

Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood

Background: In a previous controlled study, we demonstrated that preseasonal grass pollen immunotherapy for 3 years was effective in children. Moreover, a significant clinical benefit could still be observed 6 years after discontinuation of specific immunotherapy (SIT). In the current study, we examined the same group of patients again to investigate whether there is a prolonged benefit 12 years after SIT is stopped.

Methods: Twenty-two patients with previous SIT (from 1989 through 1991) or standardized seasonal pharmacotherapy only were prospectively followed during the grass pollen season of 2003. Primary end points were symptom score, medication use, and combined symptom and medication score. In addition, skin prick test reactivity, development of new sensitizations, and prevalence of seasonal asthma were evaluated.

Results: Total hay fever symptom score ($P < 0.03$), use of medication ($P < 0.05$), and combined symptom and medication score ($P < 0.03$) remained lower in patients with previous SIT when compared with the control group. Decreased immediate skin response to grass pollen returned 12 years after cessation of SIT. The percentage of new sensitization, however, continued to be significantly smaller in patients with previous SIT (58%) compared with the controls (100%, $P < 0.05$). There was a tendency for lower prevalence of seasonal asthma in the post-SIT group ($P = 0.08$).

Conclusion: This prospective controlled prolonged follow-up study demonstrates the ongoing clinical benefit 12 years after discontinuation of SIT. Furthermore, the reduction in onset of new sensitization, which was found 6 years after discontinuation of SIT, is sustained 6 years later.

**P. A. Eng¹, M. Borer-Reinhold¹,
I. A. F. M. Heijnen², H. P. E. Gnehm¹**

¹Department of Pediatrics, Kantonsspital Aarau, Aarau; ²Centre of Laboratory Medicine, Kantonsspital Aarau, Aarau, Switzerland

Key words: childhood; follow up; grass pollen; immunotherapy; natural course.

Dr P. A. Eng
Allergologie/Pneumologie
Kinderklinik
CH-5001 Aarau
Switzerland

Accepted for publication 17 September 2005

New data demonstrate the efficacy of specific immunotherapy (SIT) not only as a therapeutic agent but also as a preventive strategy to reduce onset of new sensitization to nonrelated allergens (1–3), progression from allergic rhinitis to asthma (4, 5), and to improve long-term outcome of already established asthma (3, 6).

However, only limited knowledge exists about the duration of the preventive and therapeutic effects after discontinuation of SIT. The main objectives of this study were to evaluate whether grass pollen SIT in childhood is still effective 12 years after discontinuation and to test whether the reduced onset of new sensitization is prolonged.

Material and methods

Patients and study design

The study population has been described previously (3, 7). Briefly, in 1988 we recruited 28 children with a history of severe grass pollen allergic rhinoconjunctivitis for at least 2 years with or without seasonal asthma but with immunoglobulin (Ig)E-mediated sensi-

tivity to seasonal allergens only (grass pollen with or without tree pollen). Subjects with a history of other allergic disease or sensitization to nonpollen allergens were excluded.

The original study was a nonrandomized controlled open trial. The SIT was proposed to all patients fulfilling the inclusion criteria, but some children and/or their parents declined to receive SIT. These patients were included as controls (3, 7). From 1989 through 1991 patients were either treated with grass pollen depot-allergoids (Allergovit®; Allergopharma, Rheinbeck, Germany) in a preseasonal immunotherapy protocol ($n = 14$) or received standardized pharmacotherapy alone during the grass pollen season ($n = 14$). A first 6-year follow-up study was performed during the grass pollen season of 1997 (3). The present study is a second follow-up study 12 years after discontinuation of SIT, designed as a prospective controlled open study during the grass pollen season of 2003. Except for one subject who could no longer be traced, all patients of the previous follow-up study could be recruited.

Assessments

Primary end points were the presence of symptoms and the need for medication from May 1 until July 31. Symptom scores, medication scores, and combined symptom and medication scores

were calculated exactly as detailed before (3). Secondary end points included skin prick test (SPT) reactivity and allergen-specific IgE to grass pollen (3), assessment of newly developed sensitization by SPT using the same panel of allergens as at study enrollment and at the first follow up (3, 7), and prevalence of seasonal asthma defined as occurrence of at least two of the following symptoms during the grass pollen season: cough, wheeze, dyspnea, and exercise intolerance. In contrast to our previous follow-up study, conjunctival provocation tests were not performed. A substantial number of patients declined to undergo the provocation test resulting in too low numbers of subjects for statistical analysis.

Statistics

The two-tailed Mann-Whitney *U*-test (Statview Software, Cary, NC, USA) was used for comparison between groups regarding symptom and medication scores. Assessment of seasonal asthma and occurrence of new sensitization were compared by means of chi-squared test. A 5% significance level was used.

Results

The two study groups, observed over a total length of 15 years, were matched for gender, age, prevalence of seasonal asthma, and wheal size in response to SPT with grass pollen at study enrolment (Table 1).

Clinical efficacy

Scores for hay fever symptoms ($P < 0.03$), for use of medication ($P < 0.05$) and combined symptom and medication score ($P < 0.03$) expressed as area under the curve for the grass pollen season remained significantly lower in patients 12 years after cessation of SIT compared with the controls. The scores were temporally related to pollen counts (Fig. 1).

Table 2 compares the data of the current 12-year follow up with those of the 6-year follow-up study. In 2003, grass pollen release began at the end of April already and peaked for several consecutive weeks in May and June resulting in an increased number of days with high grass pollen concentration compared with 1997.

Table 1. Characteristics of patients studied from 1988 to 2003

	SIT (1989-1991)	No SIT
Number of patients recruited during 1988	14	14
Median age (years) and range	9.5 (5-16)	9.1 (7-16)
Gender (M/F)	10/4	10/4
Result of skin prick testing at study enrolment*	2.49	2.27
Number of patients at first follow up (1997)	13	10
Number of patients at second follow up (2003)	12	10
Median age (years) and range	23.8 (20-31)	23.4 (22-31)
Gender (M/F)	9/3	7/3

*Values represent the quotient of mean wheal area to grass and mean wheal area of histamine control.

The difference in symptom scores between the two groups was smaller in 2003 when compared with 1997, but still reaching statistical significance. However, in contrast to 1997, control patients used significantly more medication for symptom relief in 2003 than patients in the post-SIT group. Symptom plus medication score remained markedly lower in patients with previous SIT than in controls.

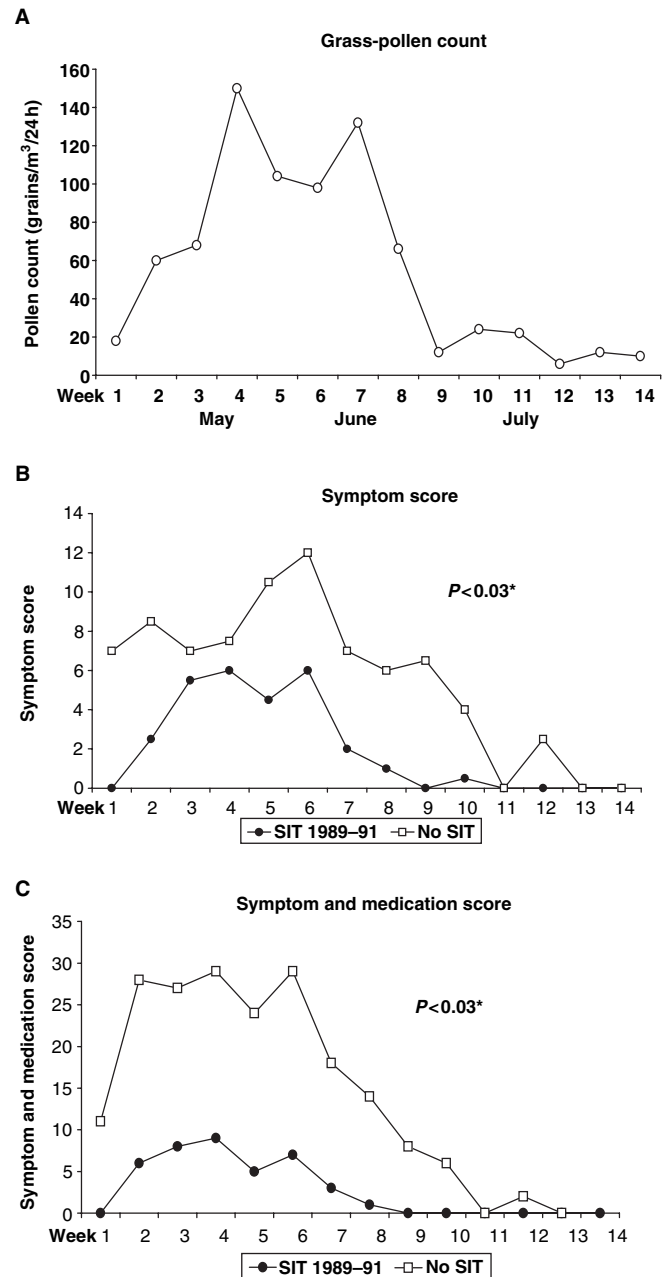


Figure 1. Median weekly pollen count, total hay fever symptom score, and combined symptom plus medication score during the pollen season 2003. **P*-values are for the comparison between the two groups (analysis of the area under the curve). (A) Median weekly grass pollen count; (B) hay fever symptom score; (C) symptom and medication score.

Table 2. Pollen concentration, median scores for total hay fever symptoms, and symptom plus medication scores during the pollen seasons 1997 and 2003

	1997	2003
Number of days with high-grass pollen concentration (>50 grains/m ³ /24 h)	32	43
Median total symptom score (range)		
SIT	45.0 (0–154)	36.5 (0–178)
No SIT	104.0 (42–344)	73.5 (36–546)
<i>P</i> -value*	<0.005	<0.03
Median medication score (range)		
SIT	10.0 (0–141)	15.0 (0–122)
No SIT	30.5 (0–138)	62.0 (4–421)
<i>P</i> -value*	ns	<0.05
Median symptom plus medication score (range)		
SIT	66.0 (0–278)	46.0 (0–300)
No SIT	146.0 (44–764)	167.0 (42–967)
<i>P</i> -value*	<0.005	<0.03

**P*-values are for the comparison between the two groups in 1997 and 2003. Analysis of the area under the curve was performed using the Mann–Whitney *U*-test.

Skin prick tests and specific IgE

The SPT reactivity to grass pollen allergens, which was significantly decreased after discontinuation of SIT in 1991 (7) and at the 6-year follow up in 1997 (3), returned to the magnitude of the controls in the present study (Fig. 2A). There were no differences in the amount of IgE specific for grass pollen between the groups at enrolment (7), at commencement and discontinuation of SIT (7) as well as at the follow-up studies in 1997 and 2003 (data not shown).

Evolution of sensitizations and asthma prevalence

Six years after discontinuation of SIT, a significantly reduced number of patients had developed new sensitizations when compared with the controls (3). This reduction in development of new sensitizations after SIT was confirmed in the current 12-year follow-up study (*P* < 0.05; Fig. 2B). Most new sensitizations occurred to house dust mites, cat, and dog dander. In addition to grass pollen, 40% of the controls and 42% of the actively treated group were sensitized to tree pollen at study enrolment. At the 12-year follow up, the prevalence of sensitization to tree pollen was 90% in the controls and 67% in the post-SIT group.

After discontinuation of SIT, prevalence of seasonal asthma because of grass pollen decreased significantly (7). This reduction was sustained in 1997 (3). In the 12-year follow up there was still a tendency for lower asthma prevalence in the post-SIT group (Fig. 2C), but without reaching statistical significance (*P* = 0.08).

Discussion

The present study assesses two groups of patients 15 years after enrolment for grass pollen SIT or

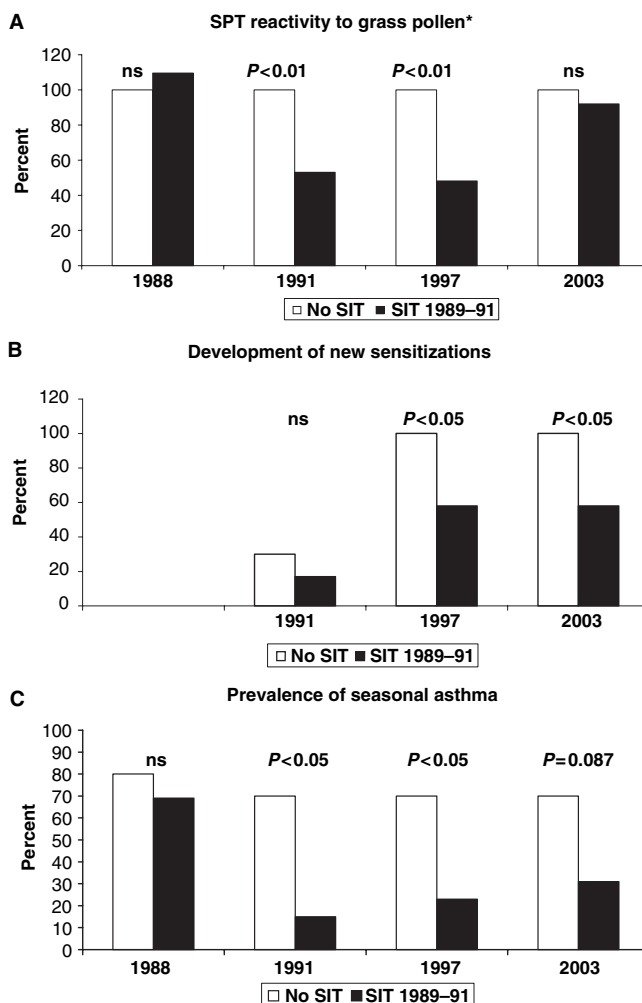


Figure 2. Course of skin prick test reactivity to grass pollen*, development of new sensitizations and prevalence of seasonal asthma due to grass pollen allergy during 1988–2003. (A) Skin prick test (SPT) reactivity to grass pollen; (B) development of new sensitizations; (C) prevalence of seasonal asthma due to grass pollen allergy (*SPT reactivity defined as quotient of mean wheal area to grass pollen and mean wheal area to histamine controls. Values expressed as percentage of SPT reactivity in patients with SIT in relation to controls).

standardized seasonal pharmacotherapy alone. To our knowledge it is the longest follow-up study of grass pollen SIT. The data demonstrate an ongoing clinical benefit 12 years after cessation of 3-year preseasonal SIT with grass pollen allergoids in childhood in terms of both a reduction of hay fever symptoms and use of medication for symptom relief. Furthermore, the reduction in development of new sensitizations to perennial allergens, which has been observed 6 years after cessation of SIT (3), is sustained also in the longer term.

Only a few papers have addressed the long-term effects of grass pollen SIT (3, 5, 8–12). Most studies demonstrate prolonged clinical benefit and some show decreased

immunologic reactivity for 3–6 years after discontinuation of SIT. The majority has been performed in adults (5, 8–12) and some of them were not controlled (5, 8). There is evidence that immunologic reactivity begins to return after 1–3 years (8, 10, 12). In our patients, recurrence of immediate skin reactivity to allergen occurred later than 6 years after cessation of SIT. However, increased reactivity to grass pollen was not accompanied by an increase of symptoms.

Changes in immunologic parameters and provocation tests may be of interest in elucidating mechanisms, but cannot replace clinical evaluation (13). The only parameter estimating clinical efficacy of SIT are reduction in symptoms and use of medication. However, individual patient behavior during the pollen season may be different. Some are using more medication for rapid symptom relief. Others may have decreased symptom perception and subjectively underestimate symptom severity. The addition of weekly combined symptom and medication scores may partly compensate for individual patient behavior. However, a shortcoming of all immunotherapy studies remains that there is currently no objective means to monitor clinical efficacy of SIT.

An important finding of recent studies is the reduction in onset of new sensitization to nonrelated allergens after SIT. Our data are in accordance with the results of two studies performed in children monosensitized to house dust mites. A significant reduction in development of new

IgE-mediated sensitization was observed 3 years after SIT when compared with controls (1, 2). Patients in the present study were observed for a longer period suggesting that onset of new sensitization is not delayed by SIT but may be permanently reduced.

Limitations of the current follow-up study are the small number of subjects and the fact that the original study had no run-in phase and was not double-blind placebo controlled. However, a study design requiring placebo injections in a randomized group of children over prolonged time is difficult to justify. It is also important to note that the selection of patients is essential for outcome of SIT. The observed beneficial long-term effects may not be translated to subjects having a broad spectrum of sensitizations. For example, SIT with multiple allergens was not effective in asthmatic children sensitized to seasonal and perennial allergens (14). Nevertheless, we believe that our results are of importance because more knowledge is needed about the long-term allergen-specific and unspecific immunomodulatory effect of early intervention by SIT in childhood.

In conclusion, this prospective controlled long-term follow-up study demonstrates that both the clinical efficacy and the preventive capacity of grass pollen SIT, observed at the 6-year follow up, is still evident 12 years after discontinuation of SIT when compared with seasonal pharmacotherapy alone.

References

- Des Roches A, Paradis L, Menardo JL, Bouges S, Daurés JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract: VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;**99**: 450–453.
- Pajno GB, Barberio G, De Luca FR, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;**31**:1392–1397.
- Eng PA, Reinhold M, Gnehm HPE. Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy* 2002;**57**:306–312.
- Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;**109**:251–256.
- Jacobsen L, Nüchel-Petersen B, Wihl JÅ, Löwenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts: IV. Results from long-term (6-year) follow-up. *Allergy* 1997;**52**:914–920.
- Johnstone JE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children – a 14-year study. *Pediatrics* 1968;**5**:793–802.
- Eng PA, Gnehm HE, Joller HI. Klinische und immunogene Wirkung der praesaisonalen Hyposensibilisierung bei Kindern mit Pollinosis. *Monatsschr Kinderheilkd* 1994;**142**:616–622.
- Mosbech H, Østerballe O. Does the effect of immunotherapy last after termination of treatment? *Allergy* 1988;**43**:523–529.
- Grammer LC, Shaughnessy MA, Suszko IM, Shoughnessy J, Patterson R. Persistence of efficacy after a brief course of polymerized ragweed allergen: a controlled study. *J Allergy Clin Immunol* 1984;**73**:484–489.
- Naclerio RM, Proud D, Moylan B, Balcer J, Freidhoff L, Kagey-Sobotka A et al. A double blind study of the discontinuation of ragweed immunotherapy. *J Allergy Clin Immunol* 1997;**100**:293–300.
- Norman PS, Creticos PS, Marsch DG, Adkinson NF, Kagey-Sobotka A, Lichtenstein LM. 2-year study of clinical results after discontinuation of ragweed allergoid immunotherapy [Abstract]. *J Allergy Clin Immunol* 1988;**81**:294.
- Durham SR, Walker SM, Varga E-M, Jacobson MR, O'Brien F, Noble W et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;**341**:468–475.
- Malling HJ. Immunotherapy as an effective tool in allergy treatment for asthma in allergic children. *Allergy* 1998;**53**:461–472.
- Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;**336**:324–331.