between the treatment arms as this is another potential confounder. A strength of the trial is that both subjective and objective outcomes were measured. It is well recognized that there is great variation in symptomatology between individual patients suffering with SAR. Therefore studies, such as this one, which analyse the effect of treatment on individual symptoms are very important. The inflammatory processes occurring in the nasal mucosa in response to allergen challenge are heterogeneous and explain the variety of symptoms experienced in SAR. It is not therefore surprising that individuals respond to treatment in variable ways. The variation in responses to leukotriene modifiers has already been demonstrated in exercise-induced asthma [29].

This study does add further to the minimal literature currently available on the efficacy of combining an antihistamine with a LTRA in the treatment of SAR. There is, however, a need for further large-scale studies to be conducted to cover the whole pollen season to assess the role of combination therapy in the management of SAR. As previously mentioned comparing fexofenadine with fexofenadine and montelukast would be important, as would comparing the combination treatment with

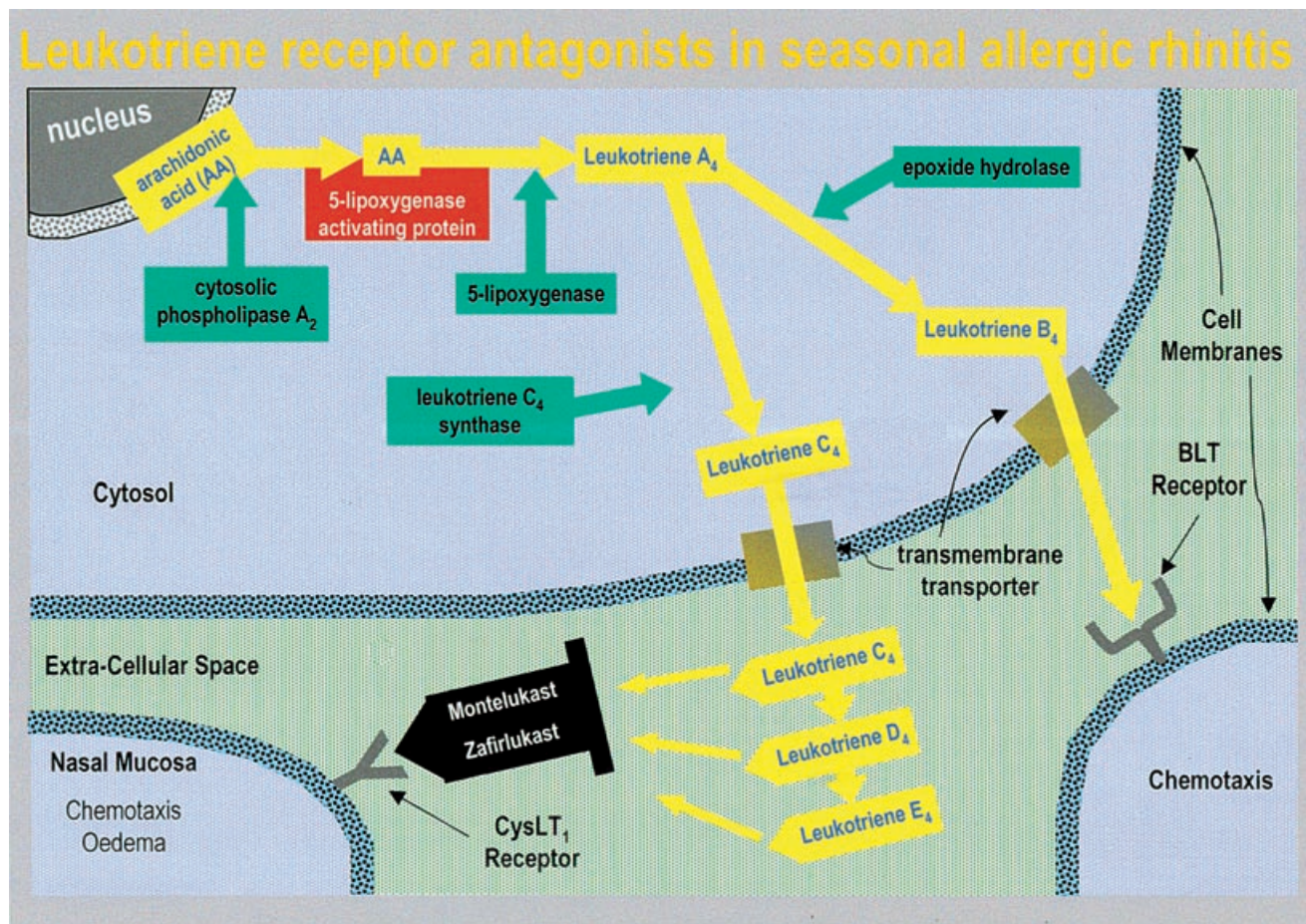


Fig. 1. The pathway of the formation and actions of leukotriene and sites of action of leukotrienes receptor antagonists.

topical steroids. Clearly this and other trials looked at a very selective group of patients. It may be that those excluded from this trial, for example those with asthma and SAR may be the group that benefits most from this treatment regimen. It would be interesting to look at both LTRAs and combination therapy in atopic rhinitic subgroups such as, aspirin-sensitive and dust mite-sensitive patients. Based on the current literature topical nasal steroid still remains the most efficacious treatment modality available for the treatment of SAR.

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