

Pollen-specific rush immunotherapy: clinical efficacy and effects on antibody concentrations

Robert Movérare, MSc*†; Erkki Vesterinen, MD, PhD‡; Tuula Metso, PhLic‡; Ritva Sorva, MD, PhD‡; Lena Elfman, PhD*; and Tari Haahtela, MD, PhD‡

Background: Studies of rush immunotherapy (RIT) with standardized extracts for the treatment of seasonal pollen allergy are few, especially for birch-pollen RIT.

Objective: The study was performed to investigate the efficacy of RIT with standardized birch- or timothy-pollen extracts. Further, the serum antibody levels were evaluated for correlation with clinical efficacy.

Methods: This open, longitudinal study included 30 allergic patients treated with RIT and 16 allergic patients serving as a control group. The therapy was continued for 3 years and blood samples were collected at regular intervals for antibody measurements using the Pharmacia CAP System.

Results: The RIT was generally well tolerated. An increase in the total and specific IgE concentrations during the early months of RIT was observed, followed by decreased levels. Specific IgG and IgG4 increased continuously for 2 years. The symptom and medication scores were significantly decreased, compared with preRIT, at both the first and third pollen seasons after the start of RIT treatment ($P < .0001$ and $P < .001$, respectively). The clinical improvement during RIT was significantly greater compared with the control group ($P < .05$). The decreased medication and the symptom improvement during the third year of RIT correlated with the relative decrease in specific IgE ($r_s = .52$, $P < .05$) and with the specific IgG4 level before the start of RIT ($r_s = -.68$, $P < .01$), respectively.

Conclusions: Our study indicates that RIT with standardized birch- or timothy-pollen extracts is clinically effective and safe. Measurements of specific antibody levels during treatment may be helpful in monitoring RIT.

Ann Allergy Asthma Immunol 2001;86:337–342.

INTRODUCTION

Allergen-specific immunotherapy (IT) has been used for treatment of allergic diseases since 1911, when Noon and Freeman introduced it as a treatment for allergic rhinitis. Treating hay fever and asthma with conventional pollen-specific IT has been found effective in many studies,^{1–4} although contradictory results have been reported.⁵ Conventional IT with injections of gradu-

ally incremented allergen doses over a long period is considered reasonably safe, although deaths from anaphylactic shock reactions have occurred.⁶ However, patient compliance is often poor.^{7,8} One reason is that the patients have to visit the allergy clinic often, usually every week, for a few months during the induction phase.

In rush immunotherapy (RIT), the maintenance dose is reached faster. Increasing allergen doses are given during a short rush period, normally a few days, after which less frequent visits to the allergy clinic are needed. Early clinical improvement has been found in double-blind, placebo-controlled RIT studies using grass-pollen extracts or allergoids.^{9–11}

The efficacy of IT in grass- and ragweed-pollen allergy has been frequently investigated, although stud-

ies of IT in tree-pollen allergy are few.⁴

In this study, we followed the immunologic responses of patients treated with birch- or timothy-pollen RIT with standardized extracts for 3 years by measuring serum antibody levels using the Pharmacia CAP System. The clinical efficacy was followed by recording symptom scores together with the use of drugs. The usefulness of antibody measurements to predict clinical efficacy and to monitor RIT was evaluated.

METHODS

Study Population

Forty-six patients, both children and adults, with a history of birch- or timothy-pollen allergy were recruited. All patients had had rhinitis or conjunctivitis and some also had asthma during at least three pollen seasons. All but one of the patients had used symptomatic medication. The patients were skin-prick tested to a panel of 10 common allergens in Finland (birch, timothy, meadow fescue, mugwort, *Cladosporium herbarum*, cat, dog, horse, cow, and *Dermatophagoides pteronyssinus*; SoluPrick SQ, 10 HEP, ALK-Abello, Hørsholm, Denmark) and had a positive test (wheal ≥ 3 mm) to birch or timothy pollen. Further, all patients had specific serum IgE to birch or timothy pollen (> 0.35 kU/L; the Pharmacia CAP System, Pharmacia Diagnostics AB, Uppsala, Sweden). Thirty patients were randomly selected for treatment with allergen-specific RIT (RIT group) and the other 16 patients served as controls (control group). Patient characteristics are given in Table 1. The symptom scores were slightly higher in the RIT group, but the medication scores were the same between the two groups (see "Results").

* Pharmacia Diagnostics AB, Uppsala, Sweden.
† Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden.

‡ Department of Allergology, Helsinki University Central Hospital, Helsinki, Finland.

Received for publication December 8, 1999.
Accepted for publication in revised form August 14, 2000.

Table 1. Patient Characteristics

	RIT group	Control group
Number	30	16
Age, years (mean $\pm$ SD)	20.9 $\pm$ 10.9	19.1 $\pm$ 10.5
Sex (F/M)	13/17	8/8
Sensitization (birch/timothy)	26/4	15/1
Clinical allergy, n (%)		
Rhinoconjunctivitis	28 (93)	9 (56)
Rhinitis	2 (7)	6 (38)
Conjunctivitis	0 (0)	1 (6)
Asthma	14 (47)	9 (56)

Study Design

Patients were enrolled in this open, longitudinal study between November and January at the Outpatient Clinic at the Department of Allergology, Helsinki University Central Hospital, Helsinki, Finland. The RIT group was treated and followed for 3 years. The control subjects were followed for 1 year and then were offered an active RIT treatment. The control patients who started RIT left the study. Five of the remaining control subjects were followed up with a clinical evaluation 2 years later.

The study was approved by the ethics committee of Helsinki University Central Hospital, and all subjects gave their informed consent.

RIT Treatment

Treatment was started with an initial rush phase with standardized aqueous extracts of birch-pollen allergens and timothy-pollen allergens (Aquagen, ALK-Abello) in 26 patients and 4 patients, respectively. The patients were given three subcutaneous injections daily with gradually increasing doses up to the highest individually tolerated dose at the end of the first week. The target dose was 10,000 SQ. Thereafter, treatment was continued with standardized depot preparations (Alutard, ALK-Abello), which were injected subcutaneously every third week in increasing doses until the individual maintenance dose was reached (mean 73,000 SQ, range 20,000 to 100,000 SQ). The aimed maintenance dose was 60,000 to 100,000 SQ. The maintenance dose was administered every third week for 3 years.

Before and 30 minutes after an injection, the lung function of the patient was monitored using PEFr measurements. If large local skin reactions occurred (> 5 cm), allergen injections were interrupted until the next day, when they were continued with half the allergen dose.

Seven patients were withdrawn from the RIT group during the first year. In one case, this was because of systemic side effects (fever after an injection). Other reasons for withdrawal were pregnancy, high serum calcium, acute urinary infection, use of anabolic steroids, and in two cases, lack of compliance. During the RIT phase, the first week of treatment, three patients had generalized urticaria and one had mild asthmatic symptoms. However, these patients continued RIT with a decreased dose.

Both the RIT and the control group were allowed symptomatic medication during the pollen seasons.

Symptom and Medication Scoring

The patients evaluated their allergy symptoms and use of medication by giving a single visual analog score on a scale ranging from 0 to 100 for each of the two parameters during the pollen season preceding RIT treatment (baseline) when visiting the clinic. This was repeated during the first and third pollen seasons after start of RIT. No separate score for each type of symptoms was used. In Finland, the birch-pollen season normally starts in late April and peaks during May. The timothy-pollen season is normally during June and July.

From March to October of the first year of RIT, the patients also gave a

monthly medication-index score for the different types of medicine they used for treatment of their allergic symptoms in upper and lower airways and eyes. The scores were: 0 = no use of medication; 1 = occasional use of medication; and 2 = regular use of medication. The average monthly medication index was achieved by dividing the total medication index score by 8.

Specific Antibody Measurements

Blood was drawn at the start of treatment (day 0), after one week (week 1), and at month 2, month 4, month 6, month 9, and after one year of RIT (year 1). In the RIT group, blood was also collected during November to February of the second and third year of the treatment (years 2 and 3). Serum was stored at -20°C until total IgE, and specific IgE, IgG, and IgG4 to birch- or timothy-pollen allergen was assayed. The measurements were performed in duplicate using the Pharmacia CAP System.

Statistical Methods

Antibody concentrations were expressed either in concentration units or as percent of the baseline value. The Wilcoxon signed rank *t* test was used for within-group comparisons and the Mann-Whitney *U* test for comparisons between the groups. Spearman's rank correlation test was used to establish the significance of correlation between clinical and immunologic parameters. A two-tailed *P*-value $< .05$ was considered an indication of statistical significance.

RESULTS

Changes in Total IgE and Specific Serum Antibody Levels

No significant differences between the serum levels of total IgE or specific IgE, IgG, or IgG4 were found between the RIT and control groups at the start of the study.

Total serum IgE increased during the first 2 months of RIT and then slowly declined (Fig 1A, Table 2). No significant changes of the total IgE level occurred in the control group (data not shown). The relative increase

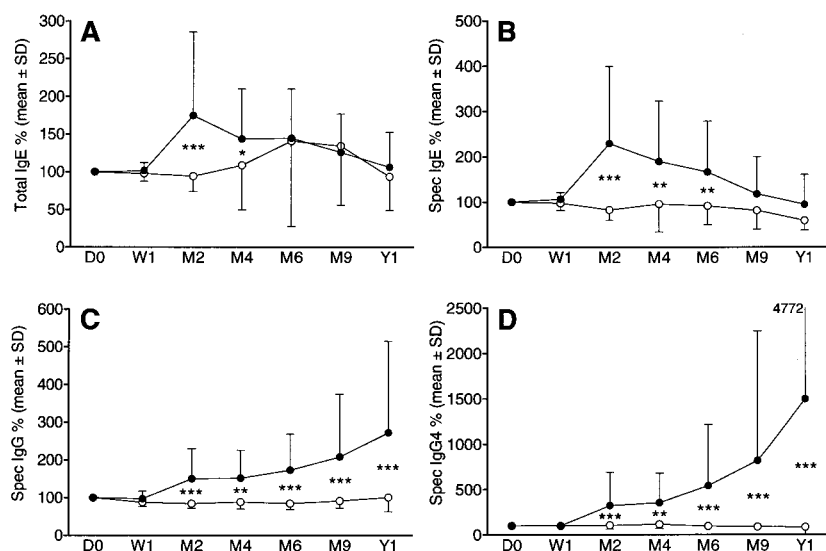


Figure 1. The mean relative change (with standard deviation) from baseline concentrations at day 0 of total IgE (A), specific IgE (B), specific IgG (C), and specific IgG4 (D) in the RIT group (●), and in the control group (○). D, day; W, week; M, month; and Y, year. *, $P < .05$; **, $P < .01$; ***, $P < .001$ as compared with the relative change in the control group.

in total IgE observed during RIT was significant, compared with the control group, at months 2 and 4 (Fig 1A).

The allergen-specific IgE increased early and strongly during RIT. The change was significant already after one week of treatment (Table 2). The level peaked at months 2 to 4, which was before the pollen season. Later, the specific IgE slowly declined. At years 1 and 3, the decrease from day 0 was significant (Table 2). In the control group the specific IgE level declined throughout the 1-year observation period, perhaps as a result of the relatively weak birch-pollen season that year (<100 grains/ m^3 /day at the peak). In the RIT group, the relative increase in specific IgE was significant, compared with the control group, between months 2 and 6 (Fig 1B).

After the first week of RIT, the specific IgG and IgG4 increased continuously for 2 years (Table 2). The change in specific IgG4 was more profound; at year 2 it had increased to 22-fold the baseline concentration. In the control group, only minor seasonal changes in birch- or timothy-pollen-specific IgG or IgG4 were observed (data not shown). In the RIT group, the relative increase in specific IgG and IgG4 was

significant, compared with the control group, from month 2 (Fig 1C and D). The antibody responses observed in the patients treated with birch-RIT versus timothy-RIT were very similar (data not shown).

Change in Symptoms and Medication

The change in symptom scores (Δ -score) was significantly different between the RIT group and the control group during the pollen season of the first year ($P < .05$), although patients in both groups reported improvements (Table 3). It should be noted that the birch-pollen season was weak the first year (data not shown). The mean symptom score was higher in the RIT group compared with the control group before the start of RIT (baseline), but during the pollen season of the first and third year of RIT, the mean symptom score in the RIT group had become significantly lower compared with the control group ($P < .05$). During the pollen season of the third year, when birch-pollen counts were high (>1000 grains/ m^3 /day at the peak), the patients in the RIT group reported great symptom improvements (Table 3).

The use of medication was the same between the two study groups before

start of RIT (Table 3). It decreased significantly from baseline during both the first and third pollen seasons in the RIT treated patients ($P < .0001$ and $P < .001$, respectively), and became significantly lower ($P < .01$) in the RIT group compared with the control group. Consequently, the changed use of medication (Δ -score) within the groups during the study period differed significantly ($P < .05$) between the RIT and control group (third year; Table 3).

The patients also reported their quantitative use of drugs for their allergic symptoms (medication index) during and after the first pollen season after start of RIT (March to October). The average monthly medication index in the RIT group and the control group was 1.59 ± 1.82 (mean $\pm$ SD) and 3.29 ± 1.77 ($P < .05$), respectively.

There was no difference in clinical efficacy between the patients receiving birch-pollen RIT and those receiving grass-pollen RIT.

Correlation between Serum Antibody Levels and Clinical Outcome

Correlations between serum levels of total IgE, specific IgE, IgG, and IgG4 at day 0, month 2, month 6, year 1, year 2, and year 3 and clinical outcome scores were sought in the RIT group. No significant correlation was found between the antibody levels or their relative change and the changes in symptoms or medication during the pollen season of the first year. However, as shown in Figure 2A, there was a significant correlation between the relative decrease in specific serum IgE and the decreased use of medication during the third year of RIT. Further, the baseline levels (day 0) of specific IgG4 in the RIT group correlated with decreased symptom scores during the third year of treatment (Fig 2B).

DISCUSSION

In the present RIT study, measurements of serum antibodies using the Pharmacia CAP System identified early immunologic responses after injections of allergens, and by following the antibody concentrations, RIT could be monitored.

Table 2. Median Concentrations (with 25% and 75% Percentile) for Birch- or Timothy-Specific Serum Antibodies and Total IgE in the RIT Group

	n	Total IgE (kU/L)	Spec IgE (kU/L)	Spec IgG (mg/L)	Spec IgG4 (mg/L)
Day 0	27	196 (112–530)	84 (28–171)	5.30 (4.30–6.40)	0.60 (0.37–0.91)
Week 1	27	205 (120–547)	99 (29–176)*	5.30 (3.60–7.10)	0.70 (0.31–1.07)
Month 2	26	383 (147–551)**	133.5 (70–242)**	6.70 (5.45–8.45)**	1.20 (0.72–2.22)**
Month 4	25	296 (139–492)*	141 (54–196)**	7.20 (5.60–8.40)*	1.67 (0.80–2.40)**
Month 6	25	270 (158–475)*	113 (44–163)*	8.60 (5.20–11.3)**	1.98 (0.69–3.43)**
Month 9	22	320 (190–483)	87 (29–148)	8.55 (5.40–12.6)**	2.46 (0.97–3.96)**
Year 1	23	232 (107–510)	61.5 (26–138)*	10.2 (6.90–17.4)**	4.51 (1.44–6.44)**
Year 2	12	227 (102–555)	53 (16–157)	24.8 (16.1–41.2)**	13.2 (6.30–31.3)**
Year 3	17	253 (75–424)	53 (15–97)*	15.7 (11.4–21.7)**	9.28 (5.83–11.8)**

Probability of difference from level at Day 0:

* $P < .01$.

** $P < .001$.

Table 3. Symptom and Medication Scores and Their Change (Δ -Score), during Pollen Season, as Reported by Patients.

The patients gave a single visual analog score, on a scale ranging from 0 to 100, describing their allergy symptoms and use of medication. Data is shown as mean value $\pm$ SD.

	RIT group	Control group	P value
Symptom scores			
Baseline	80.1 $\pm$ 15.0†‡, n = 29	69.3 $\pm$ 15.8§, n = 11	.0424
First year	21.2 $\pm$ 19.5†, n = 24	39.0 $\pm$ 15.1§, n = 11	.0173
Third year	15.8 $\pm$ 17.0‡, n = 16	55.6 $\pm$ 33.8, n = 5	.0186
Change in symptoms from baseline scores (Δ -score)			
First year	–57.3 $\pm$ 29.0, n = 24	–30.3 $\pm$ 21.6, n = 11	.0136
Third year	–59.7 $\pm$ 20.1, n = 16	–16.8 $\pm$ 31.0, n = 5	.0167
Medication scores			
Baseline	59.2 $\pm$ 28.3#¶, n = 29	58.4 $\pm$ 21.8, n = 11	.7852
First year	20.4 $\pm$ 19.9#, n = 24	45.4 $\pm$ 23.3, n = 11	.0077
Third year	15.4 $\pm$ 17.8¶, n = 16	65.4 $\pm$ 29.0, n = 5	.0057
Change in medication from baseline scores (Δ -score)			
First year	–38.0 $\pm$ 30.1, n = 24	–12.9 $\pm$ 40.6, n = 11	.1266
Third year	–41.4 $\pm$ 23.4, n = 16	+6.8 $\pm$ 35.9, n = 5	.0186

† $P < .0001$, ‡ $P = .0005$, § $P = .002$, # $P < .0001$, ¶ $P = .0006$.

The induction phase of IT often differs between protocols, but it simply represents a titration of the dose essential for an immunologic response.¹² When using a RIT schedule, the aim is normally to finish the induction phase within 1 week.^{9–11,13} To be able to reach the appropriate maintenance dose, however, the final part of the induction phase often has to be administered using a conventional dose-increase regimen to avoid severe side effects.^{12,13} Thus, in the present RIT study, the initial rush phase with aqueous pollen extracts was followed by

injections with increasing doses of depot preparations every third week until reaching the individual maintenance dose.

Many patients had very high serum concentrations of specific IgE to birch or grass pollen (>100 kU/L), and it seems that a major part of all serum IgE was birch- or grass-pollen specific. This explains the similar development of total and specific IgE levels during RIT.

Total serum IgE, as well as allergen-specific IgE, increased early during RIT and peaked at months 2 to 4. Interestingly, the specific IgE was al-

ready significantly elevated after 1 week of treatment, indicating a rapid immunologic response during the rush phase of RIT to injections of aqueous pollen extracts. Subsequently, the IgE concentrations decreased. The specific IgE dropped to a level significantly lower than the pretreatment level. Both the allergen-specific serum IgG and, in particular, IgG4 levels increased during the RIT treatment, and the increase became significant after 2 months.

Similar results have previously been found during grass- and tree-pollen IT^{1,2,9–11,14,15} even though some differences between the investigations exist, eg, the early increase in IgE was not observed in some studies.

Bousquet et al^{9,10} have shown that RIT with grass-pollen extracts or allergoids has a good efficacy and is well tolerated. Analogously, our study indicates that IT including an initial rush phase with standardized birch- and timothy-pollen extracts is well tolerated. The treatment of only 1 of 30 patients had to be interrupted because of a side effect (fever). RIT was already quite effective in the first pollen season encountered. Even if the first pollen season after the start of RIT was relatively weak, resulting in symptom improvements in both study groups, the change in symptom scores was significantly greater in the RIT group. The improvement in the RIT group was also reflected in the decreased use of medication. The quantitative use of drugs for allergic symptoms (medica-

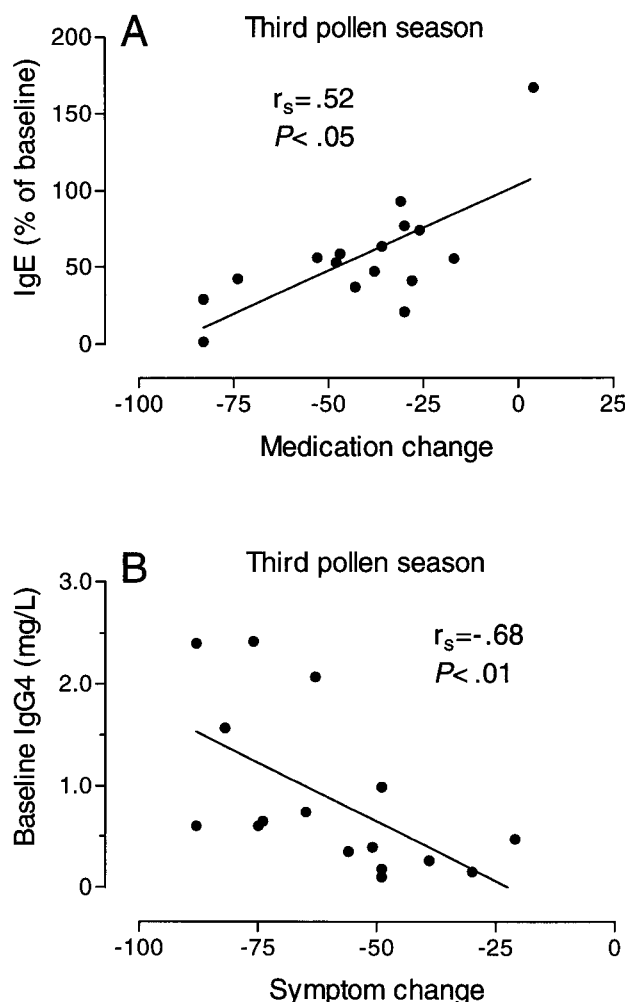


Figure 2. Correlation between the relative decrease in specific IgE and decrease in medication the third pollen season (A), and between the baseline level of specific IgG4 (day 0) and the decrease in symptoms the third pollen season (B).

tion index) during the first pollen season after start of RIT was significantly lower in the RIT group compared with the control group. The effect of the RIT was maintained through the third pollen season. There are some earlier studies of birch-pollen IT that have shown good clinical efficacy,^{14–16} but to our knowledge, the present study is the first birch-pollen-IT study performed with standardized extracts using an initial rush schedule. Even if we cannot rule out that placebo effects might have influenced the clinical results, we believe that such effects would decrease over time. However, in our study, the clinical efficacy in-

creases over the 3-year-study period, supporting the reliability of the data.

In the present study, the IgG4 levels before the start of RIT correlated with clinical improvements during the third year of RIT. Even if similar results have been shown,¹⁷ contradictory results in measuring IgG4 also exist.¹⁸ A role for IgG4 in the clinical improvements of IT is hard to realize. The effect of so-called blocking antibodies (of IgG class) has only been demonstrated in vitro by inhibition of histamine release^{19–21} and IgE-mediated antigen presentation,²² but it has so far not been proven to exist in vivo.^{4,23,24} Similarly, in our study no correlation

between increase in specific IgG and IgG4 and clinical efficacy was found, suggesting that IgG4 measurements might be used to monitor an ongoing immune reaction during IT rather than to predict clinical improvements.

In this RIT study, a significant association between the relative decrease in specific IgE and the decreased use of medication during the pollen season of the third year of RIT treatment was observed. Even if some of the beneficial effects of IT might be explained by decreased levels of allergen-specific IgE, the diminished IgE production probably reflects an immune deviation of the response of allergen-specific T cells from a Th2-like to a Th0/Th1-like phenotype.^{25–27} This has a number of effects on the immune system, and results in a reduced immediate early response and late-phase reaction.²⁸

CONCLUSION

Our study indicates that rush immunotherapy with standardized birch- and timothy-pollen extracts has a good clinical efficacy and is well tolerated. Measurements of specific serum antibodies might be useful to monitor IT.

ACKNOWLEDGMENTS

This study was supported by a grant from Helsinki University Central Hospital. We acknowledge Dr Fred Björkstén for reviewing the manuscript. We thank Margareta Svensson for her assistance in antibody measurements, and Ulrika Andersson and Johan Westerberg for their help in statistical analysis.

REFERENCES

1. Pastorello EA, Pravettoni V, Incorvaia C, et al. Clinical and immunological effects of immunotherapy with alum-adsorbed grass allergoid in grass-pollen-induced hay fever. *Allergy* 1992;47:281–290.
2. Ortolani C, Pastorello E, Moss RB, et al. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. *J Allergy Clin Immunol* 1984;73:283–290.
3. Reid MJ, Moss RB, Hsu YP, et al. Seasonal asthma in northern California: al-

- lergic causes and efficacy of immunotherapy. *J Allergy Clin Immunol* 1986;78:590–600.
4. Bousquet J, Lockey RF, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53(Suppl):4–42.
5. Adkinson NF, Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324–331.
6. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660–677.
7. Tinkelman D, Smith F, Cole WQ, Silk HJ. Compliance with an allergen immunotherapy regime. *Ann Allergy Asthma Immunol* 1995;74:241–246.
8. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993;91:734–737.
9. Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. *J Allergy Clin Immunol* 1987;80:591–598.
10. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol* 1991;88:43–53.
11. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;51:489–500.
12. Malling HJ. Practical immunotherapy. In: Kay AB, ed. *Allergy and Allergic Diseases*. Oxford: Blackwell Science Ltd, 1997:1243–1257.
13. Hejjaoui A, Ferrando R, Dhivert H, et al. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992;89:925–933.
14. Moller C, Dreborg S, Einarsson R. Immunotherapy to deciduous tree pollens: specific IgE and IgG antibody patterns. *Clin Allergy* 1987;17:551–562.
15. Balda BR, Wolf H, Baumgarten C, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. *Allergy* 1998;53:740–748.
16. Jacobsen L, Nuchel Petersen B, Wihl JA, et al. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. *Allergy* 1997;52:914–920.
17. Fennerty AG, Jones KP, Davies BH, et al. Immunological changes associated with a successful outcome of pollen immunotherapy. *Allergy* 1988;43:415–419.
18. Djurup R, Malling HJ. High IgG4 antibody level is associated with failure of immunotherapy with inhalant allergens. *Clin Allergy* 1987;17:459–468.
19. Levy DA, Lichtenstein LM, Goldstein EO, Ishizaka K. Immunologic and cellular changes accompanying the therapy of pollen allergy. *J Clin Invest* 1971;50:360–369.
20. Visco V, Dolecek C, Denepoux S, et al. Human IgG monoclonal antibodies that modulate the binding of specific IgE to birch pollen Bet v 1. *J Immunol* 1996;157:956–962.
21. Vrtala S, Ball T, Spitzauer S, et al. Immunization with purified natural and recombinant allergens induces mouse IgG1 antibodies that recognize similar epitopes as human IgE and inhibit the human IgE-allergen interaction and allergen-induced basophil degranulation. *J Immunol* 1998;160:6137–6144.
22. van Neerven RJ, Wikborg T, Lund G, et al. Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4(+) T cells by inhibiting serum-IgE-facilitated allergen presentation. *J Immunol* 1999;163:2944–2952.
23. Djurup R. The subclass nature and clinical significance of the IgG antibody response in patients undergoing allergen-specific immunotherapy. *Allergy* 1985;40:469–486.
24. Bousquet J, Maasch H, Martinot B, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol* 1988;82:439–446.
25. Secrist H, Chelen CJ, Wen Y, et al. Allergen immunotherapy decreases interleukin-4 production in CD4+ T cells from allergic individuals. *J Exp Med* 1993;178:2123–2130.
26. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. *J Clin Invest* 1993;92:644–651.
27. Akdis CA, Blesken T, Akdis M, et al. Role of interleukin-10 in specific immunotherapy. *J Clin Invest* 1998;102:98–106.
28. Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102:157–164.

Requests for reprints should be addressed to:
Robert Møværre
Pharmacia Diagnostics AB
SE-751 82 Uppsala
Sweden
E-mail: robertmoverare@hotmail.com