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The Role of Leukotrienes and Antileukotriene Agents in the Pathogenesis and Treatment of Allergic Rhinitis

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Introduction

The role of 5-lipoxygenase pathway mediators in the pathogenesis of asthma has been extensively described in this journal. The same mediators should be present during the early and late phase of the allergic reaction in the nose. Cells that can produce leukotrienes (LTs), including mast cells and eosinophils, are present in the nasal mucosa of allergic individuals *(1)*. The nasal epithelial mast cell is of the MCt subtype and the number of epithelial cells is reported to increase during the allergy season *(2)*. Although most of the mast cells in the nose are found in the basement membrane and are predominantly of the MCt subtype *(3)*, eosinophils have long been known to be present in increased amounts in the nasal mucosa of patients with allergic rhinitis. The nose is one of the most vascular organs of the body *(4)*. With vasodilation, the engorgement of the blood vessels can lead to considerable nasal obstruction.

Activation of mast cells during the alllergic response leads to the generation of the 5-lipoxygenase products LTB_4, LTC_4, LTD_4, and LTE_4, which can produce vascular permeability, vasodilation, mucous secretion, and cellular diapedesis *(5)*. In addition to these 5-lipoxygenase products, which have been shown to have eosinophilic chemoattractant properties, 5-HETE, another 5-lipoxygenase but non-LT metabolic product, has recently been shown to be the most eosinophilic chemoattractant of all the products *(6)*. Within minutes after allergen exposure, these mast cell products can be measured in nasal washings *(7,8)*. LTC_4 predominates, but LTD_4 and LTE_4 can be detected immediately as well as hours after allergen challenge *(9)*. Such changes appear to be specific

because they are not seen in nonallergic subjects challenged with antigen or allergic subjects challenged with methacholine *(9,10)*. In contrast, only minimal and inconsistent increases in LTB_4 were seen early after antigen challenge *(10,11)*. However, one study detected a significant increase in LTB_4 in 12 of 13 atopic subjects during the late allergic reaction *(12)*.

There is limited data addressing the issue of LT presence in natural allergen exposure. In one uncontrolled study, looking at nasal pharyngeal levels of LTC_4, higher levels were found during the ragweed season *(13)*. In another study looking at urinary levels of LTE_4 and grass pollen subjects in and out of the allergy season, no significant differences were seen *(14)*. However, it has been shown that when a group of allergic rhinitis patients were studied outside the pollen season and their levels of LTC_4 in nasal lavage were compared to symptomatic patients during the pollen season, there was a statistically significant increase in the LTC_4 levels during the pollen season *(15)*.

Histamine has traditionally been considered one of the most important mediators in producing allergic rhinitis symptoms. Nasal installation of histamine can cause congestion, sneezing, itching, and rhinorrhea, but treatment with H_1-receptor antagonist provides significant relief from symptoms of itching and sneezing and can decrease rhinorrhea. Treatment with H_1-receptor antagonist provides significant relief from symptoms of itching and sneezing and can decrease rhinorrhea but provide little relief from the congestion that accompanies allergic reactions *(16,17)*. Interestingly, nasal challenge with LTD_4 produces an increase in nasal blood flow and congestion, but without concomitant pruritus or sneezing *(18,19)*. Nasal challenges with LTB_4 have not been reported.

It has been noted that 5-lipoxygenase pathway products are believed to be pivotal in the pathogenesis of aspirin-sensitive asthma *(20)*. At baseline, the urinary levels of LTE_4 are approximately six times higher in aspirin-sensitive asthmatics when compared to those asthmatics who are aspirin-tolerant *(21)*. Foliowing a positive aspirin challenge in aspirin-sensitive asthmatics, there is fourfold rise in urinary LTE_4 levels 6 h after the ingestion *(21)*. This is not seen in aspirin-tolerant asthmatics. Aspirin-sensitive asthmatics have a very significant rhinosinusitis component usually with accompanying nasal polyposis *(20)*. Increased levels of LTC_4 are found in the nasal lavage fluid of aspirin-sensitive asthmatics following challenge with aspirin either orally or by direct instillation in the nose *(22,23)*. This is not seen in the lavage fluid following challenge in aspirin-tolerant asthmatics.

Anti-LT Treatment and Pretreatment in Allergic and Aspirin-Sensitive Rhinitis

In a study of eight subjects with allergic rhinitis who underwent nasal allergen challenge after receiving a 5-lipoxygenase inhibitor

(A-64077) or placebo concentrations of LTB_4 and 5-HETE were measured in the nasal fluid and nasal congestion was assessed *(24)*. Peak levels of LTD_2 and 5-HETE were markedly significantly reduced whereas the levels of prostaglandin D_2 were not. The amount of nasal congestion was also significantly attenuated following 5-lipoxygenase inhibition by this compound, although sneezing was not *(24)*. It is interesting that although levels of prostaglandin D_2, as well as other products of the cyclooxygenase pathway in nasal secretions following antigen challenge, tend to be higher than the levels of LTB_4 or LTC_4, potent inhibitors of prostaglandin synthesis have little, if any, effect on the symptoms of allergic rhinitis *(25)*.

The efficacy of single oral doses of ICI 204,219 (zafirlukskast) were tested in subjects with acute seasonal allergic rhinitis. In this study, 164 subjects who had significant baseline symptoms over a 3-d baseline period were treated with 10–100 mg of zafirlukskast or placebo *(26)*. Rhinitis symptoms, including nasal congestion, sneezing, rhinorrhea, itchy nose (throat end palate), and ocular symptoms, were all recorded during an hourly walk in a park as well as during the evening at home. Nasal congestion improved most consistently when compared to placebo although there were some changes in sneezing and rhinorrhea as well. Interestingly, the onset of action for the treatment groups was within 2 h of the first dose *(26)*.

In double-blind, placebo-controlled asthma trials with zileuton (a 5-lipoxygenase inhibitor) and montelukast (a leukotriene receptor antagonist) nasal symptom scores were also measured and found to be reduced (Abbott Laboratories, personal communication; Merck Laboratories, personal communication).

A recent report compared montelukast with loratadine and both products together in a placebo-controlled trial in 460 subjects with seasonal allergic rhinitis *(27)*. After a 1-wk single-blind run-in phase, subjects were randomized to one of the four treatment groups for a 14-d study. Interestingly, only the combination of montelukast plus loratadine and neither agent alone showed significantly better symptom scores than placebo. This study will have to be scrutinized when published in manuscript form as the data are clearly contrary to other placebo-controlled trials with loratadine in allergic rhinitis *(28)*.

Zileuton has been shown to be effective in the treatment of the rhinitis of aspirin-sensitive asthmatics *(29)*. In a study of 40 aspirin-sensitive asthmatics treated with zileuton or placebo, zileuton was noted to diminish nasal dysfunction. A "remarkable" return of smell, less rhinorrhea, and a trend for less stuffiness and higher nasal inspiratory flow was seen during treatment with zileuton.

In summary, the data noted above would suggest a significant role for 5-lipoxygenase products in the pathogenesis of allergic rhinitis as

well as possible therapeutic benefit for anti-LT medication in this condition. Clearly, double-blind, placebo-controlled trials with each of the currently available agents appear indicated.

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