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Allergic Rhinitis and its Impact on Asthma (ARIA) – What Does it Mean for the Future of SIT?

Claus Bachert

The working group ARIA, in collaboration with the WHO in Geneva, recently published a state-of-the-art review and recommendations derived from it on the link between rhinitis and asthma (1). Rhinitis is the most frequent manifestation of allergic disease in human and often is linked to other atopic diseases such as food allergy, atopic dermatitis or asthma, and may furthermore have impact on the sinuses. ARIA focuses on one of the most important out of the mentioned ones, the link between upper and lower airways in allergic disease.

The ARIA paper summarizes current knowledge on rhinitis and its link to asthma and features several main issues, presenting a new classification of rhinitis with reference to a similar classification as currently is used for asthma. Because of the long-term exposure to seasonal allergens in some countries and the seasonal variations observed also in mite allergen exposure (2), it was decided that the terms “seasonal” and “perennial” would not be very helpful for any decision in terms of treatment. Furthermore, seasonal and perennial allergens may considerably differ from one place to the other, so that the offending allergen has to be mentioned separately. It was therefore decided to use the terms “intermittent” and “persistent” allergic rhinitis. The persistent allergic rhinitis means more than four days of symptoms per week and more than four weeks of symptoms, and may be either seen during the season or due to an allergen exposure throughout the year. In contrast, intermittent means less than four days per week or less than four weeks of symptoms, which again may be based on seasonal or perennial allergens. The term persistent also reflects the concept of minimal persistent inflammation, which has been described for the nasal mucosa as an ongoing inflammation even without acute symptoms (3). It is estimated that about two thirds of the patients suffer from intermittent and one third from persistent rhinitis, and that this terminology is independent from seasonal or perennial allergic rhinitis. The severity of disease was furthermore classified as mild or moderate to severe, depending on the symptoms, but also on the impact of those symptoms on quality of life issues such as sleep, impairment of daily activities and work performance (Figure 1).

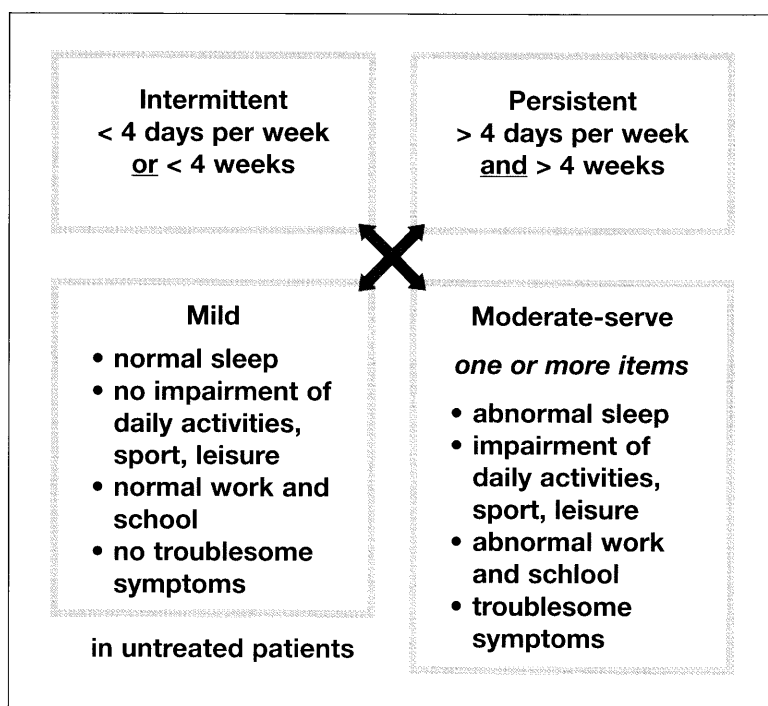


Fig. 1.
Classification of
allergic rhinitis
according to the
WHO ARIA work
group.

The large body of epidemiological studies have clearly shown that allergic rhinitis and asthma are frequent diseases, and that both diseases obviously still increase in prevalence (4,5). However, without any doubt, there is a direct link between rhinitis and asthma. Several studies in a large number of patients have clearly shown that rhinitis sufferers have an increased risk of three- to sevenfold to also develop asthma within seven years compared to normal controls. Most of this development actually lies in the early years of childhood, as was recently shown in the MAS- and PAT-studies (6,7). In the first study, five-year-old children sensitized to pollen with allergic rhinitis symptoms developed asthma within two years in 34 percent, and in the second study, children 6 to 14 years of age with pollen allergic rhinitis developed asthma within three seasons in 44 percent. Furthermore, 20 percent of children without history of asthma developed asthma symptoms within the first season, so that it can be estimated that at least 35 percent of children of this age develop asthmatic symptoms within just two seasons. This natural development of atopic disease clearly asks for intervention in terms of the prevention of disease expansion.

The WHO initiative ARIA (1) therefore formulated a number of recommendations, which are listed below:

1. Allergic rhinitis is a major chronic respiratory disease due to
 - its prevalence,
 - its impact on the quality of life,
 - its impact on work/school performance and productivity,
 - its economic burden,
 - and its links with asthma.

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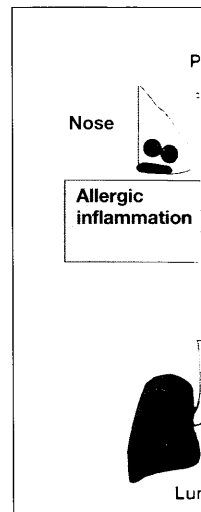


Fig. 1.
Classification of
allergic rhinitis
according to the
WHO ARIA work
group.

2. In addition, allergic rhinitis is associated with sinusitis and other co-morbidities such as conjunctivitis.
3. It is recommended to consider allergic rhinitis as a risk factor for asthma along with other known risk factors.
4. A new subdivision of allergic rhinitis has been proposed:
 - intermittent,
 - persistent.
5. The severity of allergic rhinitis has been classified as "mild" and "moderate/severe" depending on the severity of symptoms and quality of life outcomes.
6. Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed.
7. The treatment of allergic rhinitis combines:
 - allergen avoidance (when possible),
 - pharmacotherapy,
 - immunotherapy.
8. It is recommended that patients with persistent allergic rhinitis be evaluated for asthma by history, chest examination and, if possible and when necessary, assessment of airflow obstruction before and after bronchodilator.
9. It is recommended that history and examination of the upper respiratory tract for allergic rhinitis is performed in patients with asthma.
10. It is recommended to propose a strategy combining the treatment of both the upper and lower airway disease in terms of efficacy and safety.

Although we do not fully understand the pathomechanisms behind this relationship, several possibilities have been proposed, such as the nasal-bronchial reflex, aspiration of nasal contents, the effect of mouth breathing and the release of mediators due to allergen exposure in the nose. Of these, the hypothesis of a signal released at the site of exposure to the bone marrow with consecutive mobilization of inflammatory progenitor cells is currently favored (Figure 2). Several studies have contributed to this hypothesis, which is primarily based on observations in dogs, but recently gets more

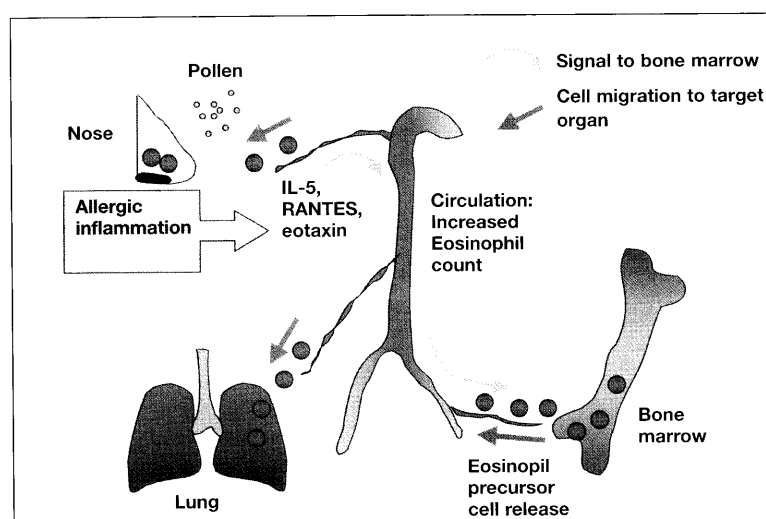


Fig. 2.
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Specific immunotherapy is the standard of care for *hymenoptera* sting-induced systemic allergic reactions and has clearly been shown also to be effective for the treatment of seasonal and perennial allergic rhinoconjunctivitis and asthma (12). It has been shown that specific immunotherapy can interfere with basic pathophysiologic mechanisms of allergic disease and may be able to prevent the development of asthma in patients with allergic rhinitis. Thus, SIT is recommended as a supplement to allergen avoidance and drug therapy to make the patient as symptom-free as possible, but also should be initiated early in the disease process to prevent further development of severe disease and to reduce the risk of side effects. According to the recommendations, subcutaneous SIT is the standard procedure; local SIT (nasal or sublingual-swallow immunotherapy) may be considered in selected patients with systemic side effects and with refusal to injection treatment.

The indications for SIT are given below:

1. Carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen, house dust mite or cat allergy. Immunotherapy is also indicated when asthma during the pollen season complicates rhino-conjunctivitis.
2. When H1-antihistamines and intranasal pharmacotherapy insufficiently control symptoms or produce undesirable side effects.
3. When patients do not want to receive long-term pharmacotherapy for their treatment.

The efficacy of subcutaneous SIT has been clearly shown in a meta-analysis of 43 double-blind placebo-controlled trials in allergic rhinitis as well as another meta-analysis of 16 double-blind placebo-controlled studies in asthma patients (13). The mean clinical improvement was 45 percent reduction in symptoms and medications scores compared with placebo in rhinitis and 40 percent in asthma patients, which exceeds the effects of drug therapy. A recent meta-analysis also confirmed that asthma responds favorably to SIT (14). However, recently it could also be demonstrated that SIT is effective in patients with house dust mite, allergic rhinitis, and asthma (15). Immunotherapy in these patients not only reduced rhinitis and asthma symptoms as well as rescue medication, but also impacted bronchial hyperreactivity over the three-year follow-up period.

Of special interest, SIT has been shown to prevent new sensitizations in controlled studies (16) and also in large open observational studies (17). In the first study, SIT was applied in children mono-sensitized to house dust mite over a three-year period. In the SIT-group, about half of the patients developed new sensitizations, whereas in the control group, all the subjects developed new sensitizations to perennial and seasonal allergens during the follow-up period. In the second study, looking at a group of more than 7.000 patients with immunotherapy compared to more than 1.000 patients with drug therapy, about 30 percent of the SIT-group were polysensitized after seven years, whereas nearly 80 percent of the drug group showed polysensitizations after this period. In this latter group, there was also a significant increase in total IgE mean values versus the SIT-treated group. Thus, SIT is able to prevent new sensitizations in allergic rhinitis subjects.

However, the question whether SIT actually could prevent the development of asthma in children with rhinitis, was answered only recently. In a study in children aged

6 to 14 years with birch or timothy pollen allergic rhinitis, who followed immunotherapy for three years, there was a significant reduction of conjunctivitis and rhinitis symptoms in the SIT-group, a significant reduction in conjunctival sensitivity and also an improvement of bronchial hyper-reactivity (7). Furthermore, significantly less children in the SIT-group developed asthma within three seasons compared to the control group, with an odds' ratio of 2.5.

In summary, the ARIA WHO workgroup emphasized the link between rhinitis and asthma and declared rhinitis a major chronic respiratory disease and a risk factor for the development of lower airway disease. It is therefore critical to treat both airway manifestations in a combined strategy, and immunotherapy has been proven to fit with this demand when patients are selected carefully. It has to be our intention to prevent the development of asthma in patients, especially children with rhinitis, and again, SIT has been shown to considerably reduce the risk of disease expansion in the group of patients that otherwise would develop asthma in about 35 to 45 percent of patients. In conclusion, SIT clearly is a treatment of choice for common airway disease as reductive and preventive treatment approach. Further studies are needed to confirm this benefit and to allow a better classification of patients suitable for preventive SIT in terms of sensitizations, age, and laboratory parameters.

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Discussion

Akdis: Do you think that SIT is a good sensitization?

Bachert: Yes, that is a good question. However, for a child, we should understand what the child should be cooperative. It has been shown, so this is a good question.

Jacobsen: The child is not much. But what is the child's biological system? The immune system is not active. So it is not a good question in the lung.

Bachert: If you are a child, it. And there are many children with eczema disease system. It can be associated with rhinitis in the nose. So there is a problem for patients suffering from small particles that are in the air. Conditions allow allergic rhinitis. It is certainly not only a disease with rhinitis.

Malling: I would like to think that from a child's point of view. There is also scientific evidence because symptoms are very carefully to see if the child is really apy before the diagnosis is definitely not recommended.

Bachert: There is a disease. And there is a child actually having symptoms. If sensitization, we certainly

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Discussion

Akdis: Do you think that one should start immunotherapy as soon as one sees an IgE sensitization?

Bachert: Yes, that is what I said. This is the best time window in order to avoid asthma. However, for a clinician of course there are some limits. One is that children should understand what you are doing when you perform injection immunotherapy and they should be cooperative. The long-term efficacy of sublingual therapy has not been shown, so this is currently not really a choice for the prevention of asthma.

Jacobsen: The link between the upper and lower airway disease is discussed very much. But what do you think about the idea that the disease is systemic? It is an immunological systemic disease. So basically the antigen is presented systemically to the immune system and you get symptoms from any shock organ that is already hyper-reactive. So it is not directly an influence from the nasal inflammation that causes inflammation in the lung. Is that a possibility?

Bachert: If you ask an immunologist, it is a systemic disease, there is no doubt about it. And there are quite some aspects, for example, that atopic dermatitis, or atopic eczema disease syndrome, how it is called according to the new nomenclature, can also be associated with an increased risk to develop asthma. You do not have to go via the nose. So there is certainly a systemic aspect to asthma, look at data where allergic patients suffering from rhinitis responded to a challenge of the bronchi. Furthermore, small particles that result from the destruction of allergen during certain weather conditions allow allergens' access to the lower airways and in turn can cause symptoms. It is certainly not only a mechanical aspect of lower and upper airways, it is also a systemic disease with it.

Malling: I would just add a little to the discussion on when to start immunotherapy. I think that from a theoretical point of view, you should start early in the disease process. There is also scientific evidence that "the shorter the race, the better the results" because symptoms have to become chronic in some way. But I would raise my hand very carefully to say that we have no documentation that we should start immunotherapy before the disease is established, that means when sensitization occurs. I would definitely not recommend clinicians to do this without doing a control trial.

Bachert: There is clear evidence that we have much more sensitization than actually disease. And there is a difference between those patients sensitized to grass pollen and actually having symptoms of allergic rhinitis. I do not think that we should treat sensitization, we certainly should treat disease, that is correct.