

## ORIGINAL ARTICLE

# Effect of AIT in children including potential to prevent the development of asthma

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## Abstract

Allergy specific immunotherapy may alter the natural course of allergic disease. Thus, it is of significant importance, particularly in paediatric populations. Four studies using the grass allergy immunotherapy tablet (AIT) for allergic rhinoconjunctivitis in children showed good clinical outcomes and good safety profiles. Allergic rhinoconjunctivitis often precedes asthma, and treatment with specific immunotherapy has the potential to reduce the development of asthma in children suffering from rhinoconjunctivitis. Since Grazax<sup>®</sup> AIT has been shown to induce disease modification the prevention of asthma might be hypothesised. The GAP (Grazax<sup>®</sup> Asthma Prevention) trial is investigating the asthma preventive effect of standardised grass AIT in grass allergic children with rhinoconjunctivitis without asthma. The trial is a 5-year, multicentre, multinational, randomised, double-blind, placebo-controlled, prospective trial for children aged 5–12 years. In a few years, the results will show if grass AIT with Grazax<sup>®</sup> can prevent the development of asthma in children suffering from allergic rhinoconjunctivitis.

This presentation is on behalf of the GAP (Grazax<sup>®</sup> Asthma Prevention) trial investigators. Four studies have addressed the efficacy of AIT in children (1–4). The Bufo and Wahn studies were 1-year double-blind placebo-controlled trials one using ALK AIT Grazax<sup>®</sup> and one using the Stallergènes Oralair tablet. The Agostininos study was a 2-year trial using Lofarma monomeric allergoid tablets, and the Blaiss study was a 1-year US study to replicate the European study using ALK grass AIT.

The Bufo study included over 200 children, aged 5–16 years. Efficacy was measured by rhinoconjunctivitis symptom scores. During high-pollen season, defined as at least 30 pollen grains per cubic meter of air, mean symptom scores were reduced by 28% relative to placebo. A subgroup of children with asthma symptoms showed a significant 81% decrease in symptom scores during high-pollen season, and no serious or systemic side effects were reported, even for treatment during the pollen season. Specific IgG<sub>4</sub> levels increased significantly from baseline with Grazax<sup>®</sup> treatment relative to placebo, and immunological aspects similar to adults were seen in children.

The Wahn trial studied children 5–17 years of age, and observed similar results to the Bufo study in terms of rhinoconjunctivitis symptoms, with a 28% mean reduction in symptoms. Thus, the two studies with grass AITs have supporting results, including similar increases in specific IgG<sub>4</sub> in treated

children. Using the same definition for high-pollen season, medication score improvement showed a median of 51.7%.

The 2-year Agostininos study included 40 children aged 4–16 years and receiving grass SLIT or symptomatic treatment. The results showed a good safety profile, similar to the Bufo and Wahn studies, and significant reduction in symptom scores after the first and second seasons. The North American Blaiss study yielded results similar to the Bufo study. The total combined symptom and medication score showed a reduction of 26%. The Bufo and Wahn studies led to the approval of the ALK's and Stallergènes' tablets for use in children over the age of five in Europe.

## AIT in asthma prevention

The Burgess longitudinal study (5) followed childhood allergic rhinoconjunctivitis and asthma incidence from age 8 to 44 years. Allergic rhinoconjunctivitis was found to predict asthma. By 7 years of age, 24.5% of children had developed allergic rhinoconjunctivitis, and this at-risk population had an over 3-fold greater risk of developing asthma in later life. Childhood allergic rhinoconjunctivitis was associated with a 7-fold increase in asthma risk for pre-adolescents, a 4-fold greater risk in adolescents and a 2-fold increase in adults. Thus, allergic rhinoconjunctivitis has serious clinical implications, and it is underestimated, underdiagnosed, and

undertreated. Allergic rhinoconjunctivitis demands more effective treatment because of the increased risk of developing asthma. This was already mentioned in a World Health Organization position paper from 1998 (6), stating that: *Preliminary data suggest that immunotherapy impedes progression from allergic rhinoconjunctivitis to asthma.* This was also stated in an Allergic Rhinitis and its impact on Asthma (ARIA) position paper (7), a World Allergy Organization paper on SLIT (8), and an update on injection immunotherapy (9). Evidence from open randomised studies suggests that SLIT reduces the risk of developing asthma in children with allergic rhinoconjunctivitis, but conclusive data does not yet exist. Thus, we know that AIT is effective in children over 5 years of age, allergic rhinoconjunctivitis is a risk factor for asthma development, and SIT may reduce asthma development.

The phase III GAP trial (10) (Fig. 1), sponsored by ALK, is investigating disease modification in children. The primary objective is to determine the effect of Grazax<sup>®</sup> compared to placebo on the risk of developing asthma. It is a 1 : 1 randomised placebo controlled, double-blind study with multinational, multicentre participation, involving almost 100 centres. Children age 6–12 will receive 3 years of daily Grazax<sup>®</sup> or placebo to determine if 3 years of treatment with Grazax<sup>®</sup> has a preventive effect on asthma development and whether treatment effects are sustained 2 years after completion of treatment. Children were screened in 2009 and 2010, and are now randomised. The trial aimed to include 620 subjects. Currently over 800 subjects with a good representation of European countries are included in the study.

Grazax<sup>®</sup> has shown disease-modifying effects in adults. It induces a similar immunological response in children as in adults, as measured by IgG<sub>4</sub> levels. This leads to the hypothesis that it may also have disease modifying effects in children. This provides a strong rationale that the 'allergic march' can be influenced and the development of asthma prevented. The GAP trial will provide the conclusive answer to these ques-

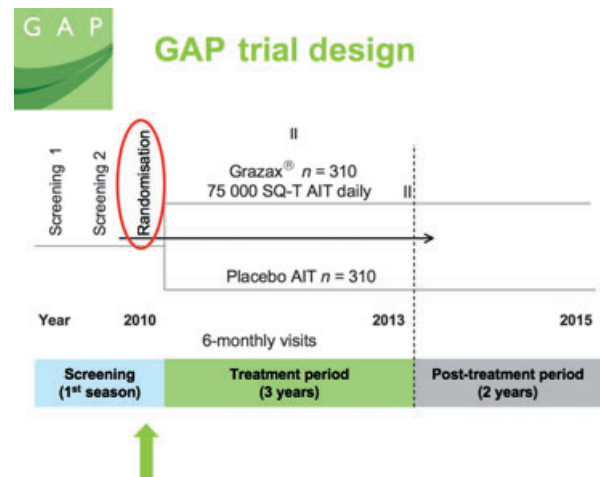


Figure 1 GAP trial design.

tions. Early introduction of treatment in allergic rhinoconjunctivitis is important. Currently, children above 5 years of age are treated. It may be possible to treat children who are even younger, but at the moment there are no studies to support this. So the message is: if we treat you today with symptomatic medication, we help you today. When we treat you with allergy specific immunotherapy, we also help you tomorrow!

### Conflict of interest

Erkka Valovirta has received consultancy fees from ALK-Abelló, MSD, GSK, Schering-Plough, Novartis and Nycomed as well as lecture fees from ALK-Abelló, GSK, Schering-Plough, UCB-Pharma and MSD.

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