



Preventing new sensitization and asthma onset by allergen immunotherapy: the current evidence

Ulrich Wahn

Purpose of review

Specific allergen immunotherapy is considered a key candidate for a successful preventive intervention in atopic diseases. The strong association of atopic manifestations such as rhinitis and asthma with atopic sensitizations (specific serum IgE) provide a rationale for early intervention in childhood and adolescence.

Recent findings

Currently, the documentation of the disease-modifying intervention effects is limited to the secondary prevention of asthma symptoms in children with allergic rhinoconjunctivitis. These effects appear to be rather allergen specific than nonspecific.

Summary

Documentation on disease modification including a reduction of asthma symptoms in children, particularly with grass pollen tablets has become quite robust. It is not clear up to now, if the new onset of allergic sensitizations can be modified. So far data on primary prevention are not conclusive.

Keywords

allergen immunotherapy, disease modification, prevention

INTRODUCTION: NATURAL HISTORY OF DEVELOPMENT OF ATOPIC AIRWAY DISEASE

The natural history of atopy development has been carefully described during the last decades by prospective observational birth cohorts. It is clear, that atopic manifestations tend to appear, persist, and – eventually – disappear early in life, with a characteristic pattern, for which the term ‘Atopic March’ has been proposed. Although IgE can be produced by the fetus prenatally after the 11th week of fetal life IgE-mediated sensitization occurs postnatally. Through standard detection techniques, specific IgE antibodies are not detectable in cord blood [1^a,2,3].

In many cases, infantile eczema is the first manifestation that may be associated or followed by clinically relevant or irrelevant sensitization to food. In most countries, hen’s egg followed by cow’s milk allergy has been shown to be the most prevalent infantile manifestation of food allergy in the first decade of life [1^a].

Sensitization to indoor (dust mites, cats) and outdoor (pollen) environmental allergens may also be initiated in the first 2 years of life; however, most cases develop later with a very high incidence in the first decade of life (2% per year) and the highest

prevalence by adolescence. Specific IgE responses clearly relate to regional exposure [4,5].

The use of molecular IgE assays have demonstrated recently, that sensitization to single indoor [5] as well as outdoor [6] allergens develops sequentially in early childhood (immunological spreading) and precedes the manifestation of upper and lower airway disease by several years. Intense and polyvalent IgE responses predict persistent airway disease manifestation such as allergic asthma [7].

Clearly, genetic factors as described by atopic manifestations in the parents or sibling are a strong determinant of both, sensitization and disease manifestation. Some of the atopic manifestations seem to be interrelated, such as atopic dermatitis [1^a] and infantile food allergy as well as preschool allergic rhinitis [8] and subsequent development of asthma symptoms in childhood. However, birth cohort studies indicate that there is considerable variation

Charité, Berlin, Germany

Correspondence to Professor Ulrich Wahn, Department for Pediatric Pneumology and Immunology, Charite-University Medicine, Augustenburger Platz. 1, D 13353 Berlin, Germany. Tel: +49 33203 79545; e-mail: Ulrich.wahn@gmail.com

Curr Opin Allergy Clin Immunol 2017, 17:443–446

DOI:10.1097/ACI.0000000000000399

KEY POINTS

- Specific AIT has a documented potential for disease modification lasting for at least 2–3 years, which includes the prevention of asthma symptoms in children.
- Up to now there is no sufficient evidence for an effect of specific AIT on the prevention of new allergen sensitizations.
- It is unclear, if there is a place for allergen ‘immunoprophylaxis’ as a strategy for primary prevention.

in the sequence of manifestations rather than a uniform pattern.

Some domestic environmental factors have been shown to either increase (pre and postnatal tobacco smoke, allergen concentration in house dust) or decrease (lipopolysaccharide, microbial exposure) the risk of allergic sensitization [1^a,3,4,9,10].

DISEASE MODIFICATION BY SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy, whether applied subcutaneously or sublingually, has been shown not only to reduce the severity of symptoms and the need for medication during treatment, but also to have profound long-lasting effects for at least 2 years after discontinuation of a treatment. This ‘disease-modifying effect’ has become an aspect of great interest for health authorities and payers in different countries. As a variety of pharmacological interventions (antihistamines, corticosteroids) have failed to demonstrate disease-modifying potential [11,12], this effect might be unique.

The US Food and Drug Administration as well as the European Medicines Agency usually request long-term documentation over at least 2 years after discontinuation of treatment in randomized, prospective, placebo controlled trials for both adults and children. In a major phase III trial on subcutaneous immunotherapy with grass pollen extract Durham *et al.* [13,14] were able to demonstrate a robust long-lasting effect on seasonal rhinitis symptoms. Recently the GRAZAX Asthma Prevention (GAP) study, a major phase III trial focusing on the prevention of asthma in grass pollen allergic children, showed, that sublingual immunotherapy with a grass pollen tablet could provide a similar long-lasting effect over 2 years after termination of immunotherapy as well [15^{aa}].

Obviously not all products which are currently registered in different countries have provided the same degree of evidence for their disease-modifying

capacities. Treatment effects may be influenced by their biological strength, their allergenic composition and the recommended dose regimens with the cumulative allergen dose applied during the treatment.

PREVENTING ASTHMA ONSET

Given the disease-modifying potential of allergen-specific immunotherapy, it was always tempting to assume that the chance of onset of asthma during as well as outside the pollen season might be reduced by early introduction of an allergen-specific immunotherapy. Several studies on asthma prevention in allergic rhinitis included patients with a history of allergic rhinitis and the need for medication combined with documented pollen allergy for several seasons. Clearly, additional costs are associated with this kind of treatment, and the question remains, whether this is outweighed by the beneficial effect for this group of patients.

About 20 years ago the preventive allergen therapy (PAT) study (subcutaneous application) in children with seasonal allergic rhinitis associated with birch and grass pollen allergy was initiated. Unfortunately, it included only an observational control group instead of a placebo group, which was not considered to be ethically acceptable in children who were given injections over a 3-year period. The study demonstrated a reduction of the risk of seasonal asthma by about 50%, which, given the study protocol, might overestimate intervention effects in the absence of a placebo group. It also found that the risk of asthma outside the pollen season was reduced, suggesting allergen nonspecific asthma preventing effects [16,17–18].

More recently, the GAP study included 800 children with grass pollen allergy in a randomized controlled trial with a five-grass pollen tablet for SLIT in comparison with a placebo tablet. Unfortunately, the primary endpoint for the study was not only related to asthma symptoms or the need for asthma medication but also to reversible airway obstruction, documented by lung function tests during a pollen season. This final criterion turned out to be met only in a small minority of the study population; therefore, statistical significant differences for the primary endpoint were missed in the study. However, there was a strong and robust effect on both, asthma symptoms as well as the need for asthma medication, which lasted also for two documented posttreatment years. It is quite clear, that for the specific study population of nonasthmatic children with grass pollen-induced allergic rhinitis the selected primary endpoint for this important study was inappropriate [15^{aa}]. The results of the GAP study are in line with previously published

findings on sublingual immunotherapy in pre-school children, providing evidence for protolerogenic effects [19].

Interestingly, the number of children with rhinitis needed to be treated to prevent one case of asthma ranged in the GAP study from 10 to 13 with a trend for a smaller number of necessary treatments in the youngest age group, suggesting a potential window of opportunity in the early disease state [16].

In recent systematic reviews including an European Academy for Allergy and Clinical Immunology guideline, which identified several randomized controlled trials, investigating the preventive effect of allergen immunotherapy (AIT) on the development of asthma in children with rhinitis, it was stated, that the majority of published studies [20–22] were not of high quality; however, in spite of a high degree of diversity, the current evidence suggests a long-term preventive effect regarding development of asthma symptoms and medication in children with seasonal rhinitis [23[•],24].

PREVENTING ALLERGIC SENSITIZATION

In a variety of studies, it has been demonstrated that allergen-specific immunotherapy provides allergen-specific benefits which means, that the applied allergen sources can be expected to reduce only symptoms related to these allergens [25]. During the last two decades, a variety of clinical trials have addressed the effect on prevention of development of new allergic sensitizations. Recent systematic reviews have assessed the data, that are currently available [23[•],24]. They state, that the published randomized controlled trials along with several low-quality studies show considerable inconsistency [26–33]. Based on the current evidence there seems to be no robust, high-quality evidence to recommend the use of AIT for either short or long-term prevention of the development of new sensitizations in healthy individuals, children with atopic predisposition, food allergy or in children and adults with allergic rhinitis.

An independent systematic review by Di Bona *et al.* [34], which was recently published, comes to a very similar conclusion and states, that currently there is only a low-grade level of evidence supporting the efficacy of AIT in preventing the onset of new allergen sensitization.

HEALTH ECONOMICS

Usually disease-modifying effects are assessed in clinical settings in a prospective way. Recently, however, long-term effects of specific immunotherapy were

evaluated in two retrospective real-world analyses, based on German longitudinal prescription databases [35,36[•]]. Allergic rhinitis patients treated with specific immunotherapy were compared with a control group not having received AIT. By multiple regression analysis, the use of rhinitis and asthma medication was assessed. The study, which included a study population up to 2.800 in the immunotherapy group as well as more than 70.000 in the control group, clearly demonstrated, that specific AIT was not only associated with slower rhinitis progression but also with less frequent asthma onset and slower asthma progression. Obviously, these reports point to the strong economic relevance of immunotherapy taking into account that 15–20% of the population of Western countries are affected.

CONCLUSION

Although documentation of intervention effects by AIT has made considerable progress, there are still some open questions to address in the future: the disease-modifying effect has been shown to last for at least 2 years after discontinuation of treatment. Whether this effect is robust and visible for a longer time period, remains to be shown. Theoretically it would seem possible, that an additional ‘booster year of AIT’ might lead to better long-term outcomes [37].

The second issue which has not really been adequately addressed is AIT’s potential role in primary prevention in high-risk or low-risk cohorts of children, before the process of sensitization and clinical disease manifestation has occurred. Animal experiments suggest that ‘allergen immunoprophylaxis’ might become a promising candidate for an antiallergic vaccine in the future; however, human data are lacking [38].

Finally, health economic studies regarding AIT given to children and adults with established disease are needed. Currently the convincing evidence for long time cost effectiveness is still to be evaluated.

Acknowledgements

None.

Financial support and sponsorship

U.W. has received Honoraria for Consultation from Novartis, Allergopharma, ALK-Abello, Stallergenes. He received lecture fees from Nestle, MEDA, Novartis, Allergopharma, Stallergenes, and ALK-Abello.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Grabenhenrich LB, Gough H, Reich A, *et al.* Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. *J Allergy Clin Immunol* 2014; 133:979–988.
- Description of the main risk factors for allergic airway disease.
2. Gough H, Grabenhenrich L, Reich A, *et al.*, MAS study group. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015; 26:431–437.
3. Wahn U, Lau S, Bergmann R, *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99:763–769.
4. Lau S, Illi S, Sommerfeld C, *et al.* Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000; 356:1392–1397.
5. Posa D, Perna S, Resch Y, *et al.* Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol* 2017; 139:541–549.
6. Hatzler L, Panetta V, Lau S, *et al.* Molecular spreading and predictive value of preclinical IgE response to Phleum pratense in children with hay fever. *J Allergy Clin Immunol* 2012; 130:894–901.
7. Hose AJ, Depner M, Illi S, *et al.*, PASTURE study groups. Latent class analysis reveals clinically relevant atopy phenotypes in 2 birth cohorts. *J Allergy Clin Immunol* 2017; 139:1935–1945.
8. Rochat MK, Illi S, Ege MJ, *et al.*, Multicentre Allergy Study (MAS) group. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol* 2010; 126:1170–1175.
9. Kulig M, Luck W, Lau S, *et al.* Effect of pre and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. Multicenter Allergy Study Group, Germany. *Allergy* 1999; 54:220–228.
10. Braun-Fahrländer C, Riedler J, Herz U, *et al.*, Allergy and Endotoxin Study Team. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; 347:869–877.
11. Warner JO, ETAC Study Group. Early Treatment of the Atopic Child. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol* 2001; 108:929–937.
12. Murray CS, Woodcock A, Langley SJ, *et al.* Secondary prevention of asthma by the use of inhaled Fluticasone propionate in wheezy infants (IFWIN): double-blind, randomized, controlled study. *Lancet* 2006; 368:754–762.
13. Durham SR, Emminger W, Kapp A, *et al.* SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012; 129:717–725.
14. Durham SR, Emminger W, Kapp A, *et al.* Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010; 125:131–138.
15. Valovirta E, Petersen TH, Piotrowska T, *et al.*, GAP investigators. SQ grass-SLIT treatment prevented asthma symptoms and asthma medication use in children with grass pollen ARC and no preexisting asthma. The disease-modifying effect persisted after end of treatment. *J Allergy Clin Immunol* 2017; doi:10.1016/j.jaci.2017.06.014.
- Large cohort study demonstrating the asthma preventive effect of sublingual allergen immunotherapy.
16. Möller C, Dreborg S, Ferdousi HA, *et al.* Immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109:251–256.
17. Niggemann B, Jacobsen I, Dreborg S, *et al.*, PAT Investigator Group. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006; 61:855–859.
18. Jacobsen I, Niggemann B, Dreborg S, *et al.*, (The PAT investigator group). Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943–948.
19. Szépfausi Z, Bannert C, Ronceray L, *et al.* Preventive sublingual immunotherapy in preschool children: first evidence for safety and pro-tolerogenic effects. *Pediatr Allergy Immunol* 2014; 25:788–795.
20. Des Roches A, Paradis L, Menardo JL, *et al.* Immunotherapy with a standardized dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997; 99:450–453.
21. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy* 2006; 61:198–201.
22. Novembre E, Galli E, Landi F, *et al.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:851–857.
23. Halken S, Muraro A, *et al.* EAACI Guideline on Allergen Immunotherapy: ■ prevention of allergy. *Pediatr Allergy Immunol* 2017; In press.
- Recent European guideline evaluating preventive effects of AIT.
24. Kristiansen M, Dhimi S, Netuveli G, *et al.* Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2017; 28:18–29.
25. Kuehr J, Brauburger J, Zielen S, *et al.* Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; 109:274–280.
26. Gulen F, Zeyrek D, Can D, *et al.* Development of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. *Asian Pac J Allergy Immunol* 2007; 25:7–11.
27. Inal A, Altintas DU, Yilmaz M, *et al.* Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Invest Allergol Clin Immunol* 2007; 17:85–91.
28. Marogna M, Tomassetti D, Bernasconi A, *et al.* Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101:206–211.
29. Purello-D'Ambrosio F, Gangemi S, Merendino RA, *et al.* Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001; 31:1295–1302.
30. Tella R, Bartra J, San Miguel M, *et al.* Effects of specific immunotherapy on the development of new sensitizations in monosensitized patients. *Allergol Immunopathol* 2003; 31:221–225.
31. Asero R. Injection immunotherapy with different airborne allergens did not prevent de novo sensitization to ragweed and birch pollen north of Milan. *Int Arch Allergy Immunol* 2004; 133:49–54.
32. Pajno GB, Barberio G, De Luca F, *et al.* Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001; 31:1392–1397.
33. Reha CM, Ebru A. Specific immunotherapy is effective in the prevention of new sensitivities. *Allergol Immunopathol* 2007; 35:44–51.
34. Di Bona D, Plaia A, Leto-Barone MS, *et al.* Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. *Allergy* 2017; 72:691–704.
35. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015; 136:1511–1516.
36. Zielen S, Devillier P, Heinrich J, *et al.* Sublingual immunotherapy provides ■ long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy* 2017. doi:10.1111/all.13213 (Epub ahead of print).
- Asthma prevention in patients with allergic rhinitis, assessed by doctor's prescriptions from Germany.
37. Marogna M, Spadolini I, Massolo A, *et al.* Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010; 126:969–975.
38. Holt PG, Sly PD. Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. *Nat Med* 2012; 18:726–735.