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3-years' long-term effect of subcutaneous immunotherapy (SCIT) with a high-dose hypoallergenic 6-grass pollen preparation in adults

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Key words

Long-term effect, grass pollen, subcutaneous immunotherapy, allergoid, adults, high-dose hypoallergenic preparation, prevention of new sensitizations, quality of life, symptom-medication score, disease-modifying effect

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Summary

Background: *Most clinical trials investigating preventive and disease-modifying effects of SCIT were performed in children for only a few allergen products. In this study we observed adult patients 3 years after the completion of treatment with a high-dose hypoallergenic 6-grass pollen preparation.* ***Methods:*** *A double-blind, placebo-controlled (DBPC) trial had proven efficacy and safety of a high-dose hypoallergenic 6-grass pollen preparation in adults (1). 3 years after termination of a 3-years' pre-seasonal SCIT symptom and medication scores, quality of life, and the development of new sensitizations were investigated. Patients who fulfilled the same inclusion and exclusion criteria at start of the DBPC study and who had not received SCIT in the meantime served as a control group.* ***Results:*** *Symptom-medication score and symptom score were significantly reduced in the Ex-SCIT group in comparison to the control group (p=0.000). Quality of life (RQLQ) was significantly better in the Ex-SCIT group (p=0.000). 20 (77%) subjects of the Ex-SCIT group did not show any new sensitizations against a defined allergen panel in comparison to 3 (23%) patients of the control group.* ***Conclusion:*** *This 3-years' controlled follow-up study in adults demonstrates long-term improvements in symptom-medication score and quality of life and reduced onset of new sensitizations after completion of SCIT.*

Introduction

Allergen-specific immunotherapy (SIT) represents the only treatment that might alter the natural course of disease (2). Using an appropriate allergen product and a correct indication, immunotherapy can significantly reduce the severity of the allergic disease, reduce the need for anti-allergic drugs, and improve quality of life of patients (2, 3). As to the recently published EAACI task force report on 'dose-response relationship in allergen-specific immunotherapy' most dose-ranging studies reported a dose-response relationship for clinical efficacy indicating that efficacy increases with higher allergen doses (4). The development of so called "hypoallergenic" preparations which retain T cell reactivity but can be used at high dose will permit safer but more effective application of SIT (5). In 1971 allergoids as the first hypoallergenic preparations were introduced by modifying the allergen extracts with formaldehyde (6). The pollen allergoid Allergovit® was one of the first commercially available hypoallergenic preparations. The WHO position paper suggests 5 – 20 µg of major allergen per injection as an optimal maintenance dose while low dose im-

munotherapy is ineffective (4). Since the maintenance dose of 0.6 ml of Allergovit® grass pollen contains 25 μg_{eq} grasses group 5 (determined at the last measurable production step) this preparation is high-dosed. Several clinical trials confirmed efficacy and safety of the high-dose hypoallergenic pollen preparation Allergovit® in adults and children (7-10). A double-blind, placebo-controlled trial with Allergovit® 6-grass pollen in 154 adult patients showed a significant difference of 26.6% in symptom-medication score (SMS) between active and placebo groups after the first treatment year which was improved to 48.4% in the second year (1). A third open-label treatment year was able to further reduce SMS (11). Quality of life constantly improved during the 3-years study. Therefore, the high-dose hypoallergenic pollen preparation was shown to be highly effective. No serious adverse events were observed indicating a good tolerability.

Up to now, there are some studies pointing out that SCIT may have the potential to provide long-term benefit following its termination and may prevent either disease progression and/or onset of new allergic sensitizations (2). Only a controlled study design is able to confirm that further improvement in disease severity after termination of SCIT is unbiased, e.g. by spontaneous remission, different pollen exposition, or different regions. Appropriate trials were mainly performed in children (12-16) and the number of trials including adults is limited (17-19) since long-term immunomodulation might be age-dependent (20).

Aim of this prospective follow-up trial was to investigate long-term effects of SCIT three years after termination of a 3-years' pre-seasonal application in adults with grass pollen allergy.

Material and methods

154 grass pollen allergic adults (18-60 years) with rhinoconjunctivitis with or without asthma (GINA I/II) had been included in a 2-years' randomized, double-blind, placebo-controlled multi-centre trial. Patients received weekly pre-seasonal subcutaneous immunotherapy (SCIT) with either Allergovit® 6-grass pollen (n=77) or placebo (n=77). Both groups received active treatment in the third treatment year. For information on demographic data and inclusion/exclusion criteria see reference 1 (1).

For the prospective follow-up investigation three years after cessation of SCIT 31 patients of the two greatest centres in Germany who had received 3 years of active treatment from 2002 to 2004 were included. 4 patients withdraw due to lack of time and 1 was lost for follow-up. Therefore 26 subjects were included in the full analysis set (FAS). Since patients from the initial placebo group had received SCIT in the meantime according to study protocol they could not serve as a non-hyposensitized control population. Therefore 13 grass pollen allergic subjects in one of these two centres who had been screened in 2002 to take part in the study but who declined to receive SCIT were observed as a control group (FAS). The inclusion/exclusion criteria were the same as those used in the original SCIT study. Not any form of SIT had been performed in these patients until inclusion into the control group. Patients in both groups had equal access to the same rescue medication and underwent the same follow-up assessment. For demographic data of the follow-up groups see Table 1.

Patients recorded symptoms and medication intake during the 2007 grass pollen season in a diary to calculate SMS. Nine different nasal, conjunctival, and bronchial symptoms were assessed on a scale from 0 (no symptoms) to 3 (severe symptoms). Patients had access to anti-symptomatic drugs like topical alpha- or beta-mimetics, topical and oral antihistamines, topical nasal and corticosteroids, disodium chromoglycate eye drops, and short-term treatment with systemic corticosteroids.

For further details see reference 1 (1). Quality of life was evaluated by means of a standardized questionnaire [RQLQ acc. to (21)]. Area-under-the-curve (AUC) of SMS and quality of life were calculated for a 42-day grass pollen period (1). 'Well days' were defined as days without intake of rescue medication and a symptom score ≤4 of a maximum of 27. Additionally, skin prick testing was performed with a panel of seasonal and perennial allergens (grass pollen, tree pollen, cat, and dog epithelia, house

Table 1 - Demographic data in 2007

	Ex-SCIT group	Control group
Number of patients (n)	26	13
Age [years]		
Mean	41.7	33.9
Min – max	24 - 63	19 - 47
Gender		
Male	7	6
Female	19	7
Sensitization in skin prick testing 2002		
to grass pollen only	11 (42.3%)	9 (69.2%)
to grass pollen and others	15 (57.7%)	4 (30.8%)

dust mites, moulds) (Allergopharma Joachim Ganzer KG, Reinbek, Germany) at screening and before the start of the grass pollen season in 2007. A wheal diameter of at least 3 mm was considered positive. New sensitization in 2007 was defined as a positive reaction in skin prick testing to at least one of the allergens which had been tested negative (wheal diameter <3 mm) at screening.
Information on pollen counts was obtained from the 'Stiftung Deutscher Polleninformationsdienst' in Bad Lippspringe, Germany.
Differences between the two groups were tested by a two-tailed Wilcoxon-Mann-Whitney U-test resp. Student's t-test.

Results

Pollen counts of at least 20/m^3 occurred on 22 individual days in 2007.
Median AUC of SMS during the 42-day observational period for the Ex-SCIT group remained very low three years after cessation of SCIT (44.0) and was significantly lower than for the control group (237.0) (p=0.000). The same was true for the median AUC of the symptom score (24.5 for the active group, 209.0 for the control group) (p=0.000) while that for the medication score did not significantly differ between the two groups (2.3 vs. 6.0) (Fig. 1). 6 of the 26 (23%) patients of the former SCIT group were completely free of symptoms and did not use any medication while this was not the case in any subject in the control group.
The median number of 'well days' for the Ex-SCIT group was nearly three times higher [39/42 (93%)] than for the control group [14/42 (33%)].
Mean overall RQLQ score was significantly lower in the Ex-SCIT group (0.9) in comparison to the control group (2.6; p=0.000) resulting in a difference of 65%. Values for all seven domains were much better for the Ex-SCIT group than for patients who had not received SCIT with inter-group differences between 55% and 69% (Fig. 2).
At screening 11/26 (42.3%) patients of the Ex-SCIT group and 9/13 (69.2%) in the control group were monosensitized to grass pollen in skin prick testing. In comparison to screening, 20 (77%) subjects of the Ex-SCIT group did not show new positive skin prick test results in 2007 compared to 3 (23%) patients of the control group. Skin prick testing with the 6-grass pollen extract changed to negative with a wheal smaller than 3 mm in diameter in 14/26 (53.8%) patients who had received SCIT and remained unchanged positive in all 13 subjects of the control group (100%).

Discussion

Various studies have suggested that allergen-specific immunotherapy may have a long-term effect (13, 17, 18), may protect from development of new sensitizations (13, 15, 22), and may prevent the development of asthma in children with allergic rhinoconjunctivitis for several years

Figure 1 - AUC of Symptom-medication score (SMS), symptom score, and medication score for the Ex-SCIT group (grey) and the control group (white) during the 42-day observational grass pollen period. The boxes show the median value (band), 25th (bottom) and 75th percentile (top), the error bars indicate 10th (bottom) and 90th percentile (top).

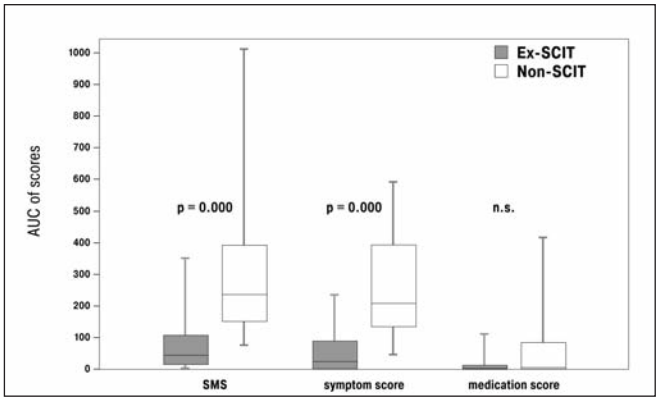
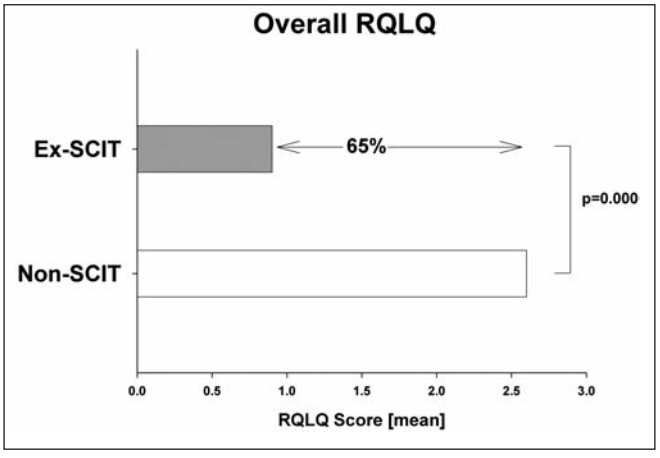


Figure 2 - Mean total RQLQ scores according to Juniper (17) for the Ex-SCIT group (grey) and the Non-SCIT group (white) that has not received SCIT during the 6-years' observation period.



after termination of SIT (12). But there are only few clinical trials which proved efficacy and safety of SCIT in a double-blind, placebo-controlled design and subsequently investigated the long-term effect (17, 23). In general, ethic committees do not approve to retain the former placebo-treated group from SCIT after the placebo phase to have a control group for follow-up. So it is difficult to find a comparable control group that did not receive SCIT but only anti-symptomatic treatment. Therefore it was decided to select patients who were screened for the double-blind, placebo-controlled trial but declined due to personal reasons. Because these patients did not receive any form of SCIT during the 6-years' evaluation period they could serve as a control group. The same procedure was performed in other trials investigating the long-term effect after SCIT (17, 23).

Compared to anti-symptomatic treatment alone some controlled trials showed that SCIT is able to significantly prevent the development of new sensitizations for the time of treatment (22, 24) while other trials failed to show this effect (25, 26). Additionally, only with SCIT the preventive effect is even lasting after the treatment period but the mechanisms are still unclear. In total, SIT seems not only to induce the immune response towards the treated allergens but also to commit the immune system non-specifically to a system tolerating allergens (20). It is well established that the risk for further sensitizations in children increases with age and that long-term immunomodulation might be age-dependent (20, 27). Therefore, most trials investigating the preventive effect of SCIT with a focus on new sensitizations were performed in children (15, 16, 22). Moreover, corresponding trials were mainly performed in monosensitized patients (15, 16, 28) because SIT is accepted to be more effective in monosensitized patients than patients suffering from multiple sensitizations (4, 29). Accordingly, only monosensitized subjects were included in the only trial proving a preventive effect on new sensitizations in adults after 4 to 6 years follow-up (28). The trial on hand therefore is the first trial investigating this aspect in mainly polysensitized adults: 15 of the 26 patients (58%) showed sensitizations to more than one allergen in skin prick testing at inclusion time. However, the number of patients who developed new sensitizations during the 3 year's follow-up was much lower in the Ex-SCIT group than in the control group which had received anti-symptomatic treatment only. These results confirm that seen in children six years after termination of SCIT with the same high-dose hypoallergenic grass pollen preparation (14).

It is worth discussing that more than half of the patients of the former SCIT group changed skin test reactivity to the grass pollen extract to smaller than 3 mm in diameter which is defined to be negative. Since the skin prick test reactivity to the positive control (histamine dihydrochloride) remained in the same range like at screening this effect was obviously not related to the intake of drugs with H1 blocking effects. Various SCIT-trials using quantitative skin tests showed reduced reactions to the respective allergen after active treatment (30-32). Our trial did use the marketed skin test concentration and therefore could only discriminate between positive and negative result but nevertheless could show improvement in skin test reactivity to grass allergen even 3 years after SCIT with this straight forward approach. Future trials determining skin test reactivity quantitatively during the long-term follow-up might provide more information on the development of skin reactivity.

Since long-term immunomodulation might be age-dependent (20, 27) it remains questionable if SCIT may also have a long-lasting effect on symptoms and intake of medication in adults. In this trial with grass pollen-allergic adults, symptom-medication score, symptom score and 'well days' are significantly reduced in the former actively treated group compared to the control group three years after cessation of SCIT ($p=0.000$). The medication score tended to be reduced without reaching significance. This missing effect on the use of medication while symptoms were significantly reduced might be caused by the variation and its coefficient which are much higher for medication that differences are more difficult to show. There are some trials which proved a long-term effect in adults for up to 9 years after starting SCIT (17, 19, 23, 33, 34). In the only two trials which also investigated symptom and medication scores (17, 23) in an identical design the improvement in scores for the Ex-SCIT groups was similar to the results we found. Nevertheless, both trials did not investigate the influence of SIT on the development of new sensitizations.

To our knowledge the trial on hand is the first investigating quality of life by means of the standardized RQLQ during long-term follow-up. Quality of life was significantly better for the former actively treated group than for the control group ($p=0.000$). The inter-group difference of mean total RQLQ score and all seven single domains ranged between 55% and 69% being therefore clinically relevant since a 20% difference between active and control or placebo group can be considered a clinically relevant improvement (35) which is in accordance with the World Allergy Organization taskforce recommendations (36).

The present study has some limitations since only the two

centres with the largest number of patients from the original 10 centres were selected. Additionally, the small number of patients observed and the open design are limiting. Nevertheless, this trial is the first concurrently investigating efficacy by means of symptom-medication score, quality of life, and the preventive effect on the development of new sensitizations in adults. Further observation of the patients will show if this effect lasts for further years.

Conclusion

A 3-years' long-term effect was shown for adults after completion of three pre-seasonal courses of SCIT with a high-dose hypoallergenic 6-grass pollen preparation in symptom-medication score, quality of life, and development of new sensitizations.

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