Review

Allergic rhinitis and asthma: inflammation in a one-airway condition

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Abstract

Background: Allergic rhinitis and asthma are conditions of airway inflammation that often coexist.

Discussion: In susceptible individuals, exposure of the nose and lungs to allergen elicits early phase and late phase responses. Contact with antigen by mast cells results in their degranulation, the release of selected mediators, and the subsequent recruitment of other inflammatory cell phenotypes. Additional proinflammatory mediators are released, including histamine, prostaglandins, cysteinyl leukotrienes, proteases, and a variety of cytokines, chemokines, and growth factors. Nasal biopsies in allergic rhinitis demonstrate accumulations of mast cells, eosinophils, and basophils in the epithelium and accumulations of eosinophils in the deeper subepithelium (that is, lamina propria). Examination of bronchial tissue, even in mild asthma, shows lymphocytic inflammation enriched by eosinophils. In severe asthma, the predominant pattern of inflammation changes, with increases in the numbers of neutrophils and, in many, an extension of the changes to involve smaller airways (that is, bronchioli). Structural alterations (that is, remodeling) of bronchi in mild asthma include epithelial fragility and thickening of its reticular basement membrane. With increasing severity of asthma there may be increases in airway smooth muscle mass, vascularity, interstitial collagen, and mucus-secreting glands. Remodeling in the nose is less extensive than that of the lower airways, but the epithelial reticular basement membrane may be slightly but significantly thickened.

Conclusion: Inflammation is a key feature of both allergic rhinitis and asthma. There are therefore potential benefits for application of anti-inflammatory strategies that target both these anatomic sites.

Introduction

Asthma is a chronic, inflammatory condition of the lower airways characterized by largely reversible airflow obstruction, airway hyperresponsiveness, and episodic respiratory symptoms, including wheezing, productive cough, and the sensations of breathlessness and chest tightness [1]. Allergic rhinitis (AR), also often associated with conjunctival symptoms, is a disorder of the upper airways

(namely, above the larynx) resulting from IgE-mediated inflammation of the nose upon contact of the nasal mucosa with allergens: symptoms include rhinorrhea, nasal itching, sneezing, and nasal obstruction [2]. The patterns of inflammation, when stable or in response to experimental allergen challenge, are similar in the upper and lower airways. Moreover, both asthma and AR may be associated with evidence of systemic inflammation.

Often, as discussed in the prior article in this supplement [3], asthma and AR are comorbid conditions [2,4], with AR being a major risk factor for the occurrence of asthma [5].

In the present article, we summarize the patterns of inflammation of the upper and lower airways; we emphasize the need to consider treating the inflammation that is common to both. We introduce briefly techniques currently used to describe characteristic cells and mediators of inflammation common to both asthma and AR. Of course, patients with asthma, as well as AR, can demonstrate a spectrum of symptoms clinically and, likewise, of inflammatory changes. As more data emerge it is likely that distinct phenotypes of both AR and asthma will become accepted. Despite this, there are some obvious similarities in the patterns of inflammation yet differences in the extent of remodeling.

Evaluating the airways for inflammation
With the exception of the anterior nares and a good proportion of the nasopharynx and larynx (which are keratinized and stratified squamous, respectively), the microscopic anatomy of normal nasal and bronchial mucosa is similar: a pseudostratified epithelium resting on a reticular basement membrane with underlying subepithelium (that is, lamina propria). The epithelium is composed of columnar ciliated cells interspersed by goblet cells [6], and beneath (in the subepithelium and submucosa) there are blood vessels, fibroblasts, nerves, mucous glands, and immune cells. The differences between nose and bronchi include the greater abundance of subepithelial capillaries and the venous cavernous sinusoids present in the nose and the presence of encircling airway smooth muscle in the lower airways, absent from the nose [6,7].

There are several techniques for evaluating inflammation in lower or upper airways in both clinical and research settings. The lower airways can be investigated by rigid or flexible fiberoptic rhinoscopy and bronchoscopy [8-10]. Bronchoscopy is used to collect endobronchial biopsies or brushings as well as bronchoalveolar lavage. Nasal sampling includes biopsy, with and without the aid of rhinoscopy, and cytology can be assessed in lavage or nasal swabs [11]. Expelled secretions for analysis include induced sputum from the lower airways and nasal mucus from the upper airways. Biopsy permits histopathological, immunohistological, and molecular examination of respiratory mucosa. Cytological examination of secretions can add useful information to that obtained by direct examination of the mucosa: these complementary techniques sample two distinct compartments [12]. Measurement of biological markers in airway and nasal secretions can also be made before and after endobronchial provocation with allergen or pharmacological or physical agents in order to study the dynamics of the inflammatory responses to such challenges [9,13].

Bronchoscopy has its limitations. It samples only a small portion of the entire lung and in its airways, only the superficial portion of the bronchial wall is sampled. While possible, examination of the smaller (2–3 mm) airways is difficult in practice and there are greater safety and ethical issues. Moreover, bronchoscopy may not be practical in severely compromised adults or pediatric patients [9] although, in the latter, recent studies have been published that aim to elucidate the patterns of inflammation and remodeling that occur as asthma becomes first recognized clinically [14-16]. The usefulness of nasal and bronchial cytology is also limited by considerable intra-individual variability as well as variability according to collection technique [11,13,17]. In disorders of airflow obstruction, there is now a greater appreciation of the need to also understand the distinct contributions to variability in the lower airways [18]. Additionally, the fractional concentration of exhaled nitric oxide may be a useful measure to assess airway inflammation in diagnostic work or to monitor the effects of anti-inflammatory therapy, even in children [19-23]. Finally, peripheral blood eosinophilia is common in AR and asthma, and it reflects the presence of systemic inflammation [24].

Changes in the upper airways in allergic rhinitis
The inflammatory cascade in the nose begins with allergen deposition on the nasal mucosa and consists of early phase responses and, in many cases, late phase responses in susceptible individuals. Upon activation by antigen via cross-linking of IgE receptors, sensitized mast cells immediately degranulate, releasing a variety of inflammatory mediators, including histamine, prostaglandin D_2, cysteinyl leukotrienes, and neutral proteases [2,25]. These mediators cause sensory neural stimulation and plasma exudation from blood vessels, which the patient experiences as itching, sneezing, nasal discharge, and congestion. Other localized cells involved in the allergic response include Langerhans' cells, which are dendritic cells that present antigen to the mast cells, and T helper type 2 lymphocytes, which indirectly regulate the production of IgE. Recruitment of inflammatory cells, including eosinophils, basophils, and T cells, results in further release of histamine and leukotrienes, as well as other compounds including proinflammatory cytokines and chemokines, sustaining the allergic response and promoting the late phase response that may occur 6–9 hours after allergen exposure [26,27].

Nasal biopsies of patients with active AR show accumulations of mast cells, eosinophils, and basophils in the epithelium and an accumulation of eosinophils in the deeper

lamina propria [27]. In time, the reticular basement membrane may appear slightly but significantly thickened, but not to the extent seen in the lower airways in asthma (see discussion of remodeling below). Remodeling in the nose appears to be less extensive than that in the lower airways [6,24]. While this requires further study, two reasons postulated for the differences in remodeling between upper and lower airways include the secretory activity of smooth muscle cells present in bronchi but not in the nose, and the differences in embryologic origins of the bronchi and the nose [6].

Changes in the lower airways in asthma: inflammation and remodeling

Both inflammation and structural changes (referred to as remodeling) occur in the tracheobronchial tree of patients with asthma. It has been generally considered that chronic eosinophilic inflammation is a prerequisite for the development of remodeling, and there is some animal experimental evidence to support this [28]. Investigations in humans to discover whether chronic inflammation leads to remodeling or whether remodeling begins first are in their infancy [14-16,29]. Such studies are required so that we may determine if and when there may be a 'window of opportunity' for prevention of the structural and inflammatory changes associated with the asthma phenotype. Moreover, it may become possible to predict which preschool 'wheezers' will go on to develop asthma.

Airway inflammation can be present even in patients with normal lung function but with symptoms indicative of asthma [30]; hence, measurements of the forced expiratory volume in 1 second do not reflect well or predict airway inflammation. Conversely, symptomatic infants with reversible airflow obstruction (that is, asthma) may not demonstrate evidence of either bronchial tissue eosinophilia or remodeling [15]. Considering that these pathological changes are present and maximal in severely asthmatic school children of median age 10 years [14], the changes must begin earlier. There are now new data indicating that the changes begin between the ages of 1 and 3 years and that there is a positive relationship between tissue eosinophilia and reticular basement membrane thickening at this time [29].

Chronic inflammation plus remodeling contribute to airway wall thickening, which encroaches upon the airway lumen and increases resistance to airflow (Figure 1). Airway secretions also contribute to the pathology of asthma, and especially to the consequences of acute, severe, life-threatening exacerbations. In those rare cases when a fatal asthma attack has occurred after a short duration of asthma, airway wall thickening may not be present – and in these cases patient demise is assumed to be secondary to asphyxiation from tenacious, sticky mucus admixed

with an inflammatory eosinophilic exudate in the airways (Figure 2) [31].

Inflammation in asthma
Lymphocytic inflammation enriched by eosinophils is characteristic of the bronchi in mild asthma in both adults and school children, and also of the bronchi and luminal secretions in fatal asthma (Figures 3 and 4). In severe disease the predominant pattern changes because, in addition to eosinophils, neutrophils increase, and the inflammation may spread to include the small airways (that is, airways 2 mm or smaller in diameter) [32].

In allergic asthma, inhaled allergens that penetrate the mucociliary lining layer enter the airway epithelium either via the tight junctions that surround the apical zone of bronchial epithelial cells or by direct uptake by the cells *per se*. As occurs in the nose, the sequence of reactions in the lungs may include both early phase and late phase responses. There is presentation of antigen to mast cells, cross-linking of cell surface IgE, degranulation of mast cells, release of mediators such as histamine and leukotrienes that markedly increase vascular permeability, followed by recruitment of more inflammatory cells, and further release of proinflammatory mediators.

In asthma, the predominant orchestrator of the chronic inflammation is the CD4 or T-helper lymphocyte, producing key regulatory cytokines such as IL-5 and IL-4 [33]. Eosinophils (originating in the bone marrow) are released into the circulation, resulting in blood eosinophilia, partly in response to IL-5. The eosinophils are selectively retained at bronchial microvascular surfaces by tumor necrosis factor alpha-induced and IL-4-induced upregulation of adhesive molecules. Once retained they are recruited into the mucosa (Figure 5) and migrate to the surface epithelium where they cross it, in response to eosinophil chemoattractants released by structural and immune elements. The then-activated eosinophils release highly toxic granules that damage the surface epithelial cells, loosening their attachments and resulting in their loss into the airway lumen, where they admix with both eosinophils and excess mucin.

Eosinophil chemoattractants include, for example, eotaxin, macrophage/monocyte chemotactic protein 4, RANTES, and cysteinyl leukotrienes [34]; these chemoattractants act on distinct cell surface receptors (CC chemokine receptor 3 and cysteinyl leukotriene type 1 ($cysLT_1$) receptor) present on the eosinophil, but not exclusively so. In support of this, challenge with leukotriene E_4 results in greatly increased numbers of eosinophils in the bronchial wall [34]. Moreover, a recent study in asthma has used the molecular techniques of *in situ* hybridization and immunohistochemistry to localize cells that express either
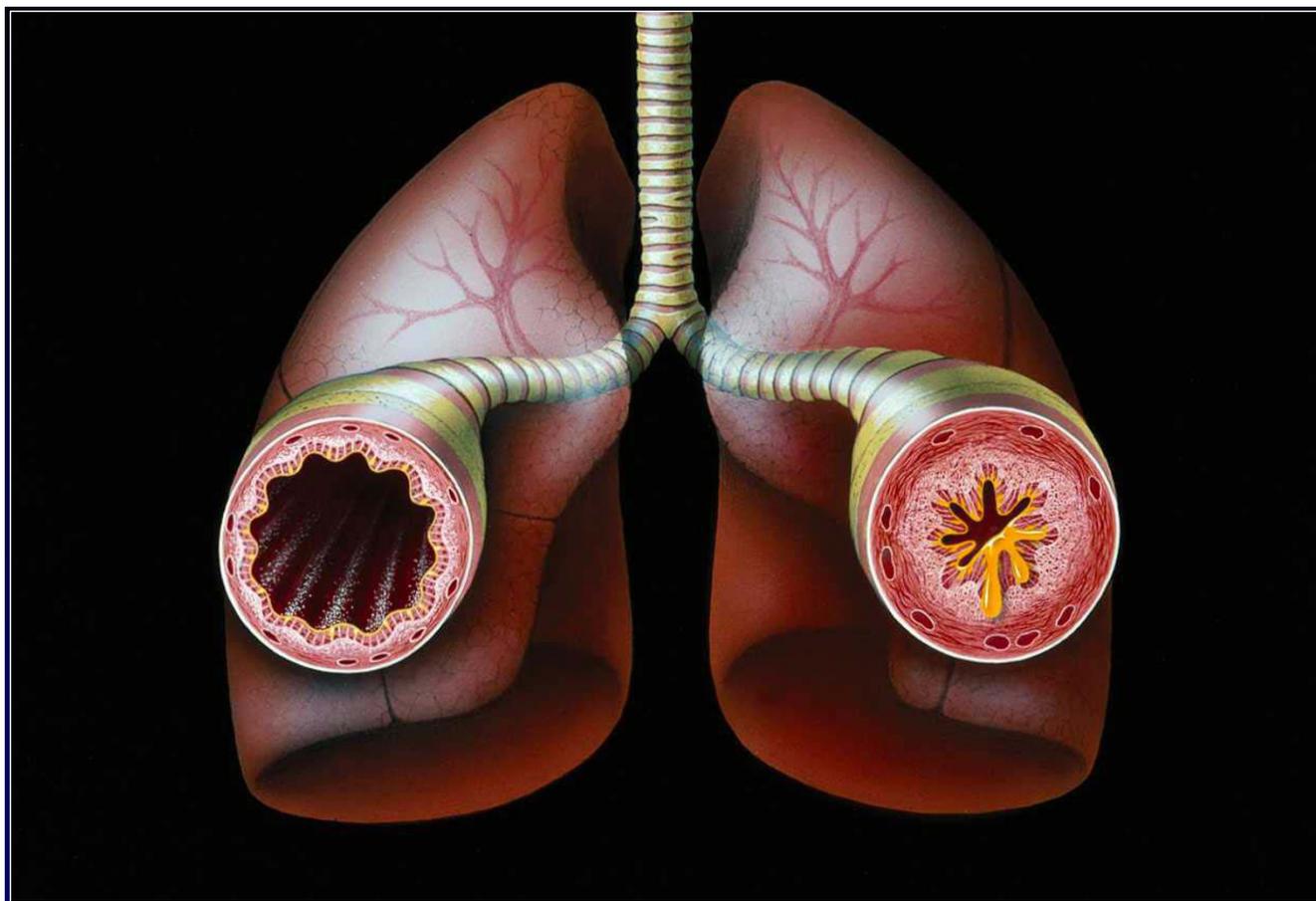
Figure 1
Thickening of the bronchial wall in asthma. Schematic illustrating the thickening of the bronchial wall in asthmatic conditions (right) as compared with normal conditions (left). Reprinted with permission from Jeffery [65].

the mRNA or the protein for the $cysLT_1$ receptor, respectively [35]. In addition to the eosinophil, the receptor appears to be present on a variety of bronchial inflammatory cells (Figure 6), including neutrophils, mast cells, macrophages, B lymphocytes, and plasma cells. The study also demonstrated that the numbers of inflammatory cells expressing the $cysLT_1$ receptor are increased – in comparison with normal healthy nonsmokers – in nonsmoking patients with mild, stable asthma and that there is a further increase among patients experiencing a severe exacerbation of asthma leading to hospitalization (Figure 7) [35].

Remodeling in asthma
Remodeling in asthma has been defined as a change in structure that is inappropriate to the maintenance of normal airway function [33]. Remodeling is evident even in newly diagnosed or mild asthma and is characterized by epithelial fragility and reticular basement membrane thickening. With increasing severity of asthma, there are

increases of airway smooth muscle mass, vascularity, numbers of fibroblasts, and interstitial collagen, as well as mucous gland hypertrophy [33]. These changes appear to be greatest in the larger, more proximal airways.

Thickening of the reticular basement membrane occurs early in asthma (Figure 8), even before diagnosis, and is detected in children with mild asthma [16]. It most probably reflects the response to ongoing epithelial injury and regeneration, in which eosinophils play a role [36]. In school children between the ages of 6 and 16 with severe asthma the membrane is already maximally thickened, but there is no significant association between its thickness and age or symptom duration [14]. These changes appear in preschool wheezy children by the age of 29 months [29].

Airway smooth muscle surrounds the airways as two opposing helices; namely, in a geodesic pattern. As the muscle shortens, therefore, it not only constricts but tends

Figure 2
Plugging of the airways in fatal asthma. Gross view of a sliced lung specimen to show plugging of the airways in fatal asthma. Reprinted with permission from Jeffery [65].

to shorten the airway against an elastic load. Leukotrienes are very powerful constrictors of airway smooth muscle, being 1000-fold or 2000-fold more active than histamine. There are at least three possible mechanisms of smooth muscle mass enlargement in asthma: myocyte hypertrophy, myocyte hyperplasia due to cell division and proliferation, or myocyte de-differentiation and migration across the mucosa in the form of myofibroblasts or fibromyocytes. It is speculated that these may then re-differentiate to form new blocks of smooth muscle that come to lie just below (external to) the epithelium [33].

Greater numbers of mast cells have recently been found located within the bronchial smooth muscle of patients with asthma than in those with eosinophilic bronchitis – the latter is also a condition of airway eosinophilia and remodeling but without the functional abnormalities characteristic of asthma. The difference in smooth muscle mast cell number that discriminates between these conditions has led to the hypothesis that the infiltration of air-

way smooth muscle by mast cells is responsible for the disordered airway function characteristic of asthma, and thus that asthma is the result of a mast cell myositis [37]. These and other data highlight the importance of the localization of inflammatory cells to distinct tissue compartments rather than their overall number *per se*. No doubt there will be many more studies to test this hypothesis.

Interactions between asthma and allergic rhinitis

Allergic asthma and AR are often considered clinical manifestations of the same condition, the chronic allergic respiratory syndrome [38,39]. The many epidemiological associations between the two conditions are reviewed in the prior article in this supplement [3]. Moreover, as discussed previously [3], bronchial hyperresponsiveness is common in people with AR, even if they have no symptoms of asthma, and bronchial inflammation can result from nasal allergen challenge in patients with AR in the
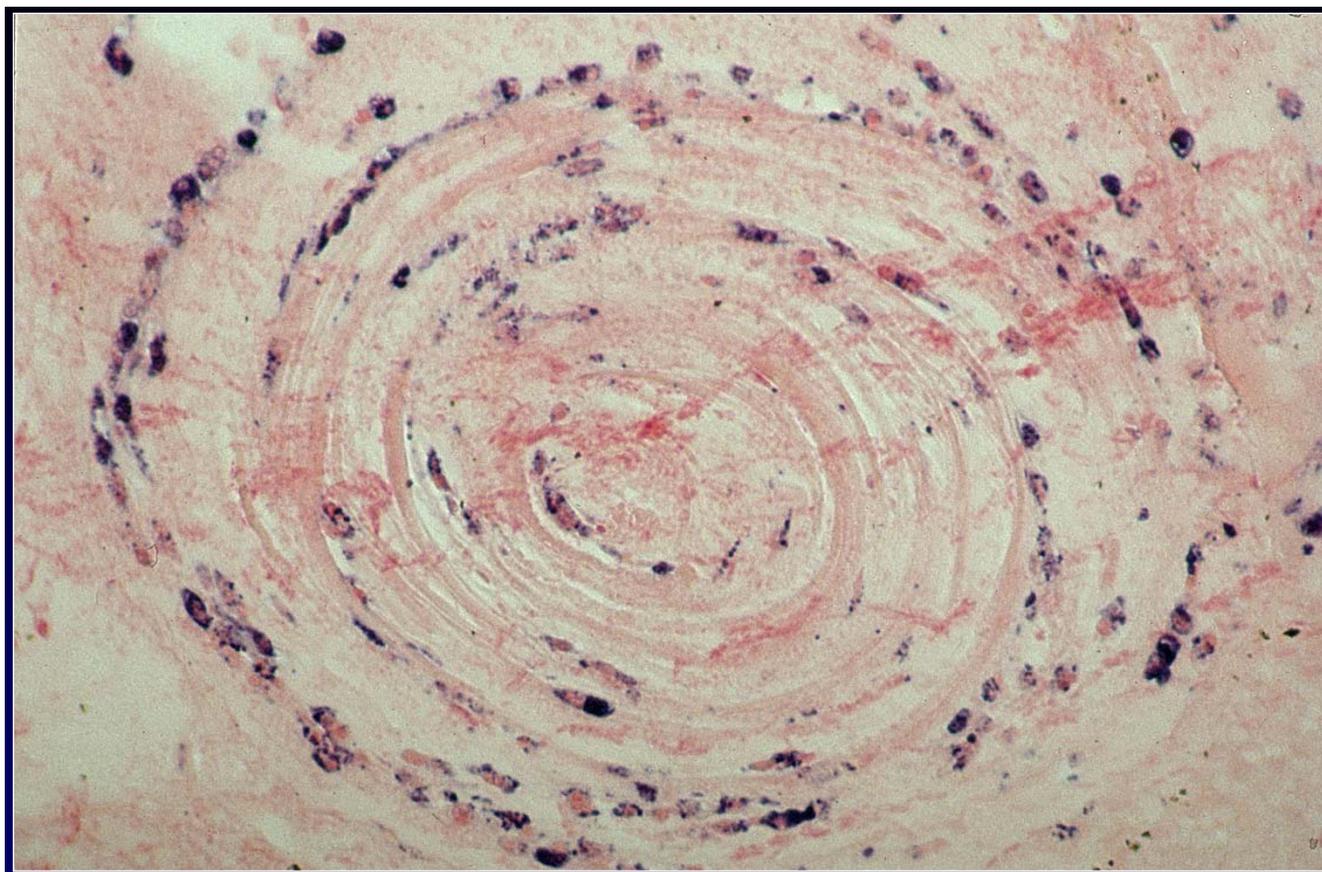
Figure 3
Plug of eosinophil-rich inflammatory exudate and mucus in the airway of a patient with asthma. Concentric lamellae of eosinophils appear blue (alkaline phosphatase antialkaline phosphatase). Reprinted with permission from Jeffery [65].

absence of obvious asthma [40]. Conversely, patients with asthma can have eosinophilic infiltration of their nasal mucosa without reporting the symptoms of rhinitis [38,39]. Segmental bronchial provocation in patients with AR but not asthma has been shown to induce nasal inflammation [41,42]. Not all patients with asthma have rhinitis, however, and not all patients with rhinitis have asthma. Genetic differences contribute to this discrepancy; for example, certain haplotypes of the newly identified GPR154 gene on chromosome 7 predispose individuals to IgE-mediated rhinitis but not to asthma [43].

Possible mechanisms for the influence of AR on lower airways include disturbance of the beneficial role of nasal mucosa in conditioning the air entering the respiratory tree; neural interaction between upper and lower airways; irritant effects of nasal secretions directly entering the lower airways; and systemic propagation of nasal inflammation to the bronchial mucosa (or vice versa) via effects

of mediators and inflammatory cells on bone marrow – 'systemic cross-talk' [38,40,44].

Effects of anti-inflammatory treatment in allergic rhinitis and asthma – proof of concept
Nasal corticosteroids, antihistamines, and the leukotriene receptor antagonist (LTRA) montelukast have each been shown to have anti-inflammatory effects on different aspects of inflammation in AR, and these effects have been recently reviewed [45].

In patients with asthma, inhalation of corticosteroids (ICS) produces reductions in bronchial inflammation by days or weeks, whereas reductions in reticular basement membrane thickening are achieved over longer periods, after about 1 year [46]. Treatment with montelukast reduces peripheral eosinophil counts and eosinophils in induced sputum [47]. Short-term treatment (that is, 4 weeks) with another LTRA, pranlukast, reduces bronchial inflammation in endobronchial biopsies [48]. Moreover,
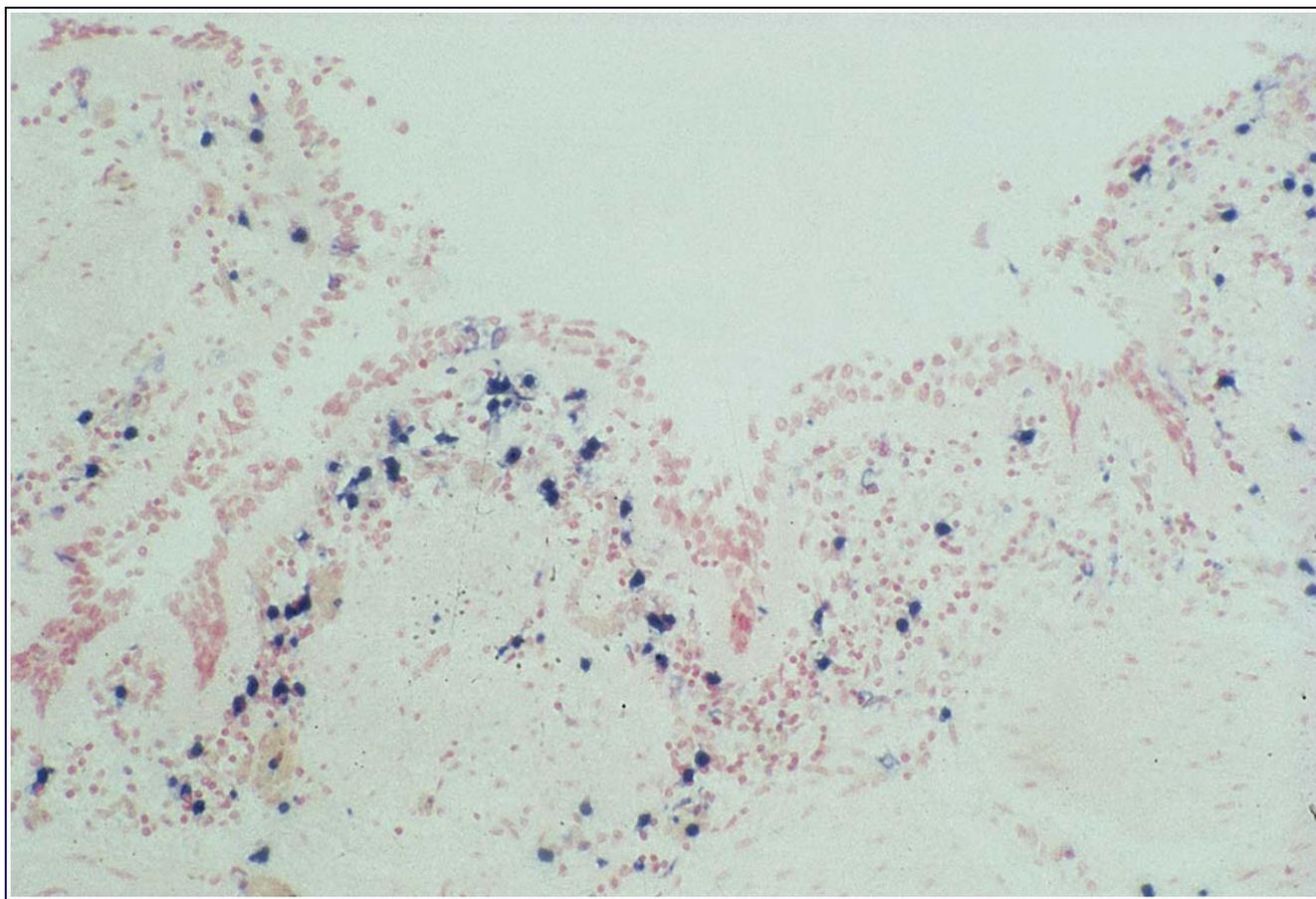
Figure 4
Eosinophils in the airway wall in fatal asthma. Fatal asthma with eosinophils (blue) in the airway wall showing the origin of the eosinophils that migrate across the mucosa, enter the lumen, and contribute to the inflammatory exudate shown in the previous figure. Reprinted with permission from Jeffery [65].

there is *in vitro* evidence from isolates and cultures of human airway smooth muscle that leukotrienes enhance myocyte proliferation and migration, processes that can be attenuated by LTRAs [49-51].

The clinical benefits of early treatment with anti-inflammatory therapy for asthma were shown in studies in the early 1990s [52,53]. In 1994, the Finnish asthma program was established to reduce morbidity of asthma in Finland with a focus on treating inflammation, as implemented by a network of asthma-responsible doctors, nurses, and pharmacists. While this program has not halted the increase of asthma in Finland, disability pensions and the number of hospital bed-days for asthma and deaths from asthma have considerably decreased over 10 years [54]. This outcome can be attributed mainly to more effective and early use of anti-inflammatory medication.

Several recent studies have shown that there is still room for improvement in anti-inflammatory treatment of patients with asthma. There are several arguments that favor the combined use of ICS and an LTRA in asthma. First, cysteinyl leukotriene levels in induced sputum remain increased in patients with asthma receiving ICS, suggesting that corticosteroids do not suppress leukotriene production [55]. Also, the addition of the LTRA montelukast improves clinical endpoints, with a 56% increase in asthma-free days, for patients with persistent disease who were receiving ICS [56]. Finally, in the IMPACT study, montelukast added to fluticasone gave the same level of protection against asthma exacerbation as did the addition of a long-acting β_2-agonist [57]. Among the Finnish patients in this study, the mean sputum eosinophil count fell significantly at week 24 in those receiving montelukast but not in those patients receiving salmeterol [57].
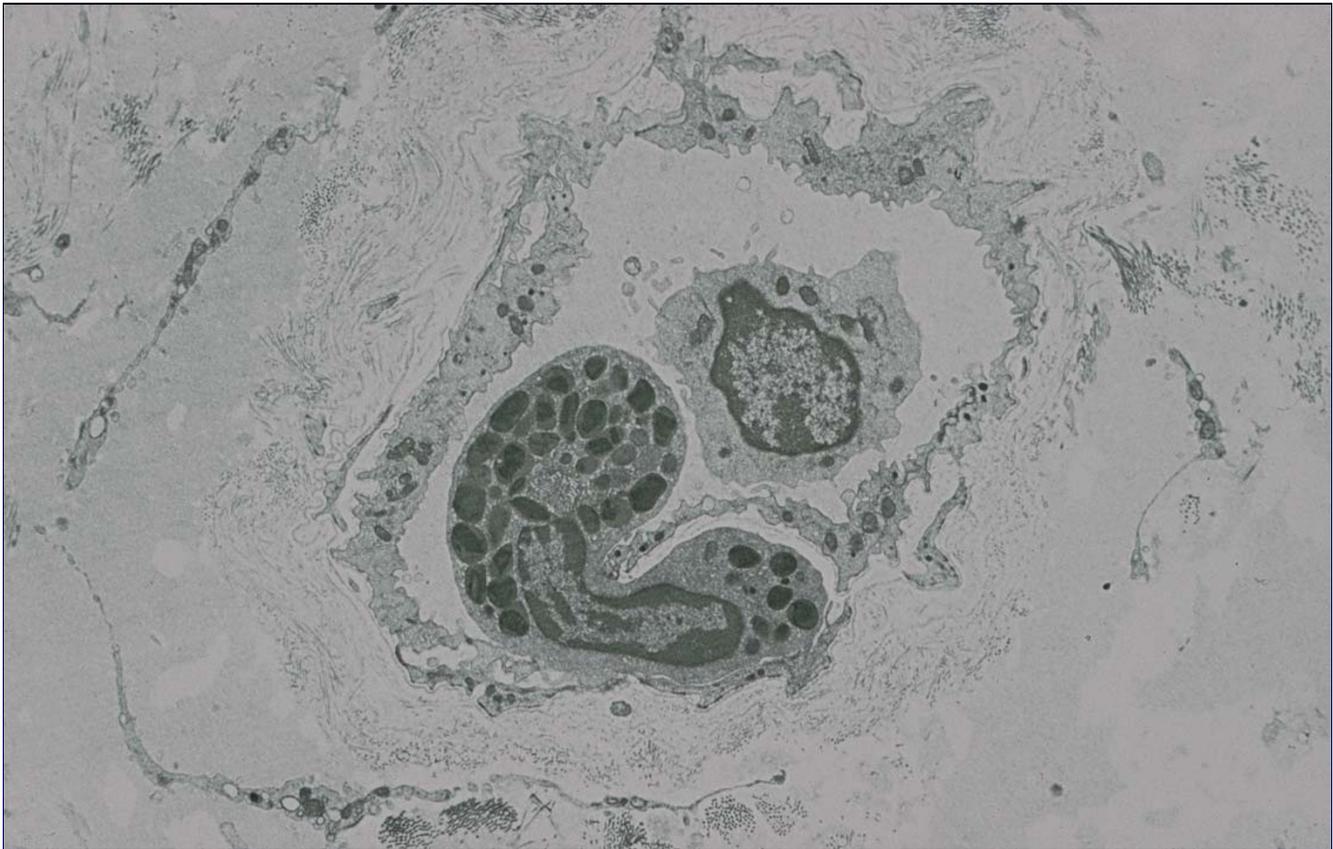
Figure 5
Eosinophil emerging from a bronchial vessel to enter the bronchial mucosa. Eosinophil emerging from a bronchial vessel to enter bronchial mucosa, as seen by transmission electron microscopy. Reprinted with permission from Jeffery [65].
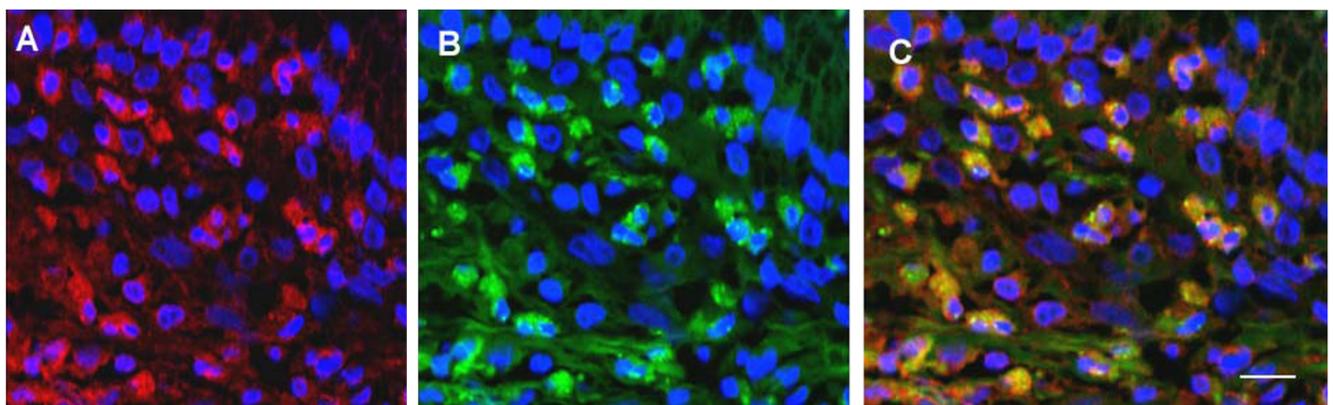

Figure 6
Colocalization of the cysteinyl leukotriene type 1 receptor with eosinophils in asthma exacerbation. Double immunofluorescence staining for identification of colocalization of the cysteinyl leukotriene type1 (cysLT$_1$) receptor with eosinophils in a bronchial biopsy from a patient with asthma with severe exacerbation. (a) cysLT$_1$-receptor protein immunopositivity is illustrated with Texas red fluorescence. (b) Eosinophils stained with anti-human EG$_2$ coupled to fluorescein isothiocyanate conjugate. (c) EG$_2^+$ eosinophils (internal scale bar = 10 μm). Nuclei are counterstained blue with 4',6-diamidino-2-phenylindole. EG$_2$ is a monoclonal antibody to the cleaved (activated) form of eosinophil cationic protein. Reprinted with permission from Zhu and colleagues [35].
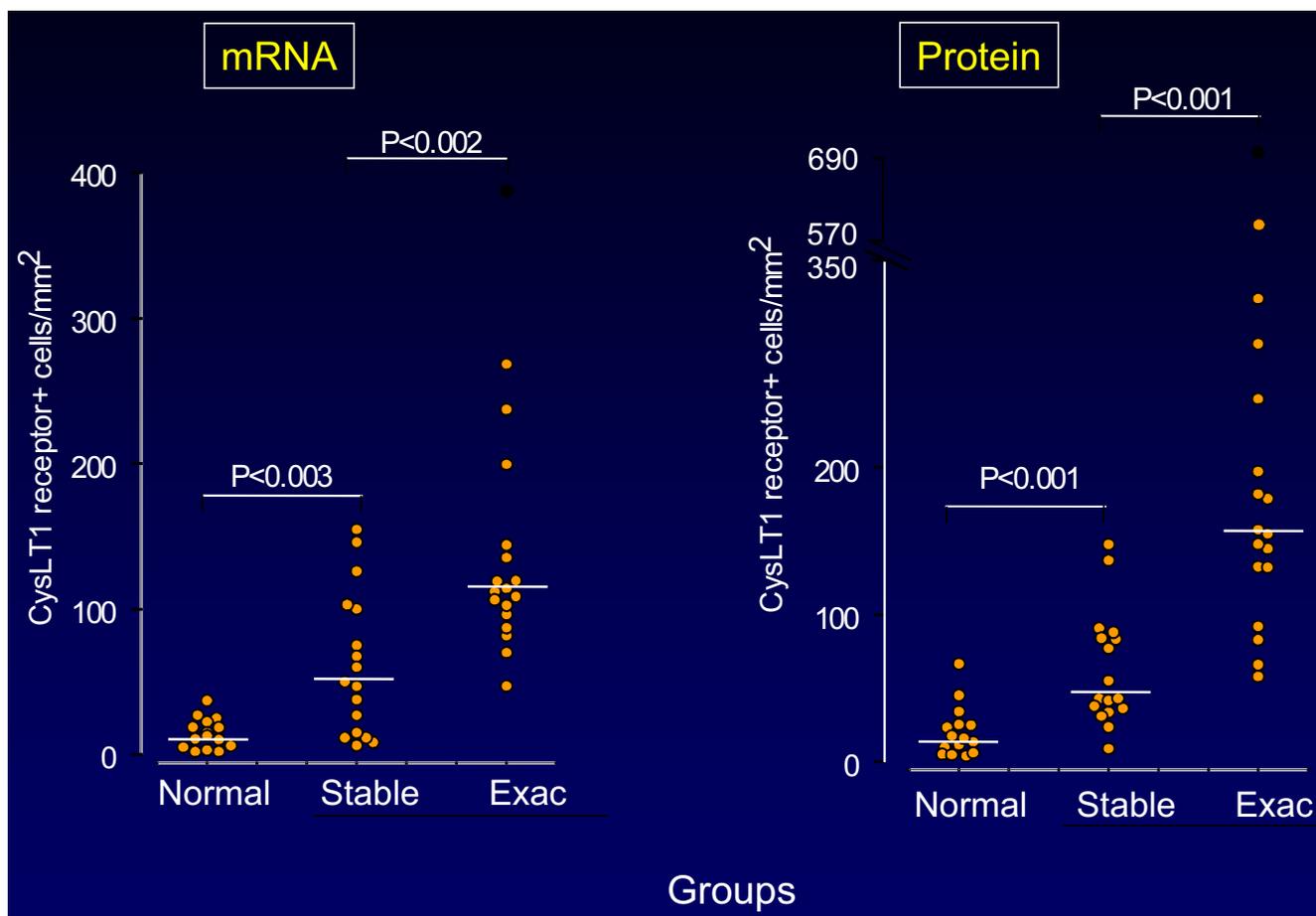
Figure 7
Cysteinyl leukotriene type 1 receptor mRNA and protein-positive cells in bronchial biopsies. Graphs of counts for cysteinyl leukotriene type 1 (cysLT$_1$) receptor mRNA and protein-positive cells in bronchial biopsies of nonsmoker control (normal), stable asthma, and exacerbated asthma (exac) groups. Data expressed as the number of positive cells per mm^2 of subepithelium. Dots show individual counts and horizontal bars show median values (Mann-Whitney U test). Reprinted with permission from Zhu and colleagues [35].

For patients with comorbid AR and asthma, effective management of their rhinitis may also improve the coexisting asthma [2]. As discussed in the preceding paper of the present supplement [3], observational studies have shown the benefits of treating rhinitis in terms of reduced risk of hospitalizations or emergency department visits for asthma [58]. Montelukast improves lung function in patients who have rhinitis [59,60], and daily rhinitis symptoms improve when montelukast is given to patients with hay fever and asthma – as do patients' and physicians' global evaluations of asthma symptoms [61].

Finally, the World Allergy Organization, in conjunction with the World Health Organization, has recently published Guidelines for the Prevention of Allergy and Allergic Asthma that include primary, secondary, and tertiary prevention strategies [62,63]. The guidelines recommend treating upper airway disease, such as AR, to prevent the development of asthma. Evidence to show any preventive effect of this strategy, however, is mostly lacking. There are indications that pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis [64], but again effects on so-called allergic march are not known. Tertiary prevention strategies in the World Allergy Organization/World Health Organization guidelines – to prevent exacerbations and disease progression – emphasize the need to treat the underlying inflammatory process.

Conclusion
As inflammation and its relationship to remodeling in AR and asthma are becoming better understood, the importance of anti-inflammatory treatment is increasingly accepted. For patients with symptoms of asthma, it is
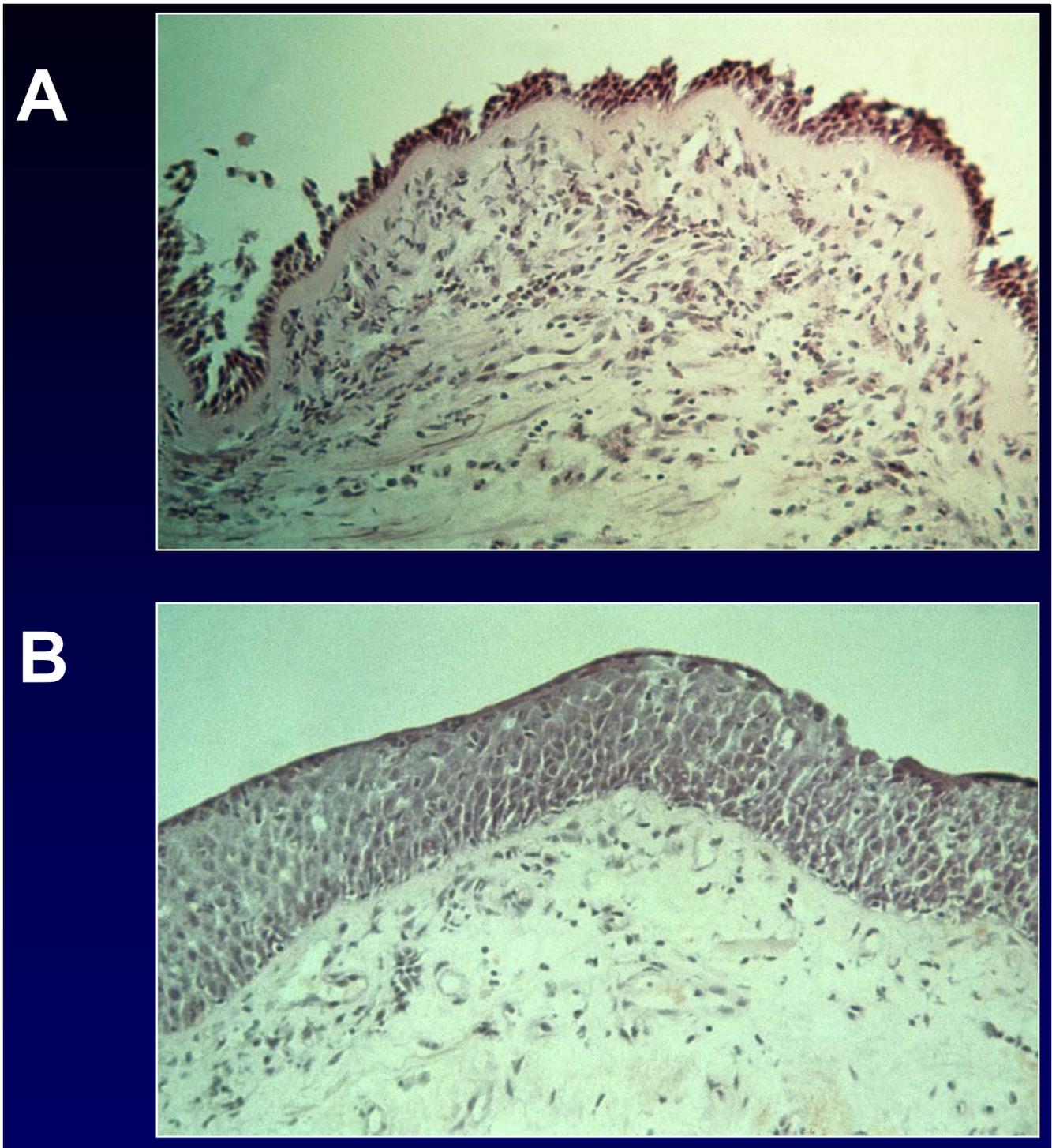
Figure 8
Bronchial biopsies in asthma and chronic obstructive pulmonary disease. (a) Bronchial biopsy in a nonsmoker with mild asthma. Note thickening of the epithelial reticular basement membrane in comparison with (b). (b) Bronchial biopsy in a smoker with chronic obstructive pulmonary disease (alkaline phosphatase antialkaline phosphatase, original ×240). Reprinted with permission from Jeffery [66].

important to detect inflammation (and remodeling) early and to control inflammation in all its stages and severities. Initial therapies comprise anti-inflammatory medication, usually ICS or LTRA in mild asthma or ICS in more severe asthma. This is usually supplemented with rapidly acting β_2-agonist as needed. In moderate to severe asthma, regular long-acting β_2-agonists are used if anti-inflammatory therapy fails to control the disease, as indicated by increasing daily requirement for short-acting β_2-agonist. The combination of ICS and oral LTRA anti-inflammatory therapy is one alternative approach to treatment and provides the option of treating airway inflammation as a whole. Given the similarity that exists between the patterns of inflammation seen in AR and asthma, patients may best benefit from an approach that considers treating the entire airway rather than only a part, as well as the skin as necessary.

Abbreviations
AR = allergic rhinitis; $cysLT_1$ = cysteinyl leukotriene type 1; ICS = inhalation of corticosteroids; IL = interleukin; LTRA = leukotriene receptor antagonist; RANTES = regulated upon activation, normal T-lymphocyte expressed.

Competing interests
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Acknowledgements

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