

Accepted Manuscript

Specific Allergy & Asthma Prevention Coming to an Age: A Milestone in Children

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PII: S0091-6749(17)31475-6

DOI: [10.1016/j.jaci.2017.08.022](https://doi.org/10.1016/j.jaci.2017.08.022)

Reference: YMAI 13014

To appear in: *Journal of Allergy and Clinical Immunology*

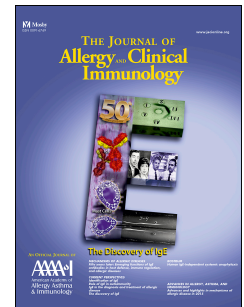
Received Date: 25 July 2017

Revised Date: 8 August 2017

Accepted Date: 17 August 2017

Please cite this article as: Bachert C, Akdis C, Specific Allergy & Asthma Prevention Coming to an Age: A Milestone in Children, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.08.022.

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Editorial**Specific Allergy & Asthma Prevention Coming to an Age: A Milestone in Children****Claus Bachert MD, PhD^{1,2} and Cezmi Akdis MD^{3,4}**¹ Upper Airways Research Laboratory and ENT-Department, Ghent University Hospital, Belgium² Division of ENT Diseases, CLINTEC, Karolinska Institute, University of Stockholm, Sweden³ Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland⁴ Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland.**Key words:** allergen immunotherapy, grass tablet, children, disease-modifying effect, prevention of asthma

It is 15 years that the first prevention of allergy (PAT) study was published in this journal,¹ trying to fulfil the dream of the allergists: whether allergen-specific immunotherapy (AIT) can alter the natural course of disease and prevent the development of asthma in children with seasonal allergic rhinoconjunctivitis. 205 children aged 6 to 14 years with grass and/or birch pollen allergy were randomized either to receive allergen-specific injection immunotherapy with an aluminium adsorbed native allergen extract subcutaneous immunotherapy (SCIT) for 3 years or to an open control group. Subjects had moderate to severe hay fever symptoms, but none of them reported asthma at the time of inclusion. Actively treated children had significantly fewer asthma symptoms after 3 years as evaluated by clinical diagnosis (odds ratio 2.52; $P < 0.05$). Methacholine bronchial provocation test results were significantly better in the active group. Thus, a 3-year course of injection AIT in children with hay fever to grass and/or birch pollen significantly reduced the risk of developing asthma. 183 of the children from both active and control groups were investigated 2 years after. The AIT receiving children had significantly less asthma compared to the open control group after 5 years as evaluated by clinical symptoms [odds ratio 2.6], confirming the prevention of asthma development, and significantly less patients reported an increase in asthma scores (also $P < 0.01$). Finally, 7 years after termination of the three-years treatment, 147 subjects, now 16 to 25 years old, were assessed again. The significant improvements in rhinoconjunctivitis and conjunctival sensitivity persisted at the 10-year follow-up.² Significantly less actively treated subjects had developed asthma at 10-year follow-up as evaluated by clinical symptoms (odds ratio: around 2.5). The longitudinal treatment effect after adjustment for bronchial hyper-responsiveness and asthma status at baseline, including all observations at 3, 5 and 10 years follow-up was statistically significant ($P = 0.0075$). The odds ratio for not having asthma was 4.6 in favour of the AIT.

Although the results were consistent and impressive, and this study was suggesting that AIT – here shown for one AIT product - was preventing asthma, the study had one major shortcoming: It was not a double-blind placebo-controlled trial! Thus, the allergy community awaited another trial, which should confirm the results of the first with a better protocol. This moment seemed to be reached when another treatment for grass pollen allergy, the SQ grass SLIT-tablet, had accumulated enough confidence in short-term registration studies in children and adults; large studies included 3260 adults and 880 children in state-of-the-art randomized placebo-controlled trials.³⁻⁵ And the SQ grass SLIT-tablet had additionally been

demonstrated to provide sustained relief in a 5-year double-blind, placebo-controlled trial in 238 adults, including 2 years of blinded follow-up after completion of a 3-year period of treatment.⁶ This remarkable study demonstrated a significant and clinically relevant daily symptom reduction in the active group over the 5 grass pollen seasons. Efficacy was supported by long-lasting significant effects on the allergen-specific antibody response, and no safety issues were identified. The efficacy in clinical and biological terms and the safety of the SQ grass SLIT tablet has been demonstrated, and now followed by the next milestone study, the grass tablet asthma prevention (GAP) trial.

The GAP study, awaited for many years, is now published in this issue of the Journal of Allergy and Clinical Immunology; involved 812 children (5-12 years, slightly younger than those in the PAT study) with a clinically relevant history of grass pollen allergic rhinoconjunctivitis and no medical history or signs of asthma.⁷ In contrast to previously published studies, GAP now is a randomised, double-blind, placebo-controlled state-of-the-art trial, comprising 3 years treatment and 2 years follow-up. Treatment with the SQ grass SLIT tablet significantly reduced the risk of experiencing asthma symptoms or using asthma medication at the end of the trial (odds ratio=0.66, $p<0.036$), during the 2 years post treatment follow-up, and during the entire 5-year trial period. Unfortunately, the primary endpoint was defined by pre-specified asthma criteria relying on documented reversible impairment of lung function in the physician's office, and was not achieved; this criterion has been chosen to have an objective and uniform asthma diagnosis in all of the participating countries. The difficulty of demonstrating reversible impairment of lung function in just beginning asthma could be one of the reasons for this. However, analysing asthma symptoms, as it was successfully done in the PAT trial and as it would be used in everyday practice, revealed the potential of preventive study. SLIT-tablet treatment reduced the proportion of children reporting any asthma symptoms during the entire 5-year trial period and during the 2-year post-treatment period. The prevention of clinical asthma symptoms or the use of asthma medication – which is important for the young patients and their parents – was demonstrated based on these data. The treatment effect on asthma medication use was primarily due to a reduction in beta-2-agonist use.

Another major finding for this study is the demonstration of the disease modifying potential of grass tablet AIT for the first time in children. Grass allergic rhinoconjunctivitis symptoms

and need for additional pharmacotherapy were significantly reduced for all 5 years by replicating the findings of the adult trials mentioned above. Thus, we cannot state that the SQ grass SLIT tablet postponed the onset of asthma as defined in this study, but certainly that it reduced the risk of asthma symptoms and need for medication, as well as the symptoms and medication related to allergic rhinitis during the 3 years of therapy and for two years thereafter.

It appears that moving the trial to an earlier age was justified; the number needed to treat, NNT increased with age, indicating that the younger the children, the higher the risk of developing asthma symptoms, and therefore the higher the profit from treatment. The development from allergic rhinitis into asthma still can be documented in adulthood, and can be prevented by some forms of AIT, but considerably slows down.⁸ Further studies should be performed defining the age with the highest potential of AIT to avoid asthma development. Of interest, asthma symptoms or asthma medication use were reduced by the SQ grass SLIT-tablet treatment consistently, and this effect was apparent both during the grass pollen season and during winter, with wheeze, chest tightness and shortness of breath being impressively reduced.

This study clearly demonstrates the power of a specific AIT product, not of any AIT in general. The results achieved with this product cannot be transferred to other products, sublingual or subcutaneous, without adequate evidence. The SQ grass SLIT tablet shows a disease modifying effect for allergic rhinoconjunctivitis in children, as it has demonstrated the same in adults. The tablet furthermore reduces the risk for asthma symptoms and need of asthma medication consistently in young children, and is unique in showing this effect. This study is the peak point of a large development program for an AIT program, which allergists would love to see repeated for other allergens and products. Pulmonary function tests and biomarkers should be included in future studies to assess alterations of the natural course of disease.

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139 **Legend to the figure**140 **Figure 1.** Improved features of asthma and allergic rhinoconjunctivitis in the GAP trial:141 Asthma symptoms (OR: 0.543, $p=0.017$); asthma medication use (OR: 0.337, $p=0.002$);142 asthma symptoms and asthma medication use (OR: 0.278, $p=0.0004$); asthma symptoms,143 asthma medication use and FEV1 reversibility $\geq 12\%$ (OR: 0.177, $p=0.013$); asthma144 symptoms, inhaled corticosteroid use and FEV1 reversibility $\geq 12\%$ (OR: 0.205, $p=0.028$).

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**Children aged 5-12 years with grass allergy, no asthma
3 years treatment and 2 years follow up**

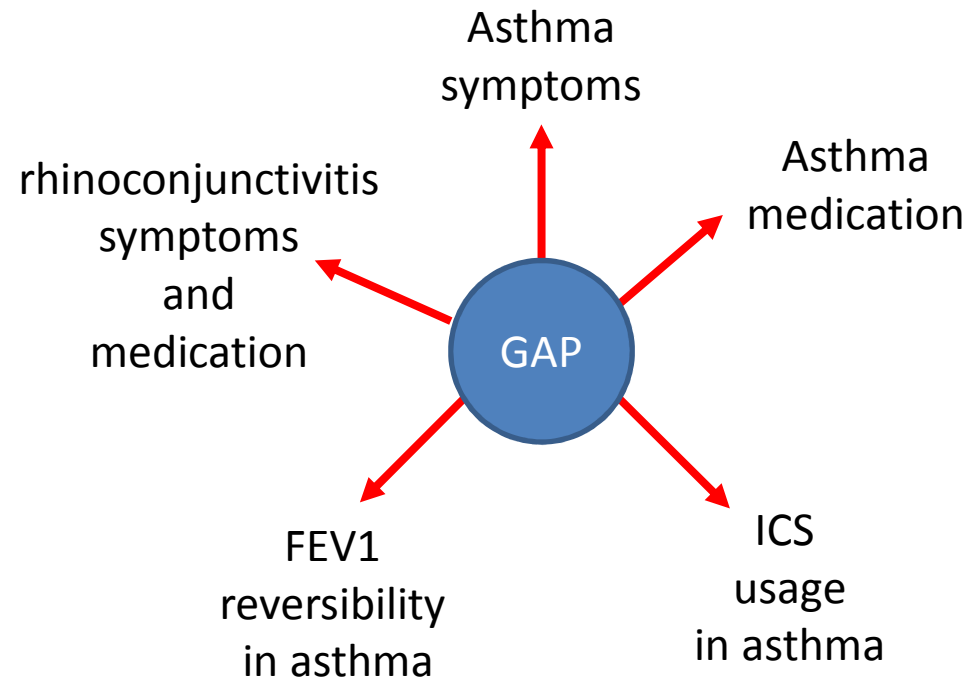


Figure 1. Bachert & Akdis