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Sustained clinical efficacy of sublingual immunotherapy with a high-dose grass pollen extract

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KEY WORDS

Sublingual immunotherapy; grass pollen; high-dose preparation; symptom score; medication score; well days; efficacy; safety; sustained efficacy

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SUMMARY

Background: Sublingual immunotherapy (SLIT) with a high-dose 6-grass pollen SingleDose preparation was shown to be effective and safe in a 2-year randomized, double-blind, placebo-controlled trial. **Objective:** We evaluated the effect of the third year of SLIT in comparison to the second year. **Methods:** 46 grass pollen-allergic patients who had received active treatment for 3 consecutive years were included in the safety set. Diary data from 39 subjects were evaluated to calculate symptom and medication scores as well as 'well days'. **Results:** Symptoms and medication intake further decreased in the third year of SLIT during the grass pollen season in comparison to the previous years and the number of 'well days' increased accordingly. No serious adverse events occurred during the three years of SLIT. **Conclusion:** The third year of SLIT with the high-dose 6-grass pollen preparation results in sustained and even further increased clinical efficacy.

Introduction

Efficacy of sublingual immunotherapy (SLIT) has been controversial in the past (1). Due to novel products with increased allergen contents which have shown clinical efficacy in large controlled clinical trials the acceptance of such products for the treatment of allergic rhinitis has been revisited. However, until to date most clinical trials applying sublingual immunotherapy (SLIT) with grass pollen prepa-

rations are limited to a duration of 1 to 2 years (2-4). Therefore, information is limited whether and to what extent a third year of SLIT can further improve efficacy. The high-dose 6-grass pollen preparation used in this study was shown to be effective and safe in a randomized, double-blind, placebo-controlled (DBPC) trial for two years (5, 6). The aim of the present evaluation was to study whether an additional third year of SLIT would lead to sustained or even further increased clinical efficacy.

Material and Methods

The present trial was performed in a DBPC multi-centre design with 185 grass pollen allergic adults suffering from rhinitis or rhinoconjunctivitis with or without asthma. Patients were randomized to a high-dose 6-grass pollen (*Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Festuca elatior*) SingleDose preparation (AllerSlit® forte) (Allergopharma Joachim Ganzer KG, Reinbek, Germany) (n=94) or placebo (n=91). The maintenance dose contained 40 µg group 5 allergen, as measured in an enzyme-linked immunosorbent assay (ELISA) in house system. After dose escalation on the first day at the investigator's site the study solution was self-administered daily. After a baseline year in 2003, patients received treatment for two years in a double-blind design (2004 and 2005) while the subjects received the active preparation unblinded in 2006. Patients were included if they had an IgE-mediated grass pollen allergic rhinitis or rhinoconjunctivitis ($\pm$ bronchial asthma (GINA I or II)), confirmed by a positive skin prick and conjunctival provocation test result and specific IgE to grass pollen. Additionally, patients had to report rhinitis or conjunctivitis during the baseline period. Exclusion criteria were in accordance with those in the EAACI position paper (7). For further details on inclusion and exclusion criteria, patients' characteristics and patient flow see (5, 6).

Patients recorded symptoms and medication intake every day during the grass pollen season. Overall, 10 single conjunctival, nasal, and bronchial symptoms were evaluated with 0 to 3 score points each. Therefore the maximum symptom score was 30. Medication was scored according to drug class and dosage administered. The following order of rescue medication was permitted: topical levocabastine nasal spray and eye drops for mild to moderate symptoms and loratadine or cetirizine dihydrochloride tablets (10 mg) for more severe symptoms. Lower airway symptoms could be treated with salbutamol sulphate as required or inhaled corticosteroids (up to 400 µg of budesonide equivalent). In case of more severe symptoms, investigators could prescribe oral corticosteroids for 1 to 7 days. The primary endpoint was the change in the area under the curve (AUC) of the daily sum of the symptom-medication score (SMS) during a 42-day evaluation period (10 days before and 31 days after the peak pollen count per region and per center). The number of 'well days', defined as days with a symptom score ≤ 4 and without use of any rescue medication, was evaluated, as well. Compliance was calculated by the number of days with or without drug intake.

The absolute and relative differences of AUC of daily sum of SMS between 2005 and 2006 and baseline and 2006, respectively, were calculated for each patient. A univariate t-test was used to investigate if the absolute differences between 2005 and 2006 show further improvement. The adverse events were coded with MedDRA, version 8. Out of the 49 actively treated subjects from Germany and Poland in the Main Data Set (MDS) during the 2-year DBPC phase (5) we report here on patients who had received at least one dose of study medication in the third year of SLIT (follow-up set; n=46). Patients having at least 1 efficacy evaluation of the primary end point available were included for efficacy evaluation (n=39) (Figure 1). Reasons for drop out were: poor compliance, removal, adverse event without relationship to the study medication, or too much diary data missing.

Results

No major differences were seen between the grass pollen seasons in both treatment years (37 days with at least 20 pollen/m³ in 2005 and 32 days in 2006). The day of grass pollen peak in the different centres varied between June 8th and June 14th in 2005 and between May 28th (Germany) and July 1st (Poland) in 2006.

Figure 2 shows that allergic symptoms as well as the need of rescue medication further decreased in the 3rd year of SLIT in comparison to the year before. 12 patients did not need any anti-symptomatic therapy during the observation

Figure 1 - Flow diagram during the 3 years of the study. DBPC=double-blind, placebo-controlled.

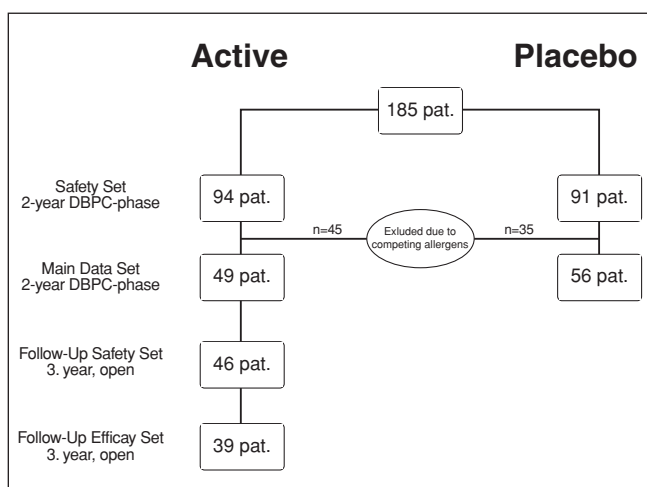
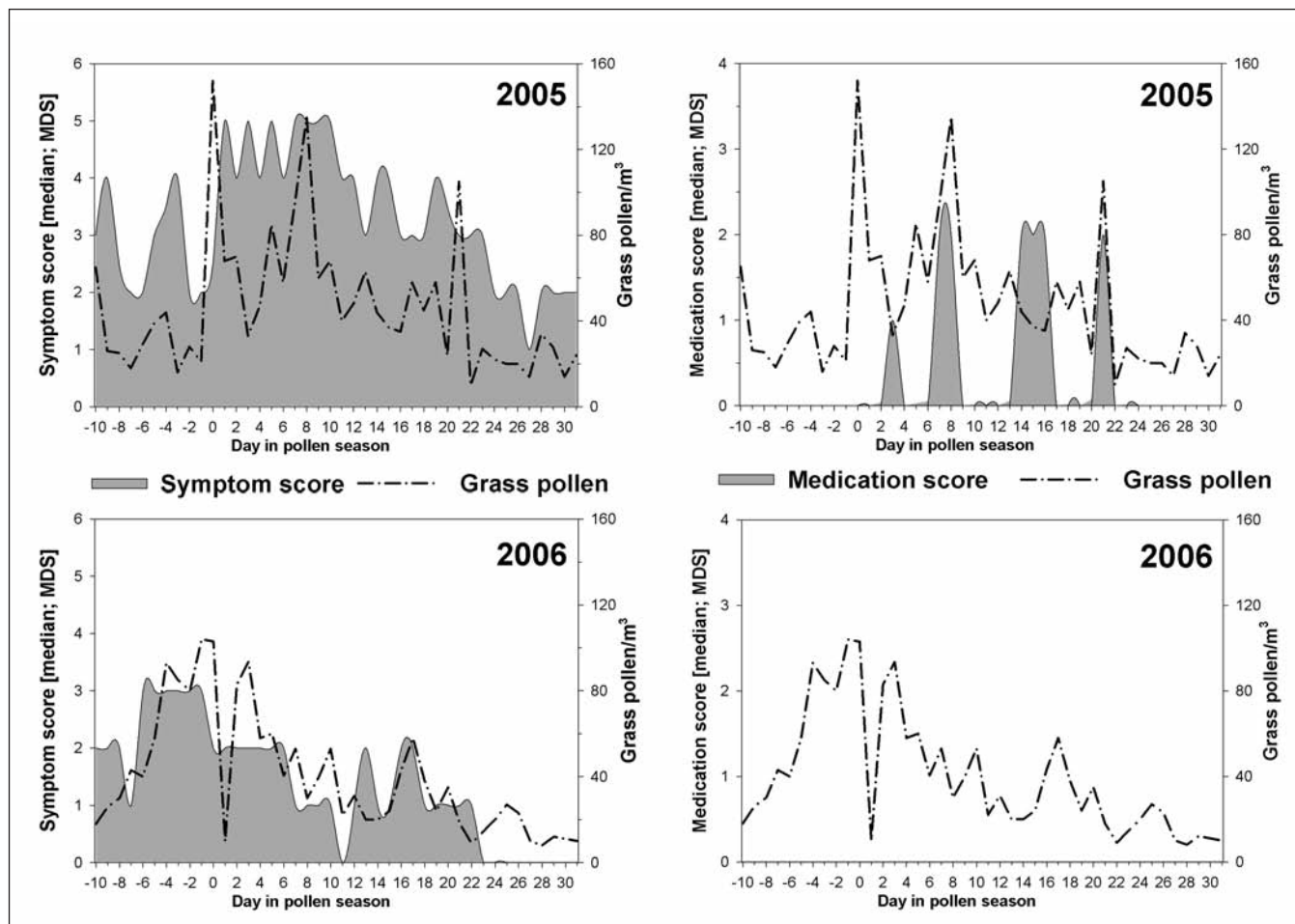


Figure 2 - Course of daily median AUC of the symptom score (left) and the medication score (right) over the 42-day evaluation period in 2005 (2nd treatment year; above) and 2006 (3rd treatment year; below). The median pollen count is shown as dash-dot line. The graph of the median medication score in 2006 is a 'zero line'.



period in 2006. There were significant improvements in mean AUC values for symptom and medication score in the 3rd in comparison to the 2nd year of SLIT (table 1). The overall mean of relative improvement after the third treatment year versus baseline was 65% for the symptom score and 68% for the medication score.

Mean AUC of symptom-medication score (SMS) was 308.9 (SD 282.10) in 2005 and 147.5 (SD 145.63) in 2006 resulting in a mean relative reduction of 34% from the 2nd to the 3rd treatment year ($p < 0.0001$) while the total reduction from baseline to the 3rd treatment year was 66%. The median number of 'well days' increased from 6 days refer-

Table 1 - Total mean AUC of symptom- and medication score during the 2nd and 3rd treatment year during the 42-day evaluation period

	2005	2006	p-value	% improvement
Symptom score	184.65 (SD 156.56)	92.18 (SD 80.04)	<0.0001	-34%
Medication score	124.22 (SD 145.65)	55.34 (SD 90.19)	0.0006	-36%

ring to the 42-day observation period at baseline in 2003 to 19.5/42 days at the end of the double-blind phase in 2005 and further to 35/42 days in 2006 (Figure 3).

The high-dose 6-grass pollen preparation was safe in the third treatment year. Data from 46 patients of the safety set were available in the third year of active treatment. Three patients (6.5%) described at least one adverse event (AE) with probable, possible or definite relationship to the study medication like nausea, oral pruritus, oral administration complication, nasal discomfort, increased viscosity of bronchial secretion, sneezing, or throat irritation. No serious drug-related AE occurred.

Compliance was high throughout the whole study. The mean percentage of days with an intake of 100% of study medication was stable with 82% in the first treatment year 2004, 88% in the second year, and 91% in the third year of SLIT. The mean percentage of days with no intake of the study medication remained low with 3% in 2004, 4% in 2005 and 2% in 2006.

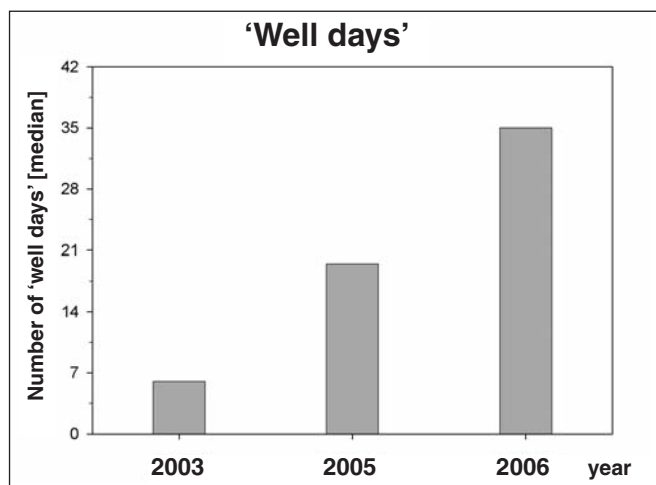
Discussion

Though it is widely accepted that 3 to 5 years of SIT are generally sufficient to achieve a sufficient clinical response the exact optimal duration of SIT is not known (8). Even for the long-established subcutaneous immunotherapy (SCIT) this question cannot be definitely answered for all allergens and products yet (9). Studies addressing this subject are generally small and cover a wide range of patients

of varying ages and disease severity, though it is difficult to come to a definitive conclusion. A recent investigation showed an additional benefit of a third year of SCIT with a hypoallergenic 6-grass pollen preparation (10). There are only three DBPC studies with longer treatment periods than 2 years concurrently investigating if the third year of SLIT can further increase efficacy in comparison to the second treatment year (11-14). A DBPC trial with a *Phleum pratense* tablet showed no improvement in mean symptom and medication scores during the second and third year when compared to the respective previous year (11, 12). Another study using a 5-grass pollen liquid formulation showed slightly stepwise reduced combined symptom and medication scores over the three pollen seasons (13). This improvement was solely caused by changes in symptom scores since there were no significant differences between active and placebo in medication scores in any treatment year. The third trial used a house dust mite extract in a one year DBPC trial with additional active treatment for the following two years for all patients (14). There were no differences in symptom and medication scores during the first year DBPC phase. Intra-group comparison in the active group yielded a trend towards reduction for symptom and medications scores for the active group in the second year while the reduction became significant in the third year. Two additional trials using house dust mite extracts which were not performed in a DBPC design confirmed that a third year of SLIT may enhance efficacy (15, 16).

The trial on hand with the high-dose sublingual 6-grass pollen preparation was performed in a randomized DBPC-design with a baseline period in 2003 and a treatment phase for two years (5, 6). During the DBPC phase, the median AUC of SMS was reduced in the active group already after 3 to 4 months of SLIT whereas it remained nearly unchanged for the placebo group. In the second year the change of the median AUC of SMS in the active group showed a significant and clinically relevant improvement, while there were almost no changes in the placebo group ($p=0.002$ active vs. placebo). In the third year all subjects received active treatment not to withhold the active preparation to the placebo group for longer than absolutely necessary. The data on hand suggest a progressive increase in efficacy in patients treated actively for three years. Patients had less allergic symptoms, used less medication and had a better quality of life ('well days') during the grass pollen season. Moreover, the preparation was safe for the whole treatment period. The compliance was high throughout the three treatment

Figure 3 - Number of 'well days' at baseline (2003), at the end of DBPC phase (2005), and during the grass pollen season in the third treatment year (2006).



years. Apparently patients estimated the preparation as “convenient” and “effective” giving no judged reason for discontinuation (17).

In conclusion, a sustained clinical effect during 3 years of treatment is suggested for this high-dose 6-grass pollen SLIT preparation. The second and third year of treatment resulted in an increased and clinically relevant benefit for the patients (‘well days’).

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