ADDITIONAL BENEFIT OF A THIRD YEAR OF SPECIFIC GRASS POLLEN ALLERGOID IMMUNOTHERAPY IN PATIENTS WITH SEASONAL ALLERGIC RHINITIS

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Aluminium-adsorbed six grass pollen allergoid therapy for 2 years was found to be efficacious and safe in patients with hay fever and seasonal asthma. Using high-dose, hypoallergenic allergen products (allergoids) enables a short-term pre-seasonal treatment regimen. However, it is not known whether further treatment beyond 2 yrs had any additional benefit.

Following an initial 2-year randomized, double-blind, multi-centre, placebo-controlled clinical trial in 154 grass pollen-allergic patients, an additional short course of specific immunotherapy with the high-dose, hypoallergenic grass pollen preparation Allergovit® was performed in 61 patients of the active treatment group during the 3rd open-label treatment year.

Further treatment of patients with the Allergovit® 6-grass pollen preparation resulted in a further reduction of symptom medication score and improved quality of life in comparison to the first and second treatment year. Changes in allergen-specific IgG4 levels supported these results.

Pre-seasonal short-term immunotherapy with the high-dose, hypoallergenic allergen preparation Allergovit® has been shown to be efficacious and safe. A course of three years of 6-grass pollen SIT further improves allergic symptoms, quality of life and reduces the need for anti-allergic medication.

Allergoid - Short-term immunotherapy - SIT - Grass pollen - Efficacy - Quality of life.

INTRODUCTION

Specific immunotherapy (SIT) is well accepted as the only treatment that may alter the natural course of allergic disease, mainly seasonal allergic rhinitis, asthma and insect sting allergy. Most of the SIT studies have used the standard non-allergoid preparations. However, the optimal duration of SIT is still unknown, though many Guidelines recommend 3-5 years of therapy for patients who have had a good therapeutic response (1). Most clinical trials investigating efficacy and safety of specific immunotherapy are limited to 1-2 years (2, 3, 4). Very limited number of trials studied the long-term benefit of non-allergoid SIT in seasonal allergic rhinitis (5) and not much of evidence exists for allergoid SIT therapy though in a recent controlled study a long-term benefit 12 years after discontinuation of SIT in children was shown (6).

SIT using allergoid preparations has also become an acceptable form of therapy, as this makes the frequency of pre-seasonal injections of between 7-10 and has less incidence of systemic side effects. Though there are some studies over three or more years of allergoid SIT therapy (7, 8), it is not known whether continuation of allergoid SIT beyond 2 years is associated with increased efficacy. In an earlier study of 154 patients with seasonal allergic rhinitis, undertaken in a double-blind, placebo-controlled manner has shown that the high-dose, hypoallergenic grass pollen preparation afforded good efficacy and safety for a two years treatment period (9). The aim of the present investigation was to study the effects of an additional 3rd year of active SIT with the grass pollen allergoid preparation in the same group of patients with seasonal allergic rhinitis and seasonal asthma.

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MATERIALS AND METHODS

In the year 2001, 154 patients with proven grass-pollen allergic rhinoconjunctivitis with or without asthma (GINA step I and II) were included in the study in 10 centres in Germany and Great Britain. During the first two consecutive years between November 2001 and October 2003 the study had had a multi-centre, double-blind, placebo-controlled design. Patients were randomized to either pre-seasonal weekly injections of grass pollen-Allergovit® (n=77) or placebo (n=77) until the expected onset of the grass pollen

season. Eleven patients in the active and 15 patients in the placebo group withdrew before the end of the placebo-controlled part of the study. Demographic data of this cohort, as well as details on skin prick testing, have been previously published (9). In January 2004 the double-blind phase was followed by an open-label active treatment phase. 61 of the initial 66 patients in the active group started treatment during this 3rd year and were included in the analysis (FAS).

The investigational product was the six-grass pollen (*Holcus lanatus, Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, Festuca pratensis*) high-dose hypoallergenic allergoid preparation Allergovit® (42 µg grasses group 5/mL in strength B) from Allergopharma Joachim Ganzer KG (Reinbek, Germany) which was administered pre-seasonally as in the two previous years (9).

All patients recorded daily symptoms and drug requirements on diary cards over periods of 12 weeks during the pollen season (from 15 May to 7 August). The primary end-point was the area-under-the-curve (AUC) of the daily sum of the symptom medication score (SMS) over a 42-day period (9).

A rhinoconjunctivitis quality of life questionnaire (RQLQ) was included to support the primary efficacy criterion (10). Patients documented their 'quality of life' on diary cards before the first injection and every 2 weeks during the grass pollen season.

Conjunctival provocation test was conducted according to Corrigan et al. (9) with increasing concentrations from 0 to 5,000 BU/mL into alternate eyes at 10-min intervals. Immediate conjunctival sensitivity was recorded as the dose that induced a minimum of irritation/pruritus and redness/hyperaemia. The tolerated grass pollen allergen concentration at the end of the pollen season was calculated for each patient.

Grass pollen-specific serum IgG4 antibody concentrations were measured immediately before and after pre-seasonal treatment periods in one centre (21 patients).

Information on regional pollen counts were obtained from the 'Stiftung Deutscher Polleninformationsdienst' (Bad Lippspringe, Germany) and by the 'National Pollen Research Unit' (University of Worcester, UK) with a pollen count station in London. Most of pollen stations reported pollen counts of at least 20/m³ on at least 21 individual days.

Differences between the different treatment years were tested by a two-tailed Wilcoxon-Mann-Whitney *U*-test.

RESULTS

All 61 patients with IgE-mediated seasonal allergic rhinoconjunctivitis with or without seasonal asthma (GINA step I or II) completed the third year of pre-seasonal treatment of the six-grass pollen preparation. Patients received an average of 9 injections (median) during the third treatment year.

Clinical efficacy:

■ **Symptom medication score (SMS):** Figure 1 shows that SMS was further improved by pre-seasonal treatment in the 3rd year. Median AUC of combined symptom medication score was significantly reduced from 174.3 score points after the second treatment year in 2003 to 131.0 score points in the grass pollen season of 2004 (p=0.0155). The symptom score was significantly reduced from 144.8 score points after 2 years to 102.0 score points in the third year (p=0.0135). There was also a tendency for reduction of medication score although the difference did not reach significance because of the low intake of medications for

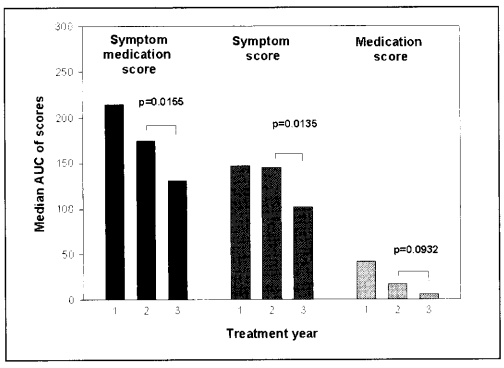


Figure 1: Symptom medication score (SMS), symptom score and medication score during treatment years 2002 to 2004 in patients treated preseasonally with the hypoallergenic preparation. Median values. Full analysis set (n=61).

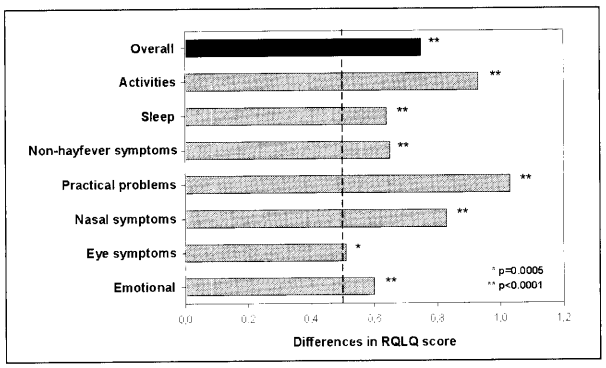


Figure 2: Impact of prolonged specific immunotherapy on quality of life. Differences in mean RQLQ during the grass pollen season between the second and third year of therapy (2003 and 2004) are shown. Dashed line corresponds to a difference of 0.5 points in the RQLQ score which is regarded as clinically relevant according to Juniper et al., 1996 (11).

year two and three. A large proportion of patients (n=26, 42.6%) did not need any anti-allergic medications during the pollen season in 2004. The grass pollen counts were comparable in 2003 and 2004.
Analysis of the sub-group of patients suffering from bronchial asthma (GINA step I and II) (n = 11) showed a reduced symptom medication score of 108.0 in 2004 compared to 167.0 in 2003 (median).

■ **Rhinoconjunctivitis quality of life questionnaire (RQLQ):** During the first two years of the study quality of life had shown a greater improvement in all seven domains in the active group by comparison with the placebo group. A 3rd year of pre-seasonal SIT with the grass pollen allergoid further improved quality of life. There were significant differences for all seven individual domains (activities, sleep, non-hay-fever symptoms, practical problems, nasal symptoms, eye symptoms, emotional) and for overall RQLQ between the second and the third treatment years. The improvements of all individual domains and the overall RQLQ for the year 2004 by comparison with 2003 were ≥ 0.5 points and therefore considered to be clinically relevant (11) (see fig. 2).

■ **Conjunctival provocation test:** Following the third year of pre-seasonal SIT, 85.2% of the patients had higher threshold dose for the conjunctival provocation test conducted after the pollen season reflecting a further improvement of conjunctival reactivity during the course of therapy without reaching statistical significance when compared with the second year (see fig. 3).

■ **Grass pollen specific IgG4:** During the 3rd year of SIT the levels of grass pollen specific IgG4 remained increased by comparison with pre-treatment levels (see fig. 4).

SAFETY

Analysis was performed on the double-blind phase. The allergoid was well tolerated and the side-effects were those typically seen in association with subcutaneous SIT (9). Local reactions were reported after 5.5% of injections in actively treated patients. Five actively treated patients experienced systemic reactions including urticaria, wheezing and itching of eyes, compared to 2 placebo patients. There were no treatment related serious adverse events including anaphylaxis. These results reflect the market experience.

DISCUSSION

Most clinical studies on SIT are limited to a duration of 1 to 2 years (2, 3, 4, 12, 13). This applies to perennial application of depot preparations as well as pre-seasonal application of hypoallergenic preparations. Generally, a significant efficacy can already be observed after the first year of SIT. Until now, using allergoid preparations, there are few data available to indicate whether therapy of more than 2 years duration affords further clinical improvement. Nevertheless, International Guidelines (14, 15) and the WHO Position Paper (1) recommend a therapy duration of 3-5 years although the evidence was mostly based on non-allergoid preparations given throughout the year rather than pre-seasonal administration.
Several clinical trials have already demonstrated the benefit of SIT on quality of life in patients with allergic rhinitis and asthma (9, 16). This is the first study investigating the influence of a pre-seasonal short-term immunotherapy with a high-dose, hypoallergenic preparation for three years on quality of life.

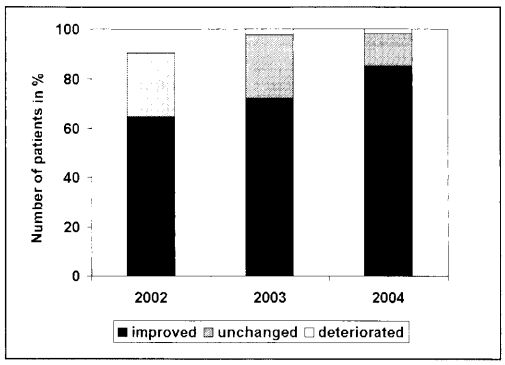


Figure 3: Changes in tolerated allergen concentration in conjunctival provocation testing comparing values before SIT and after 1, 2, and 3 years of therapy. Full analysis set (n=61).

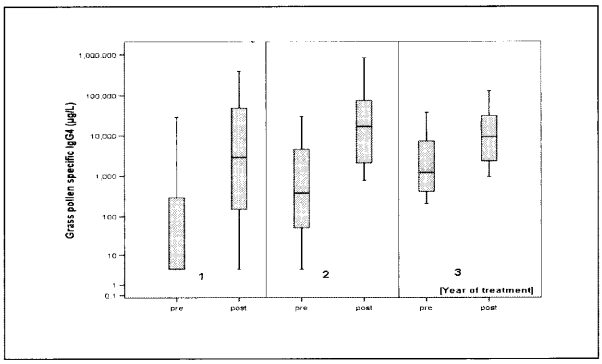


Figure 4: Serum specific IgG4-antibodies after 1, 2, and 3 preseasonal short courses of SIT with grass pollen allergoid before starting SIT (pre) and during the pollen season (post). Boxplots without outliers and extremes (n=21).

The double-blind, placebo-controlled phase of the study for two years with 154 patients provided proof of efficacy and safety of specific immunotherapy with the grass pollen allergoid (9). SMS showed a significant difference between the active and placebo groups after the first (p=0.026) as well as after the second (p=0.018) year of therapy in favour of the high-dose, hypoallergenic preparation. After the 3rd year SMS was further improved significantly (p=0.0155 3rd versus 2nd year of therapy).

There was a significant reduction of the medication score from median AUC of 42 after the first year of SIT to 17 after the second year of SIT (p=0.007) (9). The medication score could be further reduced to an AUC of 6 by the third year of SIT without reaching significance. Moreover, the fact that 42.6% of patients did not require any anti-allergic medication during the grass pollen season in 2004 emphasises the cost-benefit ratio of specific immunotherapy. A previous economic evaluation of SIT with the Allergovit® versus symptomatic treatment showed that SIT for 3 years is economically advantageous in pollen-allergic patients (17).

In addition the symptom score was significantly reduced by comparison with the previous two pollen seasons (p=0.0001 vs. 2002; p=0.0135 vs. 2003). This fact is especially interesting, because the grass pollen counts were comparable for all three years of the study period. Clinical improvements were also reflected in improved quality of life and conjunctival provocation testing.

Grass pollen allergen specific IgG4 levels could be boostered by the 3rd year of SIT to similar levels as in the previous years. This increase is clearly related to the effect of SIT as shown by a previous investigation in pollen allergic patients with and without SIT (18). In pollen allergic patients without SIT no significant differences in specific IgG subclasses could be observed during the pollen season in comparison to outside pollen season. The increases in IgG4 clearly demonstrate the immunogenic activity of the high-dose, hypoallergenic preparation.

A recent clinical study proved the long-term efficacy of specific immunotherapy of a short-term pre-seasonal application of Allergovit® in children with seasonal rhinitis (6). Reductions in symptom medication scores, asthma prevalence and onset of new sensitizations were still present 12 years after discontinuation of SIT. The results of this study support the recommendations of national and international academies for allergology to perform specific immunotherapy over a period of at least 3 years. Despite achieving significant reductions in allergic symptoms and use of anti-allergic medication during the first two year study period, the present study clearly demonstrates that a third year course of pre-seasonal application of hypoallergenic preparations results in additional benefit for the patients.

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