

Allergen immunotherapy for house dust mite-induced rhinitis: prescriptive criteria

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Abstract. Allergic rhinitis (AR) is a very common disease. In most cases, therapy is based on symptomatic drugs, while allergen immunotherapy (AIT), which is the only one to act on the cause of the disease, is reserved for patients with a greater burden of disease. In particular, the possible evolution towards asthma substantiates the use of AIT, but requires the availability of diagnostic indices related to the risk of developing asthma. We analyzed the available literature on risk factors for onset of asthma in patients with AR, including bronchial hyperresponsiveness, uncovering by respiratory function tests of airway impairment, measurement of fractionated exhaled nitric oxide, given IgE sensitization pattern, and respiratory infections detected by nasal mucus samples or by particular microbiomes. Most of these risk predictors have been investigated too little or do not have consistent results, while various studies have confirmed that early bronchial impairment in AR patients, particularly concerning small airways, should be considered as prescriptive criteria for AIT. (www.actabiomedica.it)

Key words: Allergic rhinitis, onset of asthma, allergen immunotherapy, risk factors for asthma, prescriptive criteria.

Introduction

Respiratory allergy involves various organs, including rhinitis, rhino-conjunctivitis, and asthma. A progression to asthma frequently characterizes the natural history of allergic rhinitis (AR). Consistently, a meta-analysis of 39 studies involving an overall number of 27,4489 AR patients evidenced that AR was significantly (OR 3.82) associated with asthma occurrence (1).

Allergen-specific immunotherapy (AIT) is the only treatment that acts on allergy causative factors and modifies its natural history (2). In this regard, the PAT (preventive allergy treatment) studies demonstrated that children with pollen-induced AR AIT for three consecutive years prevented asthma development for up to 10 years after its discontinuation (3). More recently, real-life studies conducted in Germany have extended these observations to large patient

populations. Schmitt and colleagues studied a consecutive cohort of 118,754 patients suffering from AR without asthma and not treated with immunotherapy as of 2005 (4). The authors stratified the patients into two subgroups: one group started injective or sublingual immunotherapy with seasonal or perennial allergens in 2006, whereas the other group started treatment with symptomatic drugs in the same year. The outcome was the possible onset of asthma up to 2012. The risk of asthma onset was significantly lower in patients treated with AIT than those treated with drugs alone. A more relevant preventive effect was observed in patients treated with AIT for at least three years compared to those treated for less than three years (4). Zielen and colleagues compared the frequency of asthma development in patients with grass pollen-driven rhinitis, respectively treated with sublingual immunotherapy (2,851 patients) using two different products (one single grass or five grasses) or treated with only symptomatic

drugs (17,275 patients). The onset of asthma was significantly less frequent ($p=0.002$) and later ($p=0.003$) in patients treated with AIT than in those treated only with drugs (5). More recently, Wahn and coworkers compared 9,001 patients treated with injective or sublingual AIT using six different allergenic extracts of birch pollen, with 45,005 patients treated with drugs alone; the patients had a 6-year follow-up. The asthma onset was significantly ($p=0.001$) less frequent in AIT-treated patients (6). Therefore, these extensive studies confirm the concept that immunotherapy, lasting as recommended for at least three years, significantly prevents the development of asthma in AR patients. However, it is not conceivable that all AR patients with pollen allergy are treated with preventive immunotherapy as they are hundreds of millions around the world (7). The decision for AIT prescription should be based on symptom severity, insensitivity to pharmacological treatments, clinical relevance of causal allergen, and patient preference. A pediatric study demonstrated that sensitization to house dust mites (HDM) was a significant (OR 2.3) risk factor for asthma onset, with an incidence of 2.4% per year (8). Again, considering that people allergic to HDM are about 500 million worldwide (9), it does not appear possible to prescribe AIT to everyone. Therefore, it is necessary to identify the risk factors associated with the development of asthma in patients with AR.

Risk factors for asthma development.

In the 1970s and 1980s, the bronchial hyperresponsiveness (BHR), measured by methacholine testing, was proposed as a predictor of asthma development in patients with AR (10-12). The 10-year follow-up on the PAT study demonstrated that BHR at baseline was significantly ($p<0.0001$) associated with increased risk of later development of asthma (3). Further, a pediatric 12-year follow-up study showed that BHR (OR 4.94) and HDM sensitization (OR 3.23) increased the risk of developing asthma in adulthood (13). Another area of research assessed early airway impairment in AR patients as a risk factor for future asthma. In 2011, the first study evaluated forced expiratory flow at 25-75% of vital capacity (FEF_{25-75}), forced expiratory volume at

1 second (FEV_1), and response to bronchodilation testing in 605 adult patients with AR. Interestingly, 8.4% of patients had impaired FEV_1 (<80% of predicted), 24.7% impaired FEF_{25-75} , and 66.1% had reversibility to bronchodilation. The authors concluded that such dysfunctions suggest to suspect a possible progression from AR toward asthma (14). This observation was confirmed by an 8-year follow-up study on 89 patients, which evidenced that the number of AR patients with FEF_{25-75} <70% of predicted significantly increased during the observation time and 34 of them developed BHR at the end of the observation (15). A pediatric study enrolling children with AR showed that small airways dysfunction after bronchodilation testing was significantly predictive of asthma development (16). In particular, it has been underlined that reduced FEF_{25-75} (<65% of predicted) should be considered a reliable marker of early bronchial impairment in AR patients and is associated with BHR and type 2 bronchial inflammation (17). Further studies showed that HDM sensitization and rhinitis duration were significantly associated with impaired FEV_1 (<80% of predicted) in adults and children with AR (18,19). Measurement of fractionated exhaled nitric oxide (FeNO) levels was investigated as a possible risk factor for asthma in adult patients with AR (20). In this study, some clinical parameters, such as the severity of rhinitis symptoms, levels of specific IgE, and expression of adhesion molecules (ICAM-1 and VCAM-1), were not significantly correlated with the risk of asthma. On the contrary, the duration of rhinitis and increased FeNO values were associated with a high risk of developing asthma (18).

The sensitization pattern was also studied as a prognostic factor. In a group of 191 children sensitized to HDM, sensitization to Der p1 or Der p 23, at the age of 5 years or less, was found to predict school-age asthma (21). This observation is of clear interest, but to date has not been confirmed by further studies. Various researches have evaluated the importance of infections in promoting asthma development in children, but the presence of AR has rarely been considered. In a 5-year study of 198 atopic children, respiratory infections (mainly due to rhinovirus and respiratory syncytial virus) were frequently associated with the later asthma onset in allergic children, but not in non-allergic children (22). Nasal mucus samples

were collected from 285 children in the first two years of life; the children were then followed up to 18 years (23). Four developmental trajectories relating to the early composition of the microbiome were identified. The microbiome dominated by *Staphylococcus* in the first six months of life was associated with an increased risk of asthma at the age of three years that persisted throughout the study. The identification of rhinoviruses and *Moraxella* during asthma episodes was also associated with the risk of developing persistent asthma in subsequent years (23). Moreover, a history of respiratory symptoms, mainly after viral infections or exercise was also reported to be predictive of further asthma in AR patients (24,25).

Conclusions

Many risk factors predicting asthma development in patients with AR have been suggested. Their clinical relevance is represented by the use of elective prescriptive criteria for AIT. Namely, the burden concerning clinical symptoms, quality of life, and direct and indirect costs, is much higher for asthma than AR. The data available so far must be interpreted based on their applicability in current clinical practice. For example, studies on the microbiome types are of undoubted scientific value but require evaluations within the first two years of life and subsequent prolonged follow-ups, which are usually not available in patients who are candidates for immunotherapy. The prescription of immunotherapy based on the IgE sensitization profile in single patients would respond to the criteria of precision medicine, but the only study that has demonstrated the predictivity of this finding has not yet received confirmation. Similarly, the predictive ability of fractionated exhaled nitric oxide levels on asthma has been suspected by a single study but not settled by the authors themselves. On the other hand, several studies demonstrated that an early bronchial impairment, particularly concerning small airways, in patients with HDM-driven AR is a reliable marker predictive of future asthma (14-19). Consequently, when asthma prevention is the main purpose, HDM sensitization with early bronchial impairment should be considered prescriptive criteria for AIT.

Conflict of Interest: Giorgio Ciprandi declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Cristoforo Incorvaia is Scientific consultant for Stallergenes-Greer.

Erminia Ridolo has recently been a speaker in a web meeting organized by ALK-Abellò.

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