Clinical efficacy and immunological response in children is similar to that of adults after the first treatment season with SQ-standardized grass allergy immunotherapy tablet in two randomized trials

A. Bufe¹, P. Eberle², B. Tholstrup³, H. Henmar³ and S.R. Durham⁴

¹Department of Experimental Pneumology, Ruhr-University Bochum, ²Pädiatrische Pneumologie/Allergologie, Kassel, ³Research and Development, ALK, Hoersholm, Denmark, ⁴Section of Allergy and Clinical Immunology, Imperial College London, United Kingdom

Clinical efficacy and immunological response in children is similar to that of adults after the first treatment season with SQ-standardized grass allergy immunotherapy tablet in two randomized trials

Background: Specific immunotherapy is the only treatment of IgE-mediated allergic diseases with the potential to modify the underlying cause of disease and prevent disease progression or even cure the disease. Treatment in children is therefore desirable. However, it is an open question whether immunotherapy in children and adolescents works as effective as demonstrated in adults.

Objective: This post-hoc study compares the clinical efficacy and immunological response in children and adults based on two separate randomized, double-blind, placebo-controlled trials with the SQ-standardized grass allergy immunotherapy tablet (AIT) (ALK, Denmark). Methods: Children and adults were treated with grass AIT or placebo prior to and during one grass pollen season. To account for seasonal and geographical variabilities in grass pollen counts between trials, data for the peak 2 weeks of the grass pollen season has been compared. Endpoints included rhinoconjunctivitis symptom scores, medication scores and percentages of well-days. Furthermore results for the entire pre- and co-seasonal periods of each trial in Phleum pratense-specific IgE-blocking factor and IgG₄ have been compared. Results: The measured treatment efficacy during the peak grass pollen season from the pediatric and the adult trials were similar in difference relative to placebo for symptom scores (27%; 28%; p-values for both <0.01), medication scores (64%; 56%; p-values for both <0.01) and percentages of well-days (44%; 46%; p-values for both <0.01). Grass AIT induced comparable IgE-blocking factor and IgG₄ responses in children and adults. All assessments were in favor of active treatment.

Conclusion: Treatment with grass AIT for one grass pollen season is as efficacious in children as in adults and induces comparable immunological responses.
Grass AIT in children versus in adults

Analyse die 2 Wochen mit der höchsten saisonalen Graspollen-Konzentration (seasonal peak) verglichen. Klinische Endpunkte waren der Symptom-Score für Rhinokonjunktivitis, der Medikamenten-Score und die Anzahl an Tagen ohne Symptome (% well days). Weiterhin wurden die Ergebnisse für die gesamte vor- und co-saisonale Periode einer jeden Studie für Phleum pratense spezifische IgE-blockierende Faktoren und IgG4 miteinander verglichen. Ergebnisse: Die gemessene Effektivität der Behandlung während der Spitzenkonzentration für Graspollen zwischen der pädiatrischen und der erwachsenen Population waren bezogen auf die relative Differenz zwischen behandelten und Placebopatienten vergleichbar: für Symptom-Scores (27%; 28%; p-Wert für beide < 0,01); für Medikamenten-Score (64%; 56%; p-Wert für beide < 0,01); % Tage ohne Symptome (44%; 46%; p-Wert < 0,01). Gras-AIT induzierte vergleichbare Werte für IgE-blockierende Faktoren und IgG4-Antikörper in Kindern und Erwachsenen. Alle Werte stiegen zugunsten der aktiven Behandlung an. Schlußfolgerung: Die Behandlung mit Gras-AIT für eine Graspollen-Saison ist bei Kindern so wirksam wie bei Erwachsenen und induziert eine vergleichbare immunologische Antwort.

Introduction

The prevalence of allergic rhinoconjunctivitis is increasing. Physical, psychological and social burdens are profound for the affected individual, and costs to society are extensive [1]. Symptoms in moderate or severe forms are associated with impaired sleep leading to daytime drowsiness, fatigue, indecision, significant impairment in learning and cognition, and lost work or school-days with a consequent significant impact on the present and possibly future life of the affected individual [1]. Disease progression often involves development of asthma and airway remodelling associated with progressive and permanent tissue damages in the airways.

Specific immunotherapy is currently the only treatment of IgE-mediated allergic diseases with the potential to modify the underlying cause of disease and prevent disease progression. The mechanism is the induction of a certain level of immune tolerance to the allergen to which the patient is allergic [2]. Early treatment initiation where the disease may still be reversible is therefore desirable [3]. The traditional subcutaneous route has been considered inconvenient especially in children and therefore during recent years clinical data supports the use of the sublingual route in this group of patients [4]. However, until the emergence of sublingual allergen tablets varying results have been published [5, 6, 7] and meta-analysis provided evidence that immunotherapy works less effective in children and adolescents than in adults. Recently three major studies on the application of allergy immunotherapy tablets (AIT) in children were published demonstrating reproducible clinical efficacy and a favorable safety profile [8, 9, 10].

One of the tablets is the SQ-standardized grass-AIT (Grazax; Phleum pratense; 75,000 SQ-T/2,800 BAU, ALK, Denmark) which has been approved in Europe as disease-modifying treatment of grass pollen-induced allergic rhinoconjunctivitis in adults and children (5 years or older). Here we use this data to evaluate the comparability of efficacy in children and adults after treatment with grass AIT and we compared treatment efficacies during the peak pollen seasons and the immune responses from two otherwise similar double-blind, placebo-controlled, randomized trials in children and adults.

Methods

Details of the randomized, double-blind, placebo-controlled trials, conducted according to the Declaration of Helsinki [11] and Good Clinical Practice, have been published previously [8, 12] (ClinicalTrials.gov numbers: NCT00408616 (pediatric trial) and NCT00227279 (adult trial)). Written informed consents were obtained from parents/guardians/participants as appropriate before initiating treatment, and relevant ethics committees approved the trials.

253 children (5 – 16 years) were included in the pediatric trial and 634 participants (18 – 65 years) were included in the adult trial. In- and exclusion criteria were comparable between the trials. Key inclusion criteria included a clinical history of grass pollen-induced allergic rhinoconjunctivitis requiring treatment, with or without mild-to-moderate asthma, a positive skin prick test against Phleum pratense (wheal diameter ≥ 3 mm),...
and a positive *Phleum pratense*-specific IgE (CAP class ≥ 2). Key exclusion criteria were severe asthma and symptomatic allergies, other than grass allergy, during the grass pollen season.

In both trials, participants were randomized (1:1) to once-daily treatment with grass AIT (a fast dissolving and neutral tasting oral lyophilisate) or an equivalent placebo tablet without allergen extract. In the pediatric trial, conducted at 26 German centres, treatment was initiated ≥ 8 weeks prior to the anticipated start and throughout the entire grass pollen season in 2007. In the adult trial treatment was initiated ≥ 16 weeks prior to the anticipated start and throughout the entire grass pollen season in 2005 (51 centers; 8 European countries).

**Efficacy**

Children (parents/guardians) and adults rated 6 rhinoconjunctivitis symptoms daily in electronic diaries during the grass pollen season on a scale from 0 – 3, where 0 corresponded to no symptoms and 3 to severe symptoms. The rhinoconjunctivitis symptoms were divided into 4 nose symptoms (runny nose, blocked nose, sneezing and itchy nose) and 2 eye symptoms (watery eyes and gritty feeling/red/itchy eyes).

Symptomatic medications were used in a stepwise fashion as needed, depending on the persistence and severity of rhinoconjunctivitis symptoms. The use was recorded daily in the electronic diary during the grass pollen season and scored according to predefined criteria not revealed to the participants (scale: 0 – 34 for children and 0 – 30 for adults). Symptomatic medications for children included loratadine tablets, levocarbastine eye drops, budesonide nasal spray and prednisolone tablets; and for adults: desloratadine tablets, budesonide nasal spray and prednisone tablets.

Due to variations in grass pollen exposure from year to year and between sites and countries, and the direct correlation between exposure and rhinoconjunctivitis symptoms, we compared data from the pre-defined peak grass pollen seasons (the 15 consecutive days with highest cumulative average pollen counts in each grass pollen season).

Average rhinoconjunctivitis daily symptom and medication scores were calculated as the sum of the individual daily scores in the peak season and divided by the number of diary recordings in the same period.

Rhinoconjunctivitis well-days were defined as days in the peak season with no rhinoconjunctivitis symptomatic medication intake and with a rhinoconjunctivitis symptom score ≤ 2.

**Immune response**

*Phleum pratense*-specific IgE-blocking factor (i.e., the presence of components blocking IgE-allergen binding) and IgG4 were determined at screening (defined as baseline), during pre-seasonal treatment, approximate at the start of the grass pollen season, during the season and at the end of the season. The immunological markers were measured in serum using the ADVIA Centaur immunoassay system (Siemens Medical Solutions, Tarrytown, NY, USA) as described previously [8].

**Statistics**

Statistics for each trial are described in details elsewhere [8, 12]. Briefly, analyses were performed on all randomized participants (full analysis set). All available data were used to their full extent, and no imputation of missing data was performed. A 2-sided significance level of 5% was used. In the adult trial, parametric analyses were done using a linear mixed effect (LME) model with the parameter in question (e.g., average rhinoconjunctivitis symptom score) as response variable and treatment group as fixed effect. Pollen region was included as a random effect. In the pediatric trial, a similar parametric analysis was done for percentage well-days. For the average rhinoconjunctivitis symptom score, it was necessary to make a square root transformation in order to obtain normally distributed data. The resulting estimates were back-transformed afterwards.

As the raw medication score in the pediatric trial or any transformation of the medication score could not approximate sufficiently to a normal distribution, the non-parametric Wilcoxon rank sum test was used,
Grass AIT in children versus in adults

Results

Participants

In the pediatric trial, 253 children were randomized (126 active; 127 placebo), with 234 (92%) completing the one-season trial. In the adult trial, 634 adults were randomized (316 active; 318 placebo), with 546 (86%) completing the first grass pollen season.

Noticeable differences in baseline characteristics in the pediatric trial vs. the adult trials were: mean age (10 vs. 34 years of age); mean number of years with grass allergy (3.5 vs. 15.8 years); less participants with severe allergic rhinoconjunctivitis (27% vs. 56%); and more participants with asthma (41% vs. 24%). Another difference between the trials was a shorter pre-seasonal treatment period in the pediatric trial (17 vs. 26 weeks). Further details and CONSORT diagrams were presented previously [8, 12].

Pollen exposure and efficacy

The daily grass pollen exposure over the entire grass pollen season was significantly lower in the pediatric trial than in the adult trial (daily mean exposure of 36 vs. 51 grains/m³). During the peak seasons the mean exposure was significantly higher in both trials (83 and 108 grains/m³, respectively) as compared to the respective mean values and well above the definition of high exposure (defined as > 50 grains/m³ per day for grass).

The relative differences in efficacy between active and placebo groups during the peak grass pollen seasons are shown in Table 1. For the overall rhinoconjunctivitis symptom scores, the separate eye and nose symptom scores, the rhinoconjunctivitis medication scores, and the percentage well-days a significant effect in favor of grass AIT treatment was found in both trials. The efficacy was comparable between the pediatric and the adult trials for all the endpoints (Table 1).

Immunological responses

In both trials, the immunological responses were significantly higher (p < 0.001) in the active groups from the first assessment after the baseline and onwards.

Despite the difference in pre-seasonal treatment, the change from baseline in IgE-blocking factor in the active groups was comparable between children and adults from the start of the grass pollen season and onwards (Figure 1A). In the placebo groups

Table 1. Mean rhinoconjunctivitis symptom scores, separate nose and eye symptom scores, and percentages of “well-days” and median rhinoconjunctivitis medication scores during the peak pollen seasons of the pediatric trial (year 2007) and the adult trial (year 2005).

<table>
<thead>
<tr>
<th></th>
<th>Children (Ngrass AIT = 117)</th>
<th>Adults (Ngrass AIT = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhinocconjunctivitis symptom score</strong> (adjusted means)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass AIT</td>
<td>2.84</td>
<td>3.81</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.91</td>
<td>5.27</td>
</tr>
<tr>
<td>Differencesa</td>
<td>1.07 (27%)</td>
<td>1.46 (28%)</td>
</tr>
<tr>
<td>p-valueb</td>
<td>0.0059</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Nose score</strong> (adjusted means)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass AIT</td>
<td>2.01</td>
<td>2.70</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.76</td>
<td>3.59</td>
</tr>
<tr>
<td>Differencesa</td>
<td>0.75 (27%)</td>
<td>0.89 (25%)</td>
</tr>
<tr>
<td>p-valueb</td>
<td>0.0088</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Eye score</strong> (adjusted means)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass AIT</td>
<td>0.72</td>
<td>1.13</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.97</td>
<td>1.70</td>
</tr>
<tr>
<td>Differencesa</td>
<td>0.25 (26%)</td>
<td>0.56 (33%)</td>
</tr>
<tr>
<td>p-valueb</td>
<td>0.0544</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Percentages well-days</strong> (adjusted means)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass AIT</td>
<td>40.6</td>
<td>32.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>28.2</td>
<td>22.3</td>
</tr>
<tr>
<td>Differencesa</td>
<td>−12.4 (−44%)</td>
<td>−10.3 (−46%)</td>
</tr>
<tr>
<td>p-valueb</td>
<td>0.0042</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Rhinocconjunctivitis medication score</strong> (medians)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grass AIT</td>
<td>0.87</td>
<td>1.33</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.40</td>
<td>3.00</td>
</tr>
<tr>
<td>Differencesa</td>
<td>1.53 (64%)</td>
<td>1.67 (56%)</td>
</tr>
<tr>
<td>p-valueb</td>
<td>0.0017</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Ngrass AIT = numbers of subjects with diary records in the active groups; Nplacebo = numbers of subjects with diary records in the placebo groups; aabsolute difference and percentage difference relative to placebo; b p-value for the difference between active and placebo; cas the medication scores in the pediatric trial were not normally distributed, a non-parametric Wilcoxon rank sum test was used and accordingly medians values are shown. For comparison, median medication scores are also shown for the adult trial.

The peak grass pollen season was defined as the 15 consecutive days with highest cumulative average pollen counts in each grass pollen season.
no changes were observed in any of the trials until the start of the grass pollen season and in the adult trial no changes were observed in the placebo group throughout the season. In the pediatric trial minor increases were observed in the placebo group after the start of the season (i.e., following the natural exposure to grass allergens).

For the change from baseline in $\log_{10}\text{IgG}_4$, comparable increases were observed in the adult and pediatric trials (Figure 1B), with a possible tendency towards a higher response in adults. The placebo groups were similar between adults and children.

**Discussion**

We suggest here that treatment with grass AIT for one grass pollen season is as efficacious in children as in adults in terms of comparable reductions in rhinoconjunctivitis symptoms and symptomatic medication use, and increases in number of well-days compared with placebo during the peak grass pollen seasons. Although the present study was not per se a head to head clinical trial but a post-hoc analysis, this comparison is considered a valuable addition to the ongoing discussion of efficacy of immunotherapy in children versus in adults. Using the same allergen preparation, the same dosage in both groups and the same study-design in both studies the comparison demonstrates that specific immunotherapy via the sublingual route is as effective in children as in adults and induces a similar immune response.

Further support of comparable efficacy of immunotherapy between adults and children, given the same treatment, comes from two recently published grass AIT trials in North American populations [9, 13]. The results from the two US trials are not only similar across the age-groups but are also similar to the results from the European trials presented here. Similar treatment effects of immunotherapy in children and adults have also been acknowledged in the latest Cochrane review on sublingual immunotherapy [14], but the heterogeneity between trials was highly significant ($p < 0.00001$). The explanation for this may be ascribed to variable dosages used in sublingual immunotherapy trials as well as variable treatment schedules.

An unusually mild grass pollen season 2007 in Germany (i.e., at the sites in the pediatric trial) compared with the grass pollen season 2005 in the 8 European countries representing the sites in the adult trial, may explain differences observed between trials during the entire grass pollen seasons (for details please refer to previous publications [8, 12]). To account for the differences in grass pollen exposure, we here evaluated the peak seasons, where the grass pollen exposure is more comparable. This is a well-known approach and it has recently been suggested to normalize the data from pollen immunotherapy trials for the peak 2 weeks of pollen exposure...
As shown here, the immune response induced by the specific immunotherapy is rather similar in both age groups. The induction patterns of *Phleum pratense*-specific IgE-blocking factor in children and adults treated with grass AIT were found to be comparable. Despite differences in the length of the pre-seasonal treatment periods, both populations had reached the same level of IgE-blocking factor at the grass pollen season start, and these inductions remained similar between populations during the season. Interestingly, a slight increase in IgE-blocking factor was induced in the placebo group in the pediatric trial at the start of the grass pollen season. This ability of showing a more healthy immunological response when exposed to the naturally occurring allergen as an alternative to the allergic response (i.e., a pure IgE-response) appears to diminish with age or with duration of disease. The observation concurs with the notion of the allergic disease being more plastic in the earlier stages [16] and supports initiation of immunotherapy as early as possible in disease history.

The induction of *Phleum pratense*-specific IgG4 was comparable between adults and children treated with grass AIT, with a tendency towards a stronger IgG4 response in adults. Although induction of allergen-specific IgG4 antibodies is the most consistent immunological finding in immunotherapy trials, a simple correlation between serum IgG4 and clinical efficacy of immunotherapy has not been established [17]. Shamji et al. [18] recently suggested that while changes in functional allergen-specific antibodies (e.g., assessed by the IgE-blocking factor assay) accounted for up to 40% of the clinical treatment effect after subcutaneous grass pollen immunotherapy, changes in specific IgG4 accounted for only 13% of the treatment effect. The relationship between clinical efficacy and immunological parameters after grass AIT treatment has not yet been fully established, but may differ from subcutaneous immunotherapy, particularly in post-treatment years [19]. However, it is recognized that quantitative serum measurements of IgG4 do not necessarily reflect the IgE-allergen blocking, as other blocking components may be present [2].

The immunomodulatory effect, in terms of the modulation of T-cell and B-cell responses and related antibody isotypes as well as effector cells of allergic inflammation, such as eosinophils, basophils and mast cells, has been associated with the potentially curative outcome of specific immunotherapy [2]. A consequent prevention of disease progression into asthma and new sensitizations has previously been shown for grass pollen allergic children [20]. In summary, the similar immune response in both age groups during one season indicates that the activation and modulation of the cellular and humoral immune parameters by the sublingual application of high dose antigen is due to similar mechanism and can be induced already earlier in life.

The adult trial was continued for an additional 2 years of treatment and 2 years of follow-up, and resulted in a demonstration of long-term and disease-modifying effect 2 years after completion of a 3-year treatment with grass AIT [19]. Disease-modification has not yet been demonstrated in children, but based on the comparable treatment efficacy and immunomodulatory changes in children and adults after treatment for one grass pollen season, the long-term and disease-modifying effect seen in adults may potentially be extrapolated to children [2], especially since the mechanisms of modulation seem to be comparable. Long-term, disease-modifying effect together with the initial relief of symptoms may reduce the burden of grass pollen allergy for sufferers, e.g., day-time drowsiness, lost work days or school days, impaired social functioning and low quality of life [1].

In both children and adults, the most frequent adverse events were local administration site-related events (e.g., oral and ear itching, mouth oedema and throat irritation). No serious adverse events were reported in the pediatric trial and the 5 serious adverse events reported in the first season of the adult trial were assessed as unrelated to treatment [8, 12]. This favorable safety profile together with the convenient administration of grass AIT provides the potential of disease-modifying allergy treatment during childhood, while the disease may still be reversible.
Conclusion

Treatment with SQ-standardized grass AIT is efficacious in children and in adults and induces comparable clinical and immunological responses after the first treatment season. Grass AIT leads to the same clinical and immunological effects in both groups, is a suitable treatment also for children and provides the potential of early treatment initiation, when the allergic disease may still be reversible.

Acknowledgments

ALK sponsored the trials and assumed overall responsibility and was involved in trial designs and conduct; data management, collection, analysis and interpretation; and publication of the trials. The authors were investigators contributing to data collection in one or both of the trials, except for B. Tholstrup and H. Henmar which are employed by ALK. A. Bufe is advisor to Boehringer, Bitop AG and NETSTAP e.V. S. Durham has consultancy and lecture fees from ALK, Allergopharma and NETSTAP e.V. S. Durham has consultancy and lecture fees from ALK. P. Eberle has declared to have no conflict of interest. All authors have contributed to the enclosed manuscript from the draft stage by outlining and reviewing the manuscript. Submission of the final manuscript was endorsed by all authors.

We thank all the investigators involved in the trials (adult trial: GT-08 and pediatric trial: GT-12), as well as the trial teams. Trial statisticians were Jens Strodl Andersen, ALK (GT-08) and Dorte Rehm, ALK (GT-12). Immunological assessments were performed by Pernille Milvang Gronager and Department for Bioanalytics at ALK. Medical writers Christina El-Naaman Gregersen and Bente Riis provided medical writing services (drafting, editing and journal submission assistance) on behalf of ALK.

References

[17] Shanji MH, James LK, Durham SR. Serum immunologic markers for monitoring allergen-


Prof. Dr. med. A. Bufe
Abteilung für Experimentelle Pneumologie
Ruhr-Universität Bochum
Bürkle-de-la-Camp-Platz 1
D-44789 Bochum
e-mail: albrecht.bufe@rub.de