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Review Series VIII: Allergy: A Global Problem

Treating the allergic patient: think globally, treat globally

G. Passalacqua, G.W. Canonica
Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa, Italy

Giorgio Walter Canonica, MD
Allergy & Respiratory Diseases
Department of Internal Medicine
Padiglione Maragliano
L.go R. Benzi 10–16132
Genoa
Italy

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1. Introduction

The pathogenic view of respiratory allergy has deeply changed during the last 10 years: epidemiological, immunological and clinical data have stringently shown that rhinitis and asthma (upper and lower respiratory airways) are strictly linked. From this viewpoint, several aspects seem to be of primary relevance: (a) the frequent coexistence of rhinitis and asthma; (b) the presence of nonspecific bronchial hyperresponsiveness in rhinitics; (c) the role of upper respiratory infections in asthma exacerbations; (d) the presence of rhinitis as a risk factor for developing asthma; (e) the existence of a common pathogenic mechanism; (f) the role of sinusitis in asthmatic patients. These aspects, taken together, lead to the operative definition of *Allergic Rhinobronchitis* (1) or *United Airways Disease* (2), to state that upper and lower respiratory airways should be regarded as a unique entity, partially sharing common pathogenic mechanisms. Moreover, many aspects of the complex inflammatory network have been detailed: the role, the effects and the mode of action of cytokines, chemokines and adhesion molecules have been clarified.

Based on those facts, new therapeutic strategies and approaches have been proposed. First, an ''integrated'' therapy of the united airways: treating the diseases of the upper airways can favourably influence the lower airways or, as well, drugs affecting the common pathogenic mechanisms can act on both the compartments. Second, the ''immunological'' treatments, i.e. drugs or monoclonal antibodies specifically targeting single components of the IgE-mediated allergic inflammation, which can control the allergic process at its earliest stages.

2. The united airways: experimental evidence

Most of the data about the link existing between the upper and the lower airways come from epidemiological studies, as previously reviewed by Annesi-Maesano (3). In cross-sectional studies it is easy to assess the coexistence of rhinitis and asthma (4–9): the occurrence of rhinitis in asthmatic patients ranges from 70% (7) to about 90%, when strict criteria are used (8). Longitudinal studies provided additional data: it is apparent that IgE-mediated allergic rhinitis usually precedes the onset of asthma, when patients are followed up for a time period long enough. In fact, in a 23-year long survey (10), about two-thirds> of subjects with allergic rhinitis appeared more likely to develop asthma with respect to controls. The same was seen in other large longitudinal studies (11–13). On the other hand, it is noteworthy that about 50% of patients with allergic asthma alone can develop clinical rhinitis (13). Allergic rhinitis has been often defined as a ''risk factor'' for asthma, but it represents more a stage of United Airways Disease, possibly evolving into asthma. In fact, a relevant fraction of patients suffering from rhinitis alone have an objectivable nonspecific bronchial hyperresponsiveness (14,15), which is a characteristic feature of asthma.

In subjects with IgE-mediated allergy, allergen-specific nasal challenge can elicit both an immediate bronchial response and an increase in bronchial responsiveness (16,17), as well as a bronchial inflammation, characterized by eosinophil influx (18). On the contrary, segmental bronchial challenge can induce nasal symptoms as well as nasal inflammation in patients with allergic rhinitis (19). Therefore, the inflammatory process is central to the allergic response

(20), as clearly demonstrated by several experimental models including nasal and bronchial challenge (21). Using the induced sputum technique, Polosa and colleagues (22) showed that subjects with allergic rhinitis alone have an increased number of eosinophils during the pollen season. Crimi and colleagues (23) recently compared the bronchial inflammatory response following allergen-specific challenge in allergic patients suffering from asthma alone or rhinitis alone. Using bronchial biopsy and lavage, the authors found no morphological difference between the two groups: the bronchial inflammatory response (cell influx and basement membrane thickening) is the same, regardless of which airway is affected by disease, confirming that subjects with IgE-mediated allergy have a common inflammatory response. A possible explanation for the functional link between nose and bronchi is the systemic connection via soluble mediators which act on precursors (24). It has been demonstrated that bone marrow can specifically respond to nasal challenge by increasing the maturation and production of eosinophilic precursors (25). Finally, the so-called neurogenic inflammation (involving neuropeptides, substance P, neurokinin A) represents a novel pathogenic aspect of the upper–lower airways link (26).

Anyway, rhinitis per se (in the absence of any marker of atopy) seems to be an independent risk factor for asthma (27), and this fact suggests that mechanisms other than allergic inflammation may be involved. The respiratory tract is, from a morphofunctional point of view, a single entity: it is entirely covered, until the smaller bronchi, by ciliate epithelium and mucinous glands and served by extensive vasculature and innervation. The type of innervation is similar in the upper and lower airways (28), therefore the nasobronchial muscarinic reflex has been hypothesized as the possible pathogenic mechanism.

The upper respiratory tract functions as a physical filter, resonator, heat exchanger and humidifier for the inhaled air. It is reasonable to expect that any failure of these functions may result in alteration of the lower respiratory airways; in fact, oral hyperventilation with cold air in asthmatics decreases the forced expiratory volume and increases the nasal resistance (29,30).

3. Immunology of the united airways

The allergic inflammation is the final and apparent result of a complex immunological status which is determined at genomic level (31) and which is properly defined as atopy (32). This status is variably influenced by nutritional, hygienic and environmental factors. The influence of these factors has been well established, although the relative weight of each of them is still matter of debate (33–37).

The Th1/Th2 imbalance in allergy is now ascertained (38) and, in this sense, the central role of the $CD4^+$ lymphocyte as a pivotal cell in the very early steps of the allergic network is well recognized (39). The Th2 lymphocytes secrete some characteristic cytokines which selectively act on the effector arms of the reaction as shown in a simplified way in Fig. 1. Two of these cytokines, IL-4 and IL-5 seem to be committed to the allergic response. IL-4 is involved in the shift to the Th2 phenotype (40) and it also stimulates the isotypic switch of B cells for IgE secretion (41). IL-5, at variance with the other pleiotropic cytokines, is selective for eosinophils: it enhances the maturation, proliferation, activation and survival of these cells (42–44). IL-4 and IL-13, together or independently, stimulate the proliferation and activation of fibroblasts (45).

IgE and mast cells are the initiators of the allergic reaction: when it is triggered by the allergen, the so-called early phase occurs within minutes. This step involves release of histamine, vasodilatation, increased permeability and bronchoconstriction. The early phase is followed by an inflammation where mediators, cytokines and adhesion molecules are involved. The adhesion machinery is crucial for the recruitment of inflammatory cells at the target organ. During the early phase, specific adhesion molecules are newly expressed or up-regulated on the surface of endothelium (selectins) and epithelium (integrins). The adhesion molecules favour the rolling over, extravasation and migration towards epithelium of inflammatory cells (46), and the ICAM-1 (CD54) molecule seems to be a good hallmark of ongoing IgE-mediated allergic inflammation. The migration of inflammatory cells to the mucosa begins within 30–60 min after a single specific challenge, increases again during the following 24 h and then slowly subsides (21). These events studied in the nose and conjunctiva seem to occur also in the bronchi of asthmatics (47,48). Interestingly, a weak inflammatory infiltration is present in the mucosa even in absence of symptoms, when a sub-threshold exposure to the allergen persists (Fig. 2). This *minimal persistent inflammation* (MPI) has been demonstrated in both mite- (49) and pollen-induced (50) allergy. The MPI involves also a weak and persistent expression of the ICAM-1 molecule, which is the major receptor for human rhinoviruses (51). MPI and ICAM-1 expression in symptom-free subjects is important since in children, asthma exacerbations are frequently related to upper respiratory viral infections (52,53) due to rhinoviruses.

4. The integrated pharmacotherapy of the united airways

If we consider the functional link existing between the upper and lower respiratory airways, as summarized above, it is reasonable to expect that an effective treatment of rhinitis (and sinusitis) can have some effect on bronchi (54). Indeed, it was observed that intranasal

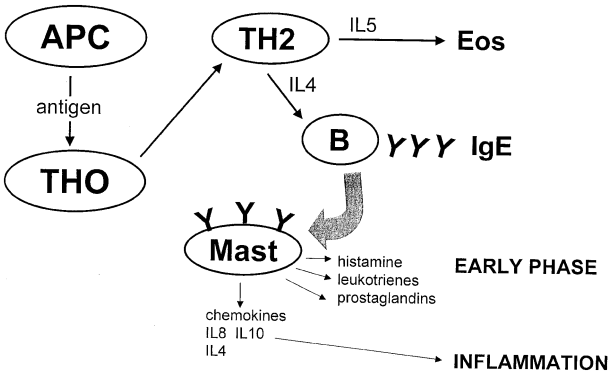


Figure 1. A simplified overview of the cellular and humoral network underlying the allergic reaction. APC = antigen presenting cell, Mast = mast cell, Eos = eosinophil.

beclomethasone 326 μg/day (55) and fluticasone propionate 200 μg/day (56) were able to significantly reduce bronchial hyperresponsiveness to methacholine in asthmatic patients. In another study (57) it was observed that intranasal beclomethasone (200 μg b.i.d) improved asthma symptoms and significantly reduced the methacholine hyperresponsiveness. In a double-blind double-dummy placebo controlled study (58), it was seen that intranasal administration of beclomethasone (100 μg q.i.d), but not the inhaled one, could reduce the carbachol-induced PD35% bronchial hyperresponsiveness. It is also interesting to notice that a detailed education of patients on how to correctly treat their rhinitis with continuous long-term nasal corticosteroids leads to a significant improvement of concomitant asthma symptoms (59).

The bronchodilatory effect of antihistamines per se is weak and of negligible clinical relevance, but their effect on the lower airway can be interpreted as the modulation of nasal allergic inflammation, due to the anti-inflammatory properties of some of the newest compounds (60). In a placebo-controlled study of 186 patients, cetirizine 10 mg was able to reduce significantly asthma symptoms during the pollen season, although no significant difference could be seen in pulmonary function parameters (61). Similar results were obtained in pollinosic patients where bronchial hyperresponsiveness was reduced (62). The administration of loratadine 5 mg + pseudoephedrine 120 mg b.i.d. could significant improve asthma symptoms, peak expiratory flow and reduce albuterol intake in patients with intermittent allergic rhinitis and mild asthma (63). Similarly, a synergistic effect has been also demonstrated for antihistamines in association with antileukotrienes. This association could reduce both rhinitis and asthma symptoms (64,65).

The link existing between upper respiratory disease and asthma was further demonstrated in children, where upper respiratory (viral) infections can exacerbate asthma or provoke asthma attacks. A one-year continuous treatment with terfenadine (vs. placebo)

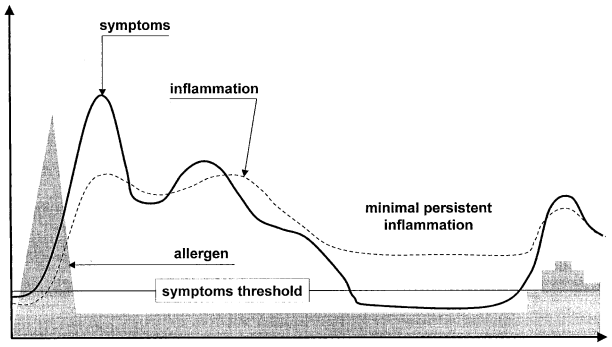


Figure 2. The concept of minimal persistent inflammation. An inflammation is present also when the allergenic load is too low to elicit symptoms.

could reduce by 50% the occurrence and severity of upper respiratory infections as well as nasal symptoms and local inflammation (66). Similarly, a six-month continuous cetirizine treatment resulted in a global significant reduction of the need for medications (67). These observations are derived from small experimental groups; nevertheless the large Early Treatment of Allergic Child (ETAC) study, showed that a continuous antihistamine treatment can affect the natural course of the disease in atopic children (68). Finally, when sinusitis coexists with asthma, a proper treatment (either pharmacological or surgical) of diseased paranasal sinuses can significantly improve asthma symptoms, as demonstrated in several studies (69–71).

A tentative scheme of the integrated therapy for respiratory allergy is depicted in Fig. 3.

5. The role of allergen immunotherapy

From a clinical point of view, allergen specific immunotherapy (SIT) has been considered an effective

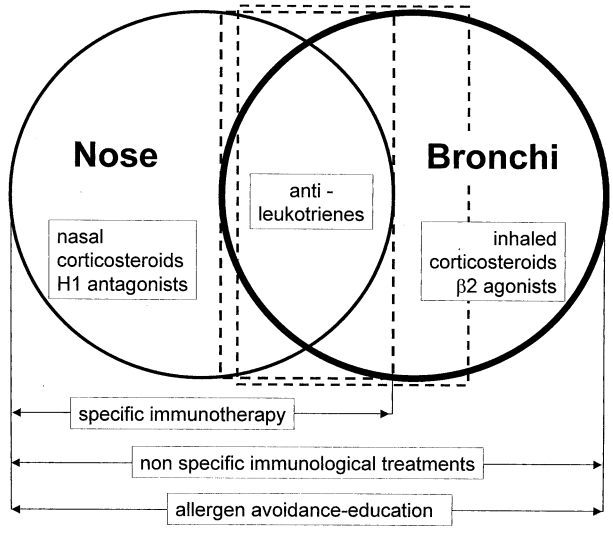


Figure 3. An integrated therapeutic approach to respiratory allergy.

treatment for respiratory IgE-mediated allergy since the beginning of the century. Nevertheless, its real immunological role began to be recognized only during the last 15 years. Stringent evidence exists that SIT acts in the earliest steps of the immunological response to the offending allergen: in particular, it seems to affect the Th1/Th2 ratio. This fact is supported mostly by indirect data coming from clinical trials (72–74). The effect of SIT on T lymphocytes and subsequently on their action also results in fact, in a long-lasting effect of the treatment (75–77), which cannot be achieved with any other of the available drugs. The immunological effects of SIT are further confirmed by the experimental observation that SIT can prevent the development of new skin prick sensitivities (78,79). Therefore SIT has to be considered as a biological response modifier, to be used in association with pharmacotherapy, in selected patients suffering form IgE-mediated allergic diseases and preferably at the earliest stages of the disease (80).

It is interesting to notice that effects similar to subcutaneous SIT can be, in principle, achieved through the mucosal (oral or inhaled) administration of allergens (81). Although local routes for immunotherapy have been accepted for routine clinical use (81,82), few data on their mechanisms in humans are presently available (83–86). The recent demonstration that sublingual immunotherapy has an optimal safety profile, especially in children (87,88), would suggest that it might be useful as an early treatment in order to modify the natural history of the disease at the earliest stage.

6. The immunological treatment

As summarized in section 3 and Fig. 1, some key-points of allergic inflammation are presently well known. Therefore, in principle, acting on each or more of them would allow blocking of relevant biological pathways of the allergic reaction. This possibility became a reality with the recent availability of monoclonal antibodies (mAbs), which can be directed to specific mediators.

One of the most realistic hypotheses is to block the triggers of the allergic reaction, the IgE antibodies; therefore a mAb against human IgE was engineered and developed for clinical use (89). The recombinant mAb E-25 (omalizumab) was recently tested in a large phase III clinical study, performed both in adults and children, and showed a satisfactory clinical effectiveness even though not complete (90). The treatment with omalizumab is, as expected, effective also on IgE-mediated allergic rhinitis (91,92). Therefore, such treatment is a prime candidate for immunological therapy of comorbid allergic asthma and rhinitis, since it blocks the reaction independently on the target organ and on the causal allergen.

Going back to the earliest phases of the allergic reaction, a beneficial effect could be hypothesized by blocking the function of $CD4^+$ lymphocytes. A phase III study with a monoclonal anti-CD4 antibody (keliximab) was performed in selected asthmatic patients, showing that the treatment could significantly reduce the severity of asthma and the need for inhaled corticosteroids (93), although the clinical benefit was not highly significant. Similarly, the effect of the "Th2-inhibitor" suplatast tosilate was investigated in some clinical trials, and showed an appreciable benefit (94,95), although far from that obtained with inhaled steroids or bronchodilators.

IL-4 is involved, as previously described, in Th2 differentiation and IgE production (96), therefore specific blockage of it should be effective on symptoms (97). Indeed, Zhang et al. demonstrated that anti IL-4 antibodies could only partially decrease the IgE production *in vitro ex vivo* (98). This latter fact is in agreement with the previous observation that IgE production is not only dependent on IL-4 (99). On the other hand, and surprisingly, the bronchial inhalational administration of the soluble IL-4 receptor (sIL-4R, Nuvance®) was significantly effective *in vivo*. In 25 asthmatic subjects, the treatment with sIL-4R could prevent the fall of FEV1 following the discontinuation of inhaled steroids (100).

Eosinophils are the most important effectors of tissue damage in asthma, due to their potent enzymatic machinery. Since IL-5 has very specific effects on eosinophils (maturation, proliferation, migration, activation and survival), it is logical to expect that its blockage globally reduces eosinophil functions (101–103). Therefore mAbs to IL-5 have been developed (104) and subsequently tested in a monkey model of asthma (105), where the antibody was reported to inhibit specific bronchial responsiveness for about 4 weeks. Very recently an anti-IL-5 Mab was used in asthmatics (106): a single dose of Mab could lower blood and sputum eosinophils, but did not affect the late asthmatic response to allergen and did not modify the bronchial response to histamine. A similar result was obtained by administering recombinant IL-12: there was a significant decrease in eosinophils without any measurable clinical effect on asthma (107). The results of these studies prompted the authors of this paper to question the real role of eosinophils in allergic inflammation. It is true that allergic inflammation which sustains respiratory allergy is the result of a redundant network of cells and cytokines and that blocking a single mediator is probably not sufficient to switch off the whole reaction.

7. Conclusions

Thanks to new pathophysiological understandings of the allergic process, therapeutic strategies have changed

greatly during the last 15 years. First, it has became clear that symptoms, although important to control, are not the only therapeutic targets; the underlying inflammation must also be controlled by therapy. Second, the strict link existing between the upper and lower respiratory airways has introduced the possibility of influencing the disease in one of the compartments by treating the other (108,109). Third, increasingly detailed knowledge of the immunology of allergic reactions has led to new targets for immunological therapeutic approaches, in particular the use of engineered monoclonal antibodies.

When taken together, all these considerations lead to an ''integrated'' model of therapy for respiratory allergy. Allergen specific immunotherapy is presently considered as a biological response modifier, which can modulate the response to allergens in the early stages, and therefore it maintains a unique role in therapy. Nevertheless, other immunological approaches were investigated (e.g., the selective antagonism of cytokines or IgE) and some of these approaches were proven to be effective, with potential for clinical use. Finally, the relationships among allergic inflammation, upper respiratory infections and symptoms allowed the possibility of controlling all these aspects together, especially in pediatric patients.

In summary, although we are still far from understanding the exact role of each individual treatment, therapeutic strategy is evolving towards an integrated model, which considers not only ''the symptoms'' but also the ''allergic disease'' in its totality and also the possible synergistic effect of different treatments.

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