

Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy

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Asthma, rhinitis,
other respiratory
diseases

Background: Birch pollen is a common allergen in northern, central, and eastern Europe. Earlier studies of specific immunotherapy using birch pollen extract were not placebo-controlled or were only preseasonal. Long-term, placebo-controlled studies with subcutaneously administered standardized birch pollen extract are lacking.

Objective: The aim of this study was to evaluate the effect of immunotherapy with birch pollen extract on airway symptoms and use of medication in adult birch pollen-allergic patients in a double-blind, placebo-controlled trial.

Methods: Forty-nine patients with histories of birch pollen allergy from the upper and lower airways, positive skin prick test and conjunctival provocation test results, and in vitro specific IgE to birch pollen (*Betula verrucosa*) extract were included. Immunotherapy with birch pollen extract was given during 2 consecutive years in a double-blind, randomized, placebo-controlled study. Clinical symptom scores from the upper and lower airways and use of rescue medication were registered throughout the pollen season.

Results: Forty-six patients reached the maintenance dose and were maintained on that dose during the 2-year study. The median symptom scores during the 1997 and 1998 seasons were 1.3 and 2.6, respectively, in the specific immunotherapy group and 2.1 and 4.3, respectively, in the placebo group. The differences between the groups were significant ($P = .05$ in 1997 and $P = .005$ in 1998). The placebo group used significantly more rescue medication during both seasons than the specific immunotherapy group ($P = .004$ for 1997 and $P = .004$ for 1998).

Conclusion: Specific immunotherapy with birch pollen extract is an effective and safe treatment for reducing clinical allergy symptoms and medication use in birch pollen-allergic patients during the pollen season. (J Allergy Clin Immunol 2002;109:777-83.)

Key words: Specific allergen immunotherapy, birch pollen allergy, placebo-controlled study

Birch is the major pollen allergen-producing tree in Scandinavia, and birch pollen is also a common allergen in northwest, central, and eastern Europe. In studies, the prevalence of positive skin prick test (SPT) results to birch in pollen-allergic patients in Europe has ranged from 5% in Netherlands to 54% in Zurich, Switzerland.¹ An increased sensitization to birch pollen has been found in recent years—eg, in northern Italy.² In Sweden, an epidemiologic study from 3 different areas showed that 15% to 17% of the population in the age group 20-46 years had positive SPT results to birch.³ There is also a high level of cross-reactivity between birch, alder, and hazel. Because of this cross-reactivity, allergic symptoms of birch-sensitized patients are extended from early spring to early summer. Although sophisticated pharmacotherapy is currently available, it is often not sufficient to control the symptoms.

Allergen-specific immunotherapy has been widely used for 90 years as a specific treatment for allergic disease.⁴ The treatment ameliorates the severity of the allergic disease and sometimes leads to cessation of allergic symptoms. During the last few decades, many double-blind, placebo-controlled studies have convincingly proved the clinical efficacy of specific immunotherapy (SIT) with standardized extracts of inhaled allergens, such as grass pollen,^{5,6} ragweed,⁷ mite,⁸⁻¹⁰ and cat dander.^{11,12} An earlier comparative study between SIT with standardized birch pollen extract and therapy with a combination of pollens from deciduous trees showed SIT to be effective in improving the springtime symptoms, but the study was not placebo-controlled.^{13,14} We have therefore undertaken a long-term, placebo-controlled trial with subcutaneously administered standardized birch pollen extract.

METHODS

Patients

This study included 49 patients (20 men and 29 women) aged 19 to 46 years (mean age, 32 years; Table I). Each of the patients had a history of birch pollen-induced symptoms from the upper airways, and 18 of the patients had asthma symptoms and had used short-acting β_2 -agonists during the previous season. The mean number of years with rhinoconjunctivitis was 17 (range, 2-36 years); the

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Abbreviations used

AUC: Area under the curve
 CPT: Conjunctival provocation test
 PEF: Peak expiratory flow
 SIT: Specific immunotherapy
 SPT: Skin prick test
 VAS: Visual analog scale

TABLE I. Clinical data pertaining to patients

	Immunotherapy	Placebo
No. of patients with (no. asthmatic) rhinoconjunctivitis	24 (9)	25 (9)
Sex: M/F	9/15	11/14
Age (y): mean (range)	33 (21-45)	31 (19-45)
SPT (mm ²): median (range)	5.5 (4.5-8.0)	5.5 (4.5-7.0)
Symptoms for 1996 season—VAS: median (range)	5.5 (1.6-7.3)	5.8 (1.7-9.0)
Specific birch IgE (SU/mL): median (range)	82 (18-530)	119 (30-443)

mean number of years with lower airway symptoms was 9 (range, 1-36 years). Each patient had a positive SPT result to *Betula verrucosa* (diameter, >3 mm; Soluprick SQ 10 HEP *Betula verrucosa*, ALK-Abelló, Hørsholm, Denmark), positive in vitro specific IgE to *B verrucosa* ($\geq$ class 2; Magic Lite SQ, ALK-Abelló), and a positive conjunctival provocation test (CPT) result ($\leq$ 10,000 SQ-U/mL; Aquagen SQ *Betula verrucosa*, ALK-Abelló).

In addition to having birch pollen allergy, 21 patients were sensitive to grass pollen; however, the grass pollen season comes later and is well separated from the time of birch pollination. None of the patients had a clinical history of perennial symptoms from the upper or lower airways. Thirty patients were also sensitized to animal dander, but none of the patients had animals at home and none were knowingly exposed during the study. Each patient had negative SPT results and a negative clinical history with respect to house dust mite and mold. None of the patients had previously been treated with SIT, and no patient was treated with topical steroids.

Study design

SPTs and CPTs were performed in the autumn of 1996, before the start of the treatment. Each patient was randomized into either the active treatment group or the placebo treatment group; patients were randomized in blocks of 4 to ensure that those with asthma would be equally distributed in the 2 groups. A computer software program produced the randomization scheme. Treatment (active and placebo) started individually during the period November 1996 to January 1997 and continued for up to 2 years over 2 pollen seasons.

Diary cards were filled in before and during the pollen seasons. After the first season, the patients again underwent conjunctival provocation testing. The study ended in June 1998; actively treated patients continued SIT for another year in an open manner. The primary end points were symptom and medication scores during the birch pollen seasons. Secondary end points were peak expiratory flow (PEF) and severity of allergic symptoms as indicated on a visual analog scale (VAS) during the seasons. An additional secondary end point was conjunctival provocation testing performed outside the pollen season after less than 1 year of treatment.

The double-blinding procedure could be evaluated by assessing the VAS data; the patients completed VAS forms in weekly intervals, parallel with symptom and medication scores. This procedure allowed the investigator to compare the VAS data from the previous season with that from the treatment season.

Skin prick testing

Each SPT was performed on the volar side of the arm. During the inclusion period, all patients were tested out of season with a standard panel consisting of birch, timothy, dog, cat dander, house dust mite (*Dermatophagoides pteronyssinus*) and mold (*Cladosporium*). An SPT result was considered positive if the wheal diameter was >3 mm (Soluprick SQ 10 HEP).¹⁵

Conjunctival provocation testing

CPTs were performed out of season before and after 8 to 10 months of treatment. We applied a drop of the test solution in the lower conjunctival sac, starting with sterile saline solution as a negative control. Aquagen SQ *Betula verrucosa* extract was administered in increasing concentrations (semilogarithmic scale) from 100 SQ-U/mL to a maximum of 100,000 SQ-U/mL. Reactions were assessed visually; a reaction was considered positive if itching as well as redness of the conjunctival mucosa occurred.

Peak expiratory flow

PEF was measured with a Mini-Wright peak flow meter (Clement Clarke International Ltd, Harlow, United Kingdom) every morning and every evening before (baseline) and during the birch pollen seasons of 1997 and 1998.

Pollen counts

The pollen count was registered daily during the birch pollen season by means of a volumetric pollen trap (Burkard Scientific Ltd, Uxbridge, United Kingdom) that was placed on the top of a 20-m-high hospital building. Pollen counts were measured daily and expressed as numbers of grains per cubic meter of air.

Treatment: immunotherapy protocol

The patients in the active group ($n = 24$) were treated with Alutard SQ *Betula verrucosa*; those in the placebo group ($n = 25$) received Alutard diluent containing histamine dihydrochloride. Alutard SQ is a depot extract containing water-soluble allergen protein with aluminum hydroxide as adjuvant. Incremented doses of the extract were given through use of a cluster protocol over a period of 7 to 8 weeks¹⁶ (Table II). After a maintenance dose of 1 mL of 100,000 SQ-U/mL Alutard SQ *Betula verrucosa* was reached, the treatment was continued for 2 consecutive years, subcutaneous injections being given every 6 weeks.

Clinical symptoms

Registration of symptoms began 1 week before the expected start of the birch pollen season. The baseline (symptoms and medication) was established out of season—during a 2-week period preceding each season, in February 1997 and February 1998. The following allergic symptoms were recorded: runny nose/sneezing, blocked nose, eye symptoms, and bronchial symptoms. Each symptom was scored as follows: 0, none; 1, slight; 2, moderate; 3, severe. The daily symptom score was calculated as the sum of all symptoms experienced on that day by each patient. The area under the curve (AUC) for the whole pollen season, containing the mean daily symptom score for each patient in the treatment groups, was then constructed. Once a week, the patients assessed their perception of the disease by using VAS forms (scale, 0-10).

Medication score

During each pollen season, patients were supplied with rescue medication. Each drug was scored for the duration of the dosing according to the recommendation of the manufacturer. No drugs other than the prescribed rescue medication were allowed. The med-

Symptom score 1997

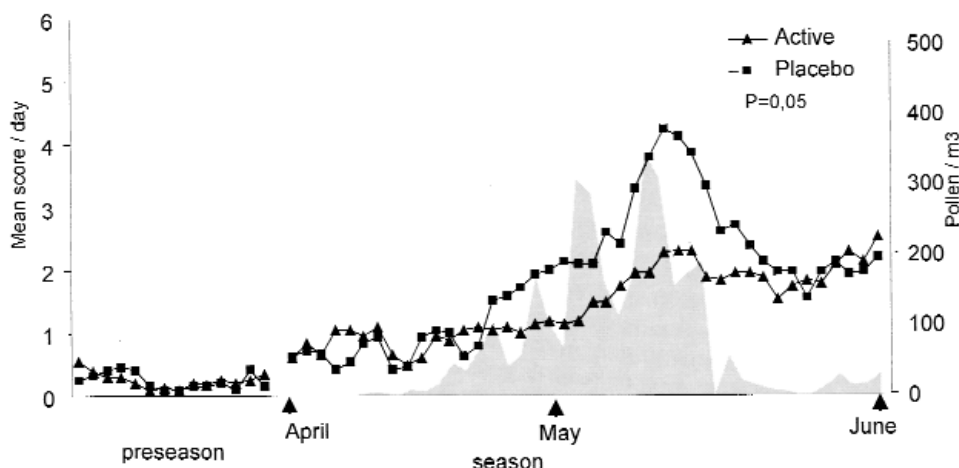


FIG 1. Mean daily symptom score values in active and placebo groups, each expressed as AUC in relation to the pollen curve during the 1997 season. The differences in AUC between groups were significant ($P = .05$, counted for the whole season).

ication was scored as follows: acrivastin capsule (Semprex) 8 mg, 1 point/capsule (short duration); terbutaline inhalation (Turbuhaler Bricanyl) 0.5 mg, 1 point/inhalation (short duration); salbutamol inhalation (Diskhaler Ventoline) 0.4 mg, 1 point/inhalation (short duration); sodium cromoglycate (Lomudal) eye drop 40 mg/mL, 2 points/drop; sodium cromoglycate nasal spray (Lomudal nasal) 5.2 mg/mL, 2 points/puff (long duration). In case of insufficient symptom control with the rescue medication, the patient was requested to consult with the responsible physician to discuss supplementation with a topical steroid, scored as follows: budesonide (Turbuhaler Rhinocort) nasal powder 100 µg/dose, 4 points/dose for nose symptoms; budesonide inhalation (Turbuhaler Pulmicort) powder 200 µg/dose, 4 points/dose for airway symptoms.

Statistics

The determination of sample size was based on previous results obtained in a seasonal immunotherapy study.⁶ A difference between the groups equal to that observed in the previous study was expected (statistically significant at a 5% level of significance), with a power of 80% if $2 \times 24 = 48$ patients were included.

The analyses of symptom and medication scores were based on the AUC method for the mean daily score per patient during the birch pollen season. The statistical test performed was an exact Wilcoxon 2-sample rank sum test with a significance level of 5%. The median difference between active and control patients and the 95% confidence limits of the median difference were estimated through use of the Hodges-Lehmann method. VAS and CPT data were analyzed by means of an exact Wilcoxon 2-sample rank sum test. All statistical analyses were performed through use of SAS version 6.12 (SAS Institute, Inc, Cary, NC) and StatXact version 3.0 (Statcon, Wittenhausen, Germany).

The study was approved by the Ethics Committee of Göteborg University. Informed consent was obtained from all patients.

RESULTS

Forty-six patients (active, $n = 22$; placebo, $n = 24$) completed the study. For family reasons, 1 patient with-

drew from the study before starting treatment but after randomization. Two patients were withdrawn during the study, one (in the placebo group) because of pregnancy and the other (in the active group) because of persistent itching nodules.

Symptoms

The median symptom scores in the SIT and placebo groups during the first pollen season (1997) were 1.3 (range, 0-5.2) and 2.1 (range, 0.6-5.6), respectively; the difference between the groups was significant ($P = .05$ [Fig 1]). During the second pollen season (1998), the median symptom scores were 2.6 (range, 0-6.5) and 4.3 (range, 2.4-9.1), respectively; the difference between the groups was significant ($P = .005$ [Fig 2]). The placebo group also had significantly more symptoms, as assessed by patients' use of the VAS forms ($P = .0005$ during the first season and $P = .04$ during the second season). There were, however, no significant differences between the groups with respect to PEF values during any of the pollen seasons. No statistically significant differences between the active and placebo groups were seen in the CPT results.

Medication

The placebo group used significantly more rescue medication than the active group during both seasons ($P = .004$ in 1997 [Fig 3] and $P = .004$ in 1998 [Fig 4]).

Adverse events

In all, 76 adverse events were reported in 22 patients in the active group and 81 events were reported in 20 patients in the placebo group. The adverse events were most frequently associated with general symptoms, such as infection symptoms (40.7% in the active group and 46.7% in

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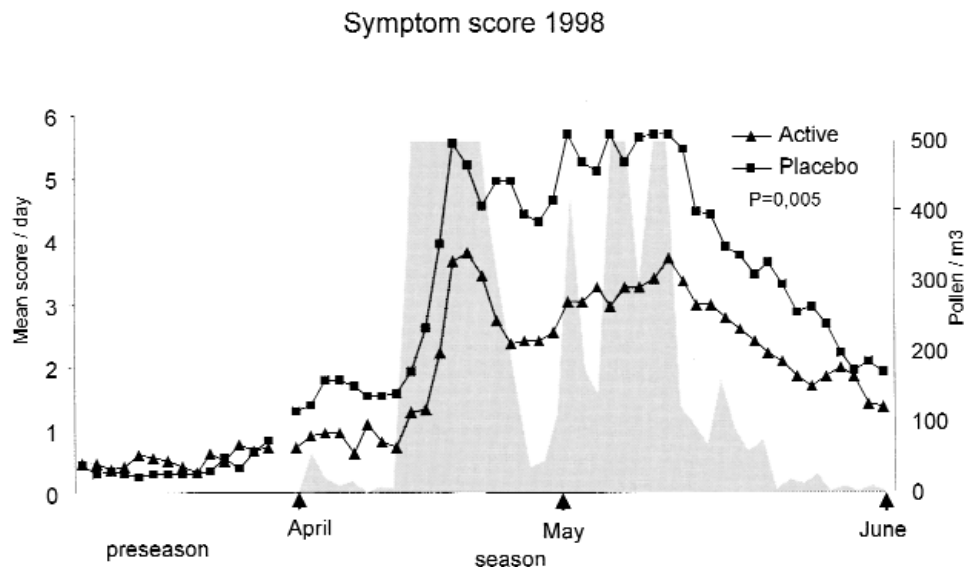


FIG 2. Mean daily symptom score values in active and placebo groups, each expressed as AUC in relation to the pollen curve during the 1998 season. The differences in AUC between groups were significant ($P = .005$, counted for the whole season). Peak value for the pollen season was 5300 pollen grains/m³, which is not depicted in the figure.

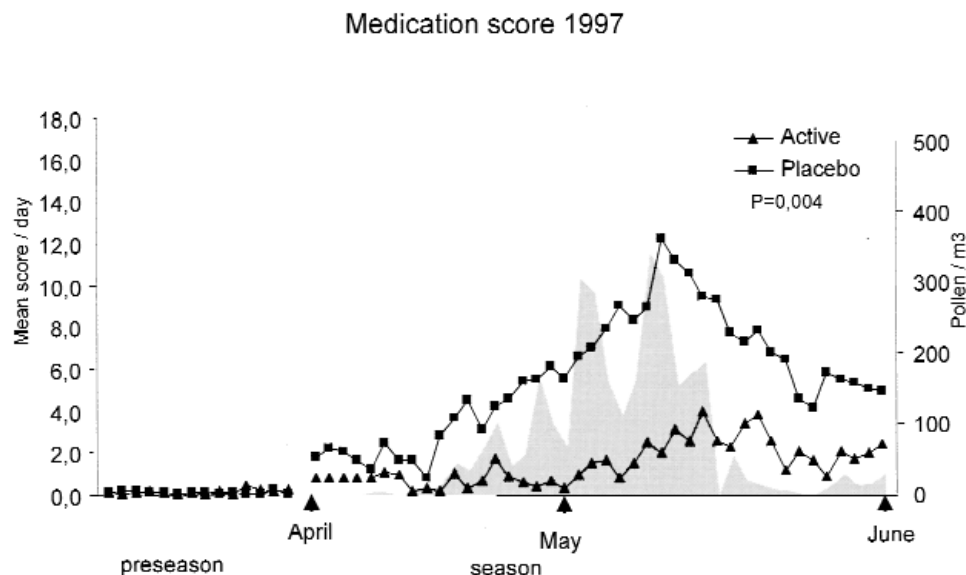


FIG 3. Mean daily medication score values in active and placebo groups, each expressed as AUC in relation to the pollen curve during the 1997 pollen season. The differences in AUC between groups were significant ($P = .004$, counted for the whole season).

the placebo group). The next most frequent adverse events were associated with the respiratory system (27.6% in the active group and 19.8% in the placebo group), rhinitis and cough dominating in both groups. As regards adverse events in connection with SIT, 4 patients in the active and 7 patients in the placebo group experienced 5 and 19 adverse events, respectively, within 30 minutes after injection. Eight of these adverse events occurred during the incremental phase, 9 occurred during the maintenance phase in 1997, and 7 occurred during the maintenance

phase in 1998. All adverse events were of mild intensity, and all of the patients recovered completely.

DISCUSSION

This is the first long-term, placebo-controlled immunotherapy study carried out with a standardized depot preparation of birch pollen extract in allergic patients sensitive to birch pollen. We have confirmed the beneficial effects of SIT on clinical symptoms and use of

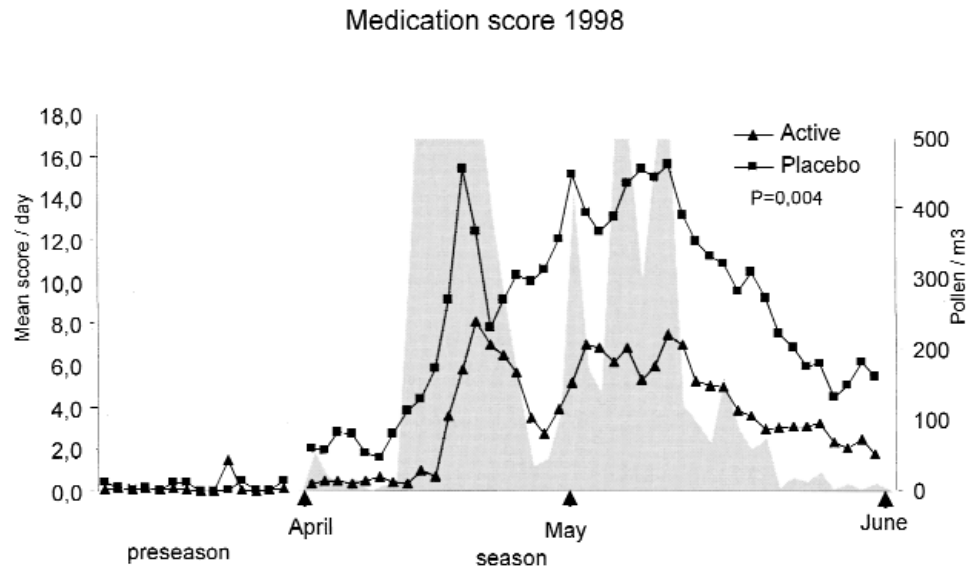


FIG 4. Mean daily medication score values in active and placebo groups, each expressed as AUC in relation to the pollen curve during the 1998 pollen season. The differences in AUC between groups were significant ($P = .004$, counted for the whole season). Peak value for the pollen season was 5300 pollen grains/m³, which is not depicted in the figure.

TABLE II. Dosage schedule

Visit no.	Injection no.	Concentration (SQ-U/mL)	Milliliters	SQ-U
1	1	100	0.1	10
1	2	1000	0.1	100
1	3	10,000	0.1	1000
2	4	10,000	0.1	2000
2	5	10,000	0.4	4000
3	6	10,000	0.6	6000
3	7	100,000	0.1	10,000
4	8	100,000	0.1	10,000
4	9	100,000	0.2	20,000
5	10	100,000	0.3	30,000
5	11	100,000	0.3	30,000
6	12	100,000	0.5	50,000
6	13	100,000	0.5	50,000
7	14	100,000	1.0	100,000
8	15	100,000	1.0	100,000

Between-visits intervals: visits 1-6, 1 week; visits 6-7, 2 weeks; visits 7-8, 4 weeks; visit 8 and subsequent visits, 6 $\pm$ 2 weeks.
Interval between injections on the same day: 30 minutes.

medication after a 2-year treatment. There have been few earlier studies in which standardized birch pollen extract was used. In a double-blind, placebo-controlled study using a standardized depot preparation of tree pollen extract (equal parts of hazel, alder, and birch), Balda et al¹⁷ showed a significant reduction in seasonal symptoms and use of medication; however, it was a short-term study in which 7 preseasonal injections of treatment extract were used. An earlier, long-term trial compared SIT birch with a tree pollen extract combination (alder, birch, and hazel), but the study was not placebo-controlled.¹³ Both treatments were considered effective in reducing symptoms and medication, certainly as the result of a high

degree of cross-reactivity. In another long-term study, patients with both birch pollen allergy and grass pollen allergy were randomized to either birch or grass SIT. A reduction of symptoms and medication use was found during the birch season in patients receiving birch SIT in comparison with those receiving grass SIT¹⁸; the study was not placebo-controlled, however. Lack of placebo-controlled birch pollen studies was observed in the World Health Organization Position Paper on allergen-specific immunotherapy.¹⁹

In epidemiologic studies, approximately 25% to 30% of patients with allergic rhinitis also have asthma.^{20,21} A strong association between perennial allergic rhinitis and

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asthma in patients sensitized to pets, house dust mite, and molds has been observed. However in seasonal allergic rhinitis this association is less certain.²²⁻²⁵ An overwhelming majority of pollen-allergic patients have rhinoconjunctivitis, whereas a much lower number also have asthma during the pollen season, mainly during periods of high pollen counts. In our study, 18 patients reported asthma symptoms and had used a short-acting β_2 -agonist as a symptom reliever during the preceding birch pollen season. A subgroup analysis of the asthmatic patients was performed; asthma patients were equally distributed between the active and placebo groups. However, no significant differences between the treatment groups in asthma symptom and medication scores during the pollen seasons were found. The low number of patients with asthma in each group (data were available from 7 patients in the SIT group and 8 patients in the placebo) probably explains the results and accounts for the difficulty in obtaining a reliable statistical analysis.

The patients in this study predominantly had symptoms from the upper airways. No patient had dominating eye symptoms, and the effect of SIT was not analyzed separately for eyes and nose. However, when conjunctival challenge with birch extract was performed to assess the allergen sensitivity in the eyes, no significant changes in the SIT group after less than 1 year of treatment were found. The CPT method that we used is at best semi-quantitative; it might not be adequate for measurement of treatment efficacy, because there are difficulties in estimating the exact limit between a positive outcome and a negative outcome when a subjective visual method is used. It seems easier to discriminate negative and positive results at provocation in nasal mucosa than in conjunctiva, as shown in a study by Malmberg et al.²⁶ Other factors, such as number of patients tested and allergen dilution, play a role.²⁷ Another important factor in our study is length of treatment, inasmuch as CPTs were performed after less than 1 year of SIT.

During the birch pollen seasons, patients were requested to use antihistamine and cromoglycates for upper airway symptoms and short-acting β_2 -agonists for lower airway symptoms. Topical steroids were allowed only if absolutely necessary and only after consultation with the investigator. Three patients in the placebo group and 2 patients in the SIT group used nasal steroids for a few days in 1997. In 1998, 1 patient in the placebo group and 1 patient in the SIT group used nasal steroids (for 15 and 11 days, respectively). Because the use of topical steroids was limited and was similar for the 2 treatment groups, we believe that it did not affect the statistical analysis.

Although a significant difference in symptoms and use of medication between the active and placebo groups was seen even during the first season, it was more pronounced during the second season despite the higher pollen count. The effect of preseasonal treatment is confirmed by earlier pollen studies. In a placebo-controlled study of grass pollen SIT with standardized grass pollen extract (Alutard SQ *Phleum pratense*), Varney et al⁶ found clinical improvement after just 8 weeks of treat-

ment. There are indications that there is an additional effect of SIT during the years following, as shown by Walker et al²⁸ and Dolz et al.²⁹

The question of the optimal length of treatment for obtaining long-term clinical efficacy after cessation of SIT has been little studied. Using standardized house dust mite extract in patients with asthma, Des Roches et al³⁰ showed that the duration of efficacy after SIT was related to the duration of SIT itself. Patients receiving a short course of SIT relapsed more often than patients receiving a longer treatment. In a double-blind, placebo-controlled study of SIT in children with house dust mite asthma in which tyrosine-adsorbed house dust mite extract was used, Price et al³¹ showed deterioration of asthma symptoms in a group of patients in whom active treatment was stopped after 1 year compared with a group of patients receiving active treatment for a second year.

SIT as treatment for birch pollen allergy is safe. The number of acute adverse events (<30 minutes after injection) was larger in the placebo group; there were no differences between the active and placebo groups with respect to nonacute adverse events (>30 minutes after injection). Patients in the 2 treatment groups had similar numbers of upper airway infections during the treatment, and these were not related to immunotherapy. One patient in the active group developed itching nodules on the upper arm at the site of injections and was withdrawn from the study. This sort of nodule was earlier described after subcutaneous injections of extract containing aluminum.³²

In conclusion, the results of this 2-year, double-blind, placebo-controlled study show that SIT with aluminum-adsorbed depot birch extract (Alutard SQ) is an effective and safe treatment method for reducing allergy symptoms and medication in birch pollen-allergic patients.

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