

Review article

Leukotrienes, leukotriene receptor antagonists, and rhinitis

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Introduction

A series of clinical studies have shown the efficacy of leukotriene (LT) receptor antagonists (LTRAs) in the treatment of bronchial asthma (1–6). LTRAs relieve bronchospasm, prevent exercise-induced asthma, and reduce bronchial hyperresponsiveness. LTRAs also have some anti-inflammatory activity in that they reduce the number of eosinophils in bronchoalveolar lavage fluid (7), and the content of NO in the exhaled air of asthmatic children (8). LTRAs have been recently introduced for the treatment of asthma, but their place in the management of the disease has not yet been defined.

As asthma and rhinitis are manifestations of similar inflammatory reactions in the lower and the upper airways, it is natural to speculate whether LTRAs may be useful also in the management of rhinitis. A beneficial effect can be taken as evidence for a role played by LTs in the upper airways.

In this paper, we present an overview of the published literature on the role of LTs in rhinitis and the effect of LTRAs. Considering the large number of studies on asthma, the number of reports on rhinitis is astonishingly low and, for that reason, this review is short.

Role of LTs in rhinitis

What role LTs play in the generation of nasal itching, sneezing, rhinorrhea, and blockage can be investigated by

- 1) animal experiments
- 2) measurement of the release of LTs in the nose after allergen provocation and exposure
- 3) the response to nasal provocation with LTs

- 4) the effect of LTRAs on the response to allergen provocation
- 5) the clinical effect of LTRAs in allergic rhinitis and in nasal polyposis.

Animal experiments

In an experimental study, guinea pigs were provoked intranasally with LTD₄ and with antigen (ovalbumin) (9). The concentration of Evans blue dye in nasal lavage fluid, after an intravenous injection, was used as a measure of the microvascular leakage induced by the nasal provocation. Both LTD₄ and antigen provocation resulted in dose-related microvascular leakage. Pretreatment with the LTRA, pranlukast, completely inhibited the LTD₄-induced extravasation, and the response to antigen was halved. It was concluded that antigen-induced release of cysteinyl LTs might play an important role in the early-phase increase of nasal vascular permeability.

When sensitized guinea pigs were challenged with ovalbumin, pretreatment with pranlukast inhibited the increase in nasal airway resistance, but it had no effect on sneezing or on nasal hypersecretion (10).

The effect of LTRAs on cysteinyl LT-induced and on antigen-induced mucus output has been studied in an *in vitro* experiment of guinea-pig trachea from ovalbumin-sensitized animals (11). LTD₄ induced an increase in the output of mucus, which was significantly inhibited by pretreatment with pranlukast (83% inhibition) and with zafirlukast (78% inhibition). In antigen challenge, a significant reduction was obtained with pranlukast (70%) and with zafirlukast (65%). The authors concluded that LTRAs may be beneficial in

the treatment of allergic airway diseases in which mucus hypersecretion is a clinical symptom.

These experimental animal studies suggest that LTs may play a role in allergic rhinitis by inducing extravasation and edema formation, and by increasing the output of mucus from submucosal glands.

Release of LTs during allergen provocation/exposure

A number of studies have shown release of cysteinyl LTs into nasal lavage fluid during the early-phase response to an allergen challenge (12–17), and one study has also shown release of LTB₄ (13). The release of LTC₄ peaks at 10 min after challenge (12, 13). The level of LTC₄ is also elevated during the late-phase response although the absolute quantity of released LT is much lower.

Increased levels of LTC₄ in nasal lavage fluid have also been found during natural exposure in the pollen season (18–20).

Nasal provocation with LTs

The major role of histamine, as a mediator of symptoms in allergic rhinitis, has been clearly shown by nasal provocation with histamine. When this mediator is sprayed into the nose, it causes immediate itching, sneezing, rhinorrhea, and nasal blockage (21, 22). The only rhinitis symptom that is not induced by histamine is nasal hyperresponsiveness (23).

Sensory nerves. When a cysteinyl LT is applied intranasally, it causes neither itching nor sneezing (21, 22), indicating that LTs do not stimulate sensory nerves in the nasal mucosa.

Glands. Human *ex vivo* studies have shown that LTs can act as secretagogues and thereby stimulate secretion from submucosal glands (24). However, in an *in vivo* study, using a radiolabeling technique to measure the ratio between secretion and lavage fluid, Bisgaard et al. (25) were unable to find any LTC₄-induced increase in the amount of nasal secretions. Nor was there any noticeable increase in mucus production reported in healthy or asthmatic subjects after inhaling cysteinyl LT (26, 27).

Blood vessels. Two human studies (21, 22) have shown that intranasal challenge with LT increases nasal blood flow and nasal airway resistance. The duration of LTD₄-induced increase in nasal airway resistance exceeded that of histamine and was similar to that observed after allergen challenge (22). In addition, one molecule of LTD₄ was 5000 times more potent than one molecule of histamine (22).

In view of the results of these nasal provocation tests, it seems unlikely that LTRAs will have any effect on

Table 1. Estimated symptom profile of H₁ antihistamines and leukotriene receptor antagonists in allergic rhinitis

	H ₁ antihistamine	Leukotriene receptor antagonist	Concomitant use
Itching	+++	–	+++
Sneezing	+++	–	+++
Watery rhinorrhea	++	–	++
Mucus hypersecretion	+	+	++
Nasal blockage	+	+	++
Olfaction	–	+	+
Hyperresponsiveness	–	+?	+?

itching, sneezing, and reflex-induced watery hypersecretion. Possibly, LTRAs may slightly influence the mucous hypersecretion induced by a direct effect of cysteinyl LTs on the seromucous glands.

Clinical effect of LTRAs

In a double-blind, placebo-controlled study involving 159 patients with ragweed pollen-induced allergic rhinitis, Donnelly et al. (28) gave a single dose of the LTRA zafirlukast, 10, 20, 40, or 100 mg, before two 8-h periods of pollen exposure in an outdoor setting (>1000 grains/m³). The onset of action of zafirlukast occurred within 2 h of dosing. The 20- and 40-mg doses significantly reduced nasal blockage ($P < 0.01$); sneezing and rhinorrhea were also decreased ($P \leq 0.05$). The number of sneezes, the amount of nasal secretions, and the nasal airway resistance were not recorded in this study, and it is possible that a change in one nasal symptom score (e.g., nasal blockage) might have had an effect on how the patients scored other nasal symptoms (sneezing and rhinorrhea).

Malmström et al. (29) performed a study combining an H₁-receptor antagonist with a LTRA. At present, the results are published in abstract form only. As many as 460 adults with seasonal allergic rhinitis were enrolled in a 2-week treatment with either placebo, loratadine (10 mg), montelukast (10 or 20 mg), or loratadine (10 mg) plus montelukast (10 mg). Surprisingly, loratadine had a significant effect only on quality-of-life scores, while montelukast significantly increased both quality-of-life and combined eye and nose scores. The combined treatment had a significant effect on all eye and nasal symptom scores. The authors concluded that concomitant treatment with an H₁-antihistamine and a LTRA provides additive beneficial effects in allergic rhinitis and conjunctivitis.

Sixteen patients with perennial allergic rhinitis were treated with an H₁-receptor antagonist (mequitazine) or with the LTRA pranlukast (450 mg daily). The LTRA, but not the antihistamine, had a significant effect on nasal blockage, measured by acoustic rhinometry (30).

In a recent double-blind study of 33 patients with grass-pollen-induced rhinitis, zafirlukast (20 mg b.i.d.)

was compared with placebo and with beclomethasone dipropionate (200 µg b.i.d.) (31). The corticosteroid significantly reduced all nasal symptoms ($P=0.01$) and the number of mucosal eosinophils ($P=0.015$), while zafirlukast was no better than placebo with regard to any of these parameters. Although the number of patients in this study was low, the results clearly indicate that a LTRA is significantly less effective in seasonal allergic rhinitis than an intranasal corticosteroid.

Clinical effect of LT synthesis inhibitors

The effect of LTs can be counteracted in two ways:

- 1) by blockage of the LT receptor
- 2) by inhibition of the LT synthesis.

In principle, LT synthesis inhibitors have the same clinical effect as a LTRA, and they have an additional effect on the synthesis of LTB₄.

Howarth et al. (32) treated pollen-allergic patients outside the pollen season with a 5-lipoxygenase inhibitor (A-78773) before a nasal allergen provocation. The medication attenuated the increase in nasal airway resistance ($P<0.02$) and, over the 40-min observation period, reduced the weighed recovery of anterior nasal secretions ($P<0.03$), in the absence of an effect on nasal itch or sneeze.

In a double-blind, placebo-controlled study, a single dose of the 5-lipoxygenase inhibitor zileuton, 800 mg, was given to eight patients 3 h before nasal allergen challenge (33). Symptoms (number of sneezes, amount of nasal secretion, and subject assessment of nasal blockage) were recorded sequentially every 12 min for 72 min. Mediators (histamine, 5-HETE, LTs, and prostaglandin D₂) were measured in nasal lavage fluid. Zileuton caused a significant inhibition of the allergen-induced nasal blockage ($P<0.02$), but the effect was modest (25% reduction) and only significant for the first 24 min. There was no effect on itching, sneezing, or the amount of nasal secretions. Zileuton reduced lavage level of LTB₄ (90%) and of 5-HETE (70%) (a surrogate marker of cysteinyl LTs), while there was no reduction of histamine and prostaglandin D₂ levels.

Israel et al. (34) gave the 5-lipoxygenase inhibitor zileuton, 600 mg, or placebo daily for 7 days followed by aspirin challenge to eight asthmatic patients with known aspirin intolerance. Zileuton significantly reduced the aspirin-induced asthma symptoms and the fall in FEV₁ ($P<0.014$), and this drug treatment also markedly reduced nasal symptom scores ($P<0.006$).

In another placebo-controlled study of patients with acetylsalicylic acid intolerance, it was shown that zileuton, 600 mg q.i.d. for 1 week, reduced combined nasal symptom scores ($P<0.05$) induced by acetylsalicylic acid provocation, and the level of cysteinyl LTs found in lavage fluid was also reduced ($P<0.05$) (35).

Dahlén et al. (36) treated acetylsalicylic acid-intolerant asthmatic patients with zileuton, 600 mg q.i.d. for 3 weeks in a double-blind, placebo-controlled study. A number of patients also suffered from nonallergic rhinitis and nasal polyposis. There was a clinically significant effect on asthma scores and on lung-function parameters. In addition, nasal symptom scores showed a clear effect of zileuton on the sense of smell ($P<0.01$), a statistically significant effect on rhinorrhea ($P<0.05$), and a trend toward an effect on nasal blockage ($P=0.63$).

Antihistamines and LTs

In a recent review, Bachert & Lange (37) presented data which indicate that the topically applied H₁-antihistamine azelastine and perhaps also the peroral H₁-antihistamine mizolastine can have an effect on the synthesis of cysteinyl LTs and that this additional effect may be of clinical significance in the treatment of rhinitis. However, controlled studies have failed to show that these two antihistamine preparations are clinically more effective than other antihistamines (38, 39).

Discussion and conclusions

Our knowledge of the role played by cysteinyl LTs as mediators of rhinitis is insufficient, and there are only a few studies on the effects of LTRAs and LT synthesis inhibitors in allergic rhinitis and in nasal polyposis. Therefore, only preliminary conclusions can be made and we can only speculate on how these new drugs will influence our treatment of allergic rhinitis and nasal polyposis. There is no doubt that histamine, which stimulates sensory nerves, causing itching, sneezing, and reflex-induced watery rhinorrhea, is a more important mediator of allergic rhinitis than LTs. Although the study of Malmström et al. (29) indicates the opposite, it is unlikely that LTRAs will be competitors to antihistamines in the treatment of allergic rhinitis. However, these two types of drugs seem to have different effect profiles, suggesting that a combined preparation might have added efficacy. We have estimated the separate and added effects of the drugs on rhinitis symptoms in Table 1. However, the published data on LTRAs are too few to allow any valid conclusion.

If a combined antihistamine and LTRA tablet is used in patients with both rhinitis and asthma, one can expect a beneficial effect in both diseases, with the antihistamine being relatively more important in the nose and the LTRA in the bronchi. This may offer a nonsteroidal oral alternative in the treatment of patients with both allergic rhinitis and asthma.

Finally, it is unknown what role cysteinyl LTs might play in the common cold. Apparently, no study of the effect of LTRAs has investigated this important question.

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