

A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma

Sabina Rak, MD, PhD,^a Christina Heinrich, MD,^b Lars Jacobsen, PhD,^c
Annika Scheynius, MD, PhD,^d and Per Venge, MD, PhD^e Göteborg, Västerås, Stockholm,
and Uppsala, Sweden, and Hørsholm, Denmark

Background: Both specific immunotherapy (SIT) and nasal steroid (NS) have been shown to effectively reduce symptoms of allergic rhinitis. Although a number of investigators have convincingly shown anti-inflammatory effects of both treatments in separate studies, few comparative studies have been performed.

Objective: The purpose of this study was to compare the effects of preseason SIT with a standardized allergen extract and NS in seasonal allergic disease (rhinoconjunctivitis and asthma).

Methods: We examined 41 patients allergic to birch pollen, 21 with rhinoconjunctivitis and 20 with both rhinoconjunctivitis and asthma; they were treated in a randomized, double-blinded comparative study with birch SIT and NS (budesonide 400 µg daily). Bronchial hyperresponsiveness was measured before and during the season. Changes in eosinophil number, eosinophil cationic protein, and eosinophil chemotactic activity (ECA) in peripheral blood were investigated.

Results: Symptoms of rhinoconjunctivitis increased significantly less in the NS-treated patients than in the SIT-treated patients during the final 2 weeks of the season ($P = .03$ and $P = .04$, respectively). Seasonal peak expiratory flow values decreased significantly only in the NS-treated patients ($P = .01$). In the NS-treated patients, bronchial hyperresponsiveness increased significantly during the season ($P = .0001$); however, SIT treatment prevented seasonal PC₂₀ increase in the asthmatic patients. Measurement of blood eosinophils, eosinophil cationic protein, and eosinophil chemotactic activity demonstrated significant seasonal increase only in the NS-treated asthmatic patients.

Conclusion: Treatment with NS was more effective than short-course preseason SIT in reducing symptoms of rhinoconjunctivitis; however, the 2 therapies were equivalent in terms of the need for rescue medication. SIT prevented seasonal increase in bronchial hyperresponsiveness, eosinophil number, eosinophil cationic protein, and eosinophil chemotactic activity only in asthmatic patients. The mechanisms underlying bronchial hyperresponsiveness developing during allergen exposure in rhinitis might be different from those operating in asthma. (*J Allergy Clin Immunol* 2001;108:921-8.)

Key words: Specific immunotherapy, nasal steroid, eosinophil, bronchial

Seasonal hay fever and asthma due to birch pollen is the most common expression of sensitization in Scandinavia.¹ Because allergen avoidance can hardly be practiced in case of pollinosis, allergic patients are often subjected to polypharmacy. Antihistamines applied orally and locally ameliorate nose and eye symptoms caused by histamine release from mast cells.² However, nasal obstruction, which reflects the inflammation caused by infiltration and activation of proinflammatory cells and their mediators, requires anti-inflammatory treatment.

Topical steroids, mostly in combination with antihistamines, are commonly used and have been demonstrated to be an effective treatment for seasonal rhinitis in a number of clinical trials. In addition, the anti-inflammatory effect of topical steroids has been proved in nasal lavage and biopsy studies.³ The other evidently effective symptomatic treatment in pollen-induced rhinoconjunctivitis is specific immunotherapy (SIT). This treatment has also been documented to be effective in placebo-controlled clinical studies with different pollens, such as birch,⁴ grass,⁵ and ragweed.⁶ Examination of nasal lavage fluids and skin and nasal biopsy specimens from treated patients has revealed decreased influx of inflammatory cells and mediators and less production of proinflammatory cytokines, thus confirming the anti-inflammatory effect of SIT.⁷

Only 1 previous study has attempted to compare the 2 treatment methods and their effects on rhinitis in the same patient population; however, the efficacy of the extract used for immunotherapy in that study was not optimal.⁸

We therefore designed a study in which a group of patients who were sensitized to birch pollen and had

From ^athe Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Göteborg; ^bthe Department of Otolaryngology, Central Hospital, Västerås; ^cALK-Abelló, Hørsholm; ^dthe Department of Medicine, Unit of Clinical Allergy Research, Karolinska Institute and Hospital, Stockholm; and ^ethe Department of Clinical Chemistry, University Hospital, Uppsala.

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Reprint requests: Sabina Rak, MD, PhD, Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.

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Abbreviations used

BHR:	Bronchial hyperresponsiveness
ECP:	Eosinophil cationic protein
ECA:	Eosinophil chemotactic activity
NS:	Nasal steroid
PEF:	Peak expiratory flow
SIT:	Specific immunotherapy

rhinoconjunctivitis with or without asthma was subjected to a double-blinded trial comparing the effects of pre-season SIT and nasal steroid (NS) on a number of parameters: symptoms of rhinoconjunctivitis and asthma, need for medication, bronchial hyperresponsiveness (BHR), blood eosinophil number, eosinophil cationic protein (ECP) level, and eosinophil chemotactic activity (ECA) in patients' sera before and during the birch pollen season.

PATIENTS AND METHODS

Patients

Forty-one birch pollen-allergic patients participated in the study. They were recruited among patients attending the ear, nose, and throat department at Västerås County Hospital. The study was approved by the Ethics Committee of Uppsala University.

There were 22 men and 19 women; the mean age was 29 years (range, 19-42 years). The diagnosis was based on history of rhinoconjunctivitis during the birch pollen season, positive skin prick test (SPT) results with birch pollen extract (ALK-Abelló, Hørsholm, Denmark), and specific serum IgE (CAP-FEIA, Pharmacia, Uppsala, Sweden). Sensitization to grass pollen was found in 30 of the 41 patients, and 30 of the 41 also had a positive SPT result with animal dander. Of patients with a history of allergy to animal dander, only those with no daily contact with animals were allowed to participate in the study. Patients with perennial symptoms and/or positive SPT results with mites or molds were not included. All patients were categorized according to whether they had rhinoconjunctivitis only ($n = 20$) or rhinoconjunctivitis with asthma ($n = 21$). The latter had histories of symptoms of the lower airways during the birch pollen season, such as dyspnea or exercise-induced symptoms, increased sensitivity to nonspecific stimuli, and need for β_2 -agonists. In this group, a positive methacholine test result ($PC_{20} \leq 8$ mg/mL) outside the pollen season was required for inclusion. Both groups were matched with regard to age, sex, and score for severity of seasonal disease; the last of these included SPT result, RAST value, and clinical score of severity during the preceding birch pollen season as measured on a visual analog scale. Subjects for an additional nonrandomized and nontreated control group ($n = 9$) were recruited to ensure that the amount of pollen during the season was sufficient to induce clinical symptoms as the other 2 groups were treated (Table I).

Clinical data

Diary cards were filled in daily for 1 week during the winter (ie, out of the birch pollen season) to obtain out-of-season baseline data and again just before and again during the birch pollen season (Fig 1). Daily symptom scores for the eyes and nose, each expressed as a number from 0 to 3 (0, no symptoms; 1, slight; 2, moderate; 3, severe) were registered. Peak expiratory flow (PEF), measured with a mini-Wright PEF-meter, was noted daily, in the morning and in the evening, and the best of 3 values was recorded.

Medication for eye and nose symptoms was recorded: decongestant (number of drops), local antihistamine (Levostine [levocabastine], number of drops) for the eyes and nose, and antihistamine tablets (Semprex [acrivastine], number of tablets). The medication score was counted as 1 for a drug with a duration of 8 hours (acrivastine), 1.5 for a drug with a duration of 12 hours (levocabastine), and 0.5 for decongestant. For asthmatic symptoms, the β_2 -agonist Ventoline (salbutamol, 0.4 mg/dose) was used when needed (number of doses).

Design

The study design is shown in Fig 1. Inclusion tests were performed during the winter of 1992-1993. After disease history was obtained, SPT, specific IgE testing for birch pollen, and methacholine challenge were performed. On the basis of history of lower airway symptoms and methacholine challenge result, each patient was classed as rhinitic, asthmatic, or both.

Patients filled in a diary card during 1 week out of season; these data served as baseline. Before the season, methacholine testing was performed and blood samples were collected for eosinophil count, ECP, and ECA.

Thereafter, the patients were randomized within the 2 groups (asthmatic and rhinitic) to either SIT with birch pollen extract (Alutard, ALK-Abelló) or placebo (diluent for Alutard spiked with histamine dihydrochloride). All patients reached maintenance dose before the birch pollen season.

Two weeks before the predicted start of the birch pollen season, the treatment with nasal topical steroids was commenced in such a manner that the actively SIT-treated patients received topical steroid placebo and the SIT-placebo-treated patients received Rhinocort Turbuhaler (budesonide) 200 μ g (Astra, Lund, Sweden) in each nostril once daily in the morning. Treatment with topical steroid continued throughout the entire birch pollen season—ie, for 6 weeks, beginning in the middle of April and lasting through the end of May. At approximately the peak of the season (the second week of May), methacholine challenge was performed and blood samples were collected.

SPT

SPTs were performed with a panel of highly standardized allergen extracts (Soluprick SQ, ALK-Abelló). The panel contained the following antigens: birch, hazel, alder, timothy, mugwort, 2 mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), 2 molds (*Cladosporium herbarium* and *Alternaria alternata*), and dog and cat dander. Glycerine solution served as a negative control and histamine dihydrochloride 10 mg/mL as a positive control.

Methacholine challenge

Challenge testing was performed according to a well-standardized procedure that has been described previously.⁹ Methacholine chloride was diluted in saline solution and delivered in nebulized form by means of a Pari Inhalerboy nebulizer (Paul Ritzau Pari Werken, Germany; output, 0.75 mL/min) via a mouthpiece during tidal breathing. Briefly, the test began with lung function measurements (Vitalograph, United Kingdom); this was followed by inhalation of saline solution for 2 minutes and then of methacholine solutions, beginning at 0.03 mg/mL and doubling at 5-minute intervals. FEV₁ was measured 2 and 4 minutes after each dilution until a decrease of 20% was obtained.

Patients who did not respond with 20% FEV₁ changes to the methacholine solution at 16 mg/mL were described as nonresponsive.

Immunotherapy

Specific immunotherapy with well-characterized and standardized depot preparations of birch pollen allergen extract (Alutard SQ, ALK-Abelló) or placebo was performed in accordance with the dosage scheme described by Nielsen et al.¹⁰ Alutard SQ is a depot extract

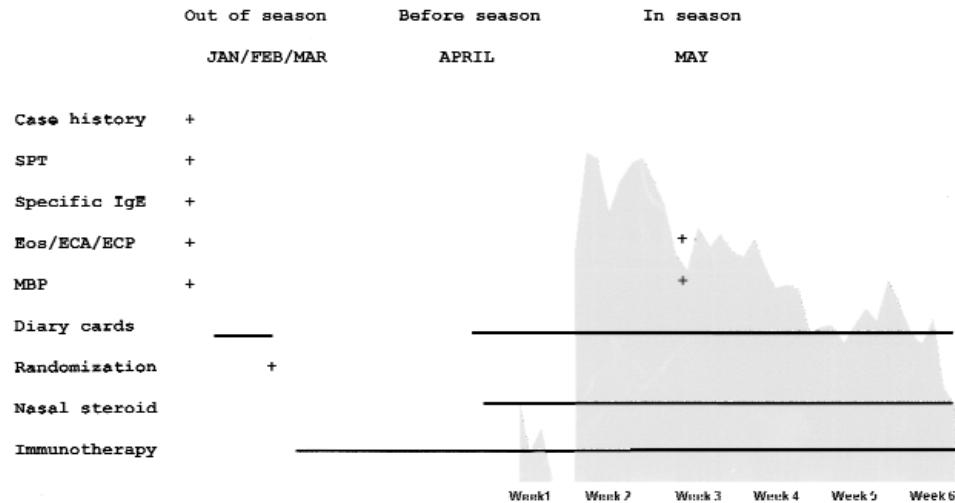


FIG 1. Design of the study. At inclusion, a case history was taken, SPT was performed, blood samples (specific IgE, Eos/ECP/ECA) were obtained, and methacholine tests were performed. After 1 week of diary card recording (the baseline), the patients were stratified into those with asthma and those with rhinitis and then randomized into treatment groups. Symptoms and medication were recorded throughout the pollen season. Blood samples and methacholine tests were performed again during the pollen season.

TABLE I. Demographic data

	Group		
	Specific immunotherapy (n = 21)	Nasal steroid (n = 20)	Control (n = 9)
Age* (y)	30 (18-41)	29 (21-42)	34 (21-45)
Sex: F/M	12/9	7/13	5/4
Specific IgE to birch* (KU/mL)	63.6 (1-674)	44.8 (1-156)	9.4 (6.7-28.9)
SPT result* (mm ²)	8.7 (4.5-11.5)	8.3 (5-11.2)	8.3 (4.5-13.5)
Visual analog scale in Spring 1992* (mm)	50.1 (1.5-95)	55.1 (6-96)	33.2 (5-52)

F, Female; M, male.

*Mean (range).

containing water-soluble allergen extract and aluminum hydroxide in which 100,000 standardized quality (SQ) units of birch extract contains 23 µg of allergen protein. Each patient reached the maintenance dose of 1 mL of 100,000 SQ and received a total of between 120 and 150 µg of allergen before the start of the season. Very few side effects were noted, and there were only local changes, such as redness and swelling. Birch SIT is usually not associated with complications, inasmuch as it is performed outside the pollen season.

Pollen count

The pollen count was registered daily with a Burkard volumetric pollen trap (Burkard Manufacturing, Herts, United Kingdom) that was placed on top of the nearby hospital building. Counts were expressed as numbers per cubic meter per 24 hours.

Blood eosinophil count

Blood eosinophils were counted on a Coulter STKS (Coulter, Electronics, Luton Beds, United Kingdom); each count was expressed as $x \times 10^6$ eosinophils per liter.

Eosinophil cationic protein

For determination of ECP, 4 mL of venous blood was collected in Becton Dickinson Vacutainer SST tubes (Franklin Lakes, NJ). The blood was left to clot for 60 minutes at room temperature and

then centrifuged at 1500g for 10 minutes and stored at -20°C . ECP was analyzed through use of Pharmacia CAP System ECP FEIA (Pharmacia Diagnostics AB, Uppsala, Sweden) according to the instructions of the manufacturer.

Eosinophil chemotactic activity

For determination of the serum ECA, 5 mL of blood was drawn and serum was stored at -70° . For the preparation of granulocytes, blood was obtained from apparently healthy subjects. Serum ECA was assayed with a modification of the Boyden chamber method, as described previously,¹¹ and expressed as percent of the migration toward normal pooled serum.

Statistics

For patient data, symptom scores, medication, and PEF variation, weekly means were calculated and compared through use of the Student *t* test. PC_{20} was calculated by linear interpolation on a logarithmic scale. The analysis of PC_{20} values was performed after logarithmic transformation to stabilize the variance. BHR, eosinophil, ECP, and ECA values are shown as medians and ranges, and nonparametric statistical analysis was used—the Wilcoxon matched-pair test within the groups and the Mann-Whitney *U* test for comparison between treatment groups. Statistica software (StatSoft, Tulsa, Okla) was used. A *P* value of less than .05 was considered to be statistically significant.

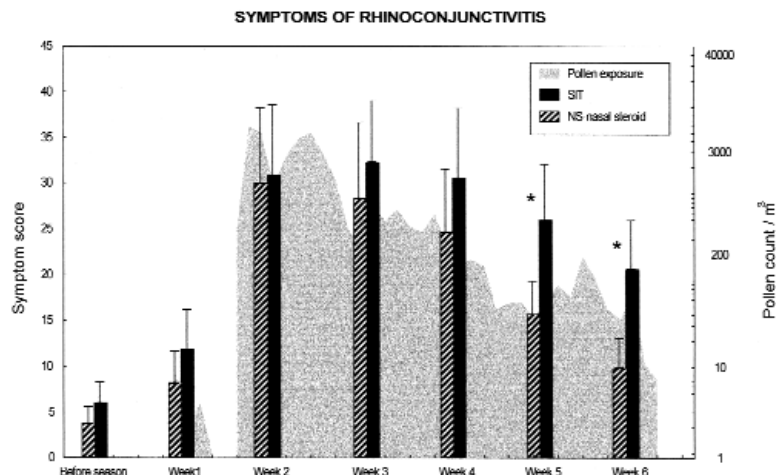


FIG 2. Significant increase in symptom scores in patients treated with SIT ($n = 21$) or NS ($n = 200$ in each week of the pollen season (beginning with week 2) in comparison with scores before the season (mean $\pm$ SD). Significance was at least $P < .05$ for each comparison. Comparison of the treatment groups shows significantly fewer symptoms in NS-treated patients than in SIT-treated patients at weeks 5 and 6 (* $P = .03$ and * $P = .04$, respectively).

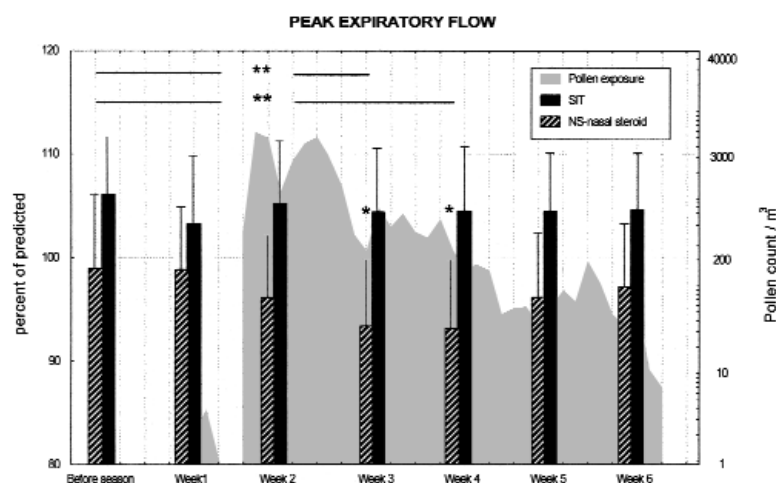


FIG 3. Unaltered PEF values throughout the pollen season in SIT-treated patients ($n = 21$). In comparison with PEF values before the season, PEF values in NS-treated patients ($n = 20$) were significantly lower during weeks 3 and 4 (** $P = .01$ and ** $P = .007$, respectively). The difference between the groups was significant for weeks 3 and 4 (* $P = .03$).

RESULTS

Birch pollen season

The birch pollen season of 1993 was exceptionally intensive, local birch pollen counts being the highest recorded in 50 years. Pollen release during May was extreme; it began at the end of April and continued through May.

Clinical data

All patients completed the study.

Symptoms of rhinoconjunctivitis. Daily symptom scores for the eyes and nose were added, and the means of daily sums per week are shown in Fig 2. The 2 treatment groups had comparable symptom scores before the

season. Rhinoconjunctivitis symptoms in the SIT group increased slightly before the start of the birch pollen season ($P = .02$), but the difference between the groups was not significant. However, significant increments in rhinoconjunctivitis symptoms were noted within each of the treatment groups in each week of the season in comparison with before-season values ($P = .002$).

When the symptoms in the 2 treatment groups were compared, significant differences were found during the final 2 weeks of the season; there were fewer symptoms among the NS-treated patients ($P = .03$ and $P = .04$ at weeks 5 and 6, respectively; Fig 2). A significant increase in symptom scores during the season (versus pre-season scores) was also found in the nonrandomized, nontreated control group ($p < .02$).

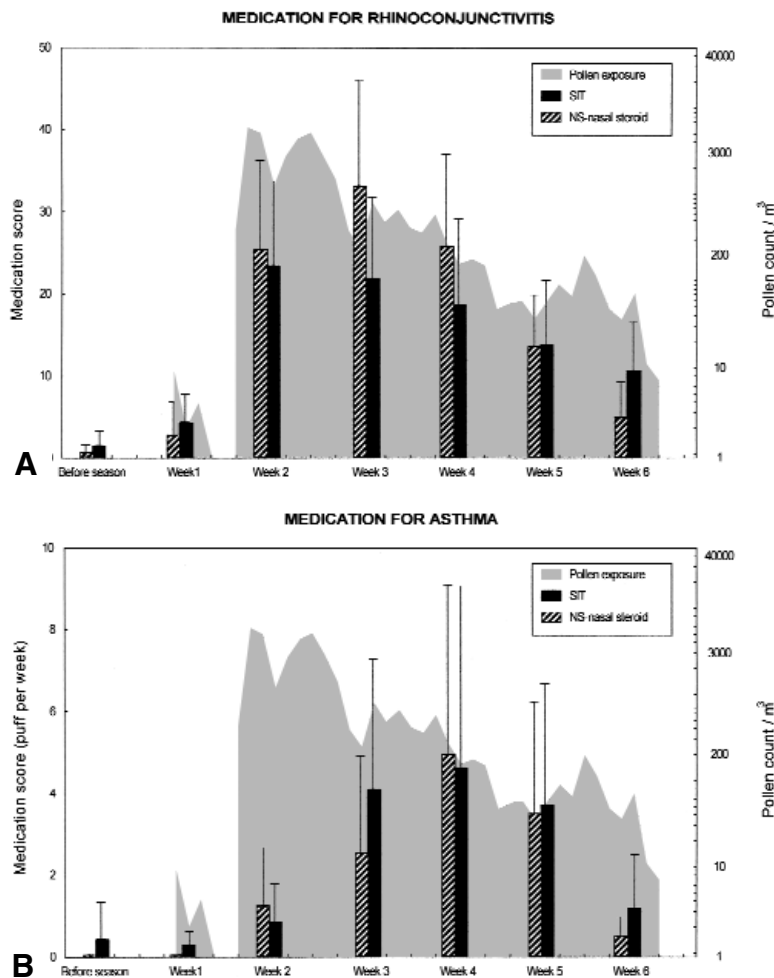


FIG 4. No significant differences were found between the SIT-treated ($n = 21$) and NS-treated ($n = 20$) groups with respect to medication for rhinoconjunctivitis. A tendency toward less medication use in the NS-treated group was noted in the last week of the season ($P = .06$). No difference in the use of β_2 -agonists was noted between the treatment groups.

Peak expiratory flow. Mean morning and evening PEF values were added, and weekly means were calculated. No significant difference between the groups was observed before the season. The SIT-treated group remained stable throughout the season. In the NS-treated group, PEF was lower during week 2, though the difference did not reach significance in comparison with preseason values ($P = .07$), and values were significantly lower during weeks 3 and 4 ($P = .01$ and $P = .02$, respectively). No differences were recorded during weeks 5 and 6 (Fig 3).

Medication

No significant differences were found between the groups with respect to medication for rhinoconjunctivitis and asthma, though in the last week of the season the NS-treated group showed a tendency to use less medication for rhinoconjunctivitis ($P = .06$). No difference in the use of β_2 -agonists was noted in the asthma group. It is interesting, however, that the peak use of medication occurred

at least 1 week later for asthma than for rhinoconjunctivitis (week 3). This agrees with our earlier experience that the peak for lower airway symptoms occurs later in the season than does the peak for upper airway symptoms.¹² Within each group, the use of medication increased significantly during the season in comparison with use before the season in both groups ($P < .05$; Fig 4)

Methacholine challenge

The median sensitivity to methacholine, measured as PC_{20} , was 12.75 mg/mL (range, 1.4-16) for all patients before the season; this increased to 1.13 (range, 0.45-4.05) during the season. The difference was highly significant ($P = .00009$).

When the patients were divided into rhinitics and asthmatics, it became clear that methacholine sensitivity increased significantly ($P = .0007$) only in rhinitics, from $PC_{20} > 16$ mg/mL before the season to a median of 3.0 mg/mL (range, 1.075-16) during the season. In contrast, methacholine sensitivity did not increase in asthmatics

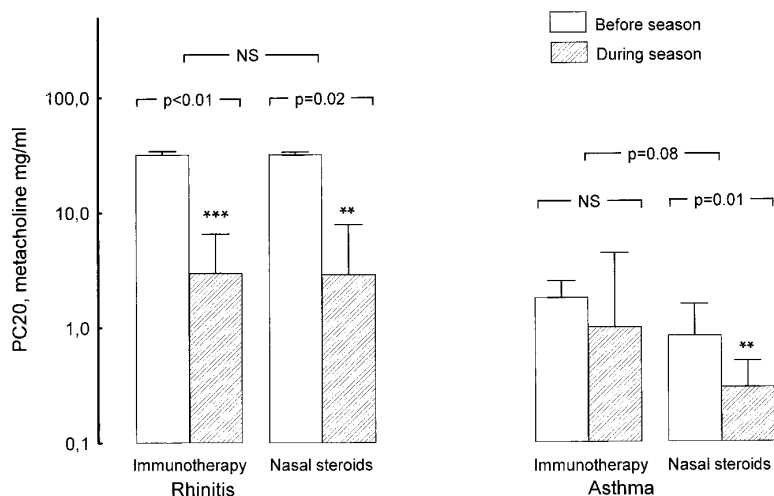


FIG 5. BHR expressed as PC₂₀ (in mg/mL) of methacholine concentration (logarithmic scale). In the SIT-treated group there was a significant seasonal increase among rhinitic patients (n = 9; ***P = .01) and no change among asthmatic patients (n = 11). In the NS-treated group there was a significant seasonal increase in rhinitic patients (n = 9; **P = .04) and asthmatic patients (n = 11; P = .02).

TABLE II. Eosinophil count, ECP, and ECA for rhinitis and asthma patients by treatment group

	Rhinitis		Rhinitis and asthma	
	NS (n = 10)	SIT (n = 10)	NS (n = 11)	SIT (n = 10)
Eos (× 10 ⁶)				
Before season	146 (100-444)	156 (60-365)	90.5 (40-434)	100 (82-603)
Seasonal	235 (60-928)	220 (108-468)	440* (120-882)	171 (90-759)
ECP (μg/L)				
Before season	8.5 (3.6-17.0)	11 (4.4-26.5)	11.2 (3.3-20.2)	8 (5-18.8)
Seasonal	13.5 (3.9-41.8)	11 (4.6-36.5)	28.3† (5.3-58.4)	11 (4.1-45)
ECA (%)				
Before season	108 (98-125)	110 (95-130)	105 (91-145)	105 (98-120)
Seasonal	115 (103-182)	115 (68-130)	138* (81-203)	133 (69-155)

All values are medians (ranges). A significant increase was found in seasonal values compared with before-season values in NS-treated patients with rhinitis and asthma.

*P = .01 (Eos and ECA).

†P = .03 (CP).

(median PC₂₀ [range]: before the season, 1.25 [0.28-2.45]; during the season, 0.4 [0.19-1.6]), treatment notwithstanding.

In the rhinitis group, 4 of 21 patients (19%) had PC₂₀ values before the season that were no greater than 16 mg/mL (16.0, 12.75, 13.0, and 13.5 mg/mL); the 17 others had PC₂₀ values before the season that were greater than 16 mg/mL. During the season, 72% became clearly hyperreactive (P < .001). Only 6 (2 SIT-treated and 4 NS-treated) of these 21 patients still had PC₂₀ values greater than 16 mg/mL. When PC₂₀ values of rhinitic patients and asthmatic patients were calculated with respect to the given treatment, all except those of the SIT-treated asthmatics showed significant seasonal increases (Fig 5).

Eosinophil count

The eosinophil counts were similar in both patient groups (rhinitic and asthmatic) before the season. All patients showed some tendency toward a seasonal

increase; however, only in the NS-treated asthma group was the increase significant (P = .017; Table II).

Eosinophil cationic protein

Preseason ECP levels were comparable in the rhinitis and asthma groups before the season (median [range]: 9.6 [3.6-26.5] and 9.6 [3.3-20.2] μg/L, respectively). No significant changes were seen during the season in either of the groups. However, when the different treatment groups were evaluated separately, no changes were seen in SIT-treated patients (rhinitic and asthmatic), whereas in NS-treated patients, a significant seasonal increase was demonstrated in asthmatic patients (P = .03) but not in rhinitic patients (Table II).

Eosinophil chemotactic activity

ECA in serum was similar in the 2 patient groups before the season. There was a significant seasonal increase in the chemotactic activity of sera from NS-treated asthmatic patients (P = .01; Table II).

DISCUSSION

A seasonal increase in BHR was noted in this study in most of the sensitized patients, both asthmatic and rhinitic. Furthermore, in rhinitic patients with no demonstrable BHR or history of symptoms of the lower airways, the very high pollen load precipitated asthmatic symptoms and caused increased BHR. Although NS protected significantly better against symptoms of rhinoconjunctivitis for at least in part of the season, short pre-season SIT offered better systemic protection (lung function); however, the need for rescue medication was equivalent in both groups. In NS-treated asthmatic patients, no such protection was seen, and the seasonal increase in BHR, eosinophil number, ECP, and ECA was significantly larger in NS-treated than in SIT-asthmatic patients treated before the season.

In the extreme pollen season during which this study was conducted, very few rhinitic patients remained free of lower airway symptoms. Earlier studies demonstrated various numbers of rhinitic patients with increased BHR, some as great as 70%.^{13,14} Among pollen-allergic rhinitic patients, many develop BHR and asthma only during the pollen season—some only in very intensive seasons.

We earlier confirmed the relationship between BHR and inflammatory markers in peripheral blood, biopsy specimens, and bronchoalveolar lavage fluid.^{12,15,16} We have observed that high pollen exposure causes a shift of more severe symptoms toward the later phase of the season, which is explained by heavy priming after daily high pollen pressure.¹² Not surprisingly, during that period the local effect of NS was stronger than the effect of short pre-season SIT, which, unlike NS, had the advantage of stabilizing PEF values. It is difficult to explain why SIT treatment prevented seasonal BHR increase in patients classified as asthmatic but not in patients classified as rhinitic. A difference mechanism behind the lower airway symptoms of rhinitic individuals that is not affected by SIT could be suggested.

The lack of an untreated double-placebo group in the present study precludes assessment of each treatment separately with respect to seasonal symptoms, though there is extensive documentation of the beneficial effects of SIT and NS treatments in the literature.

It could be argued that comparing the effects of systemic (SIT) and local (NS) treatments on disease in a distant organ (asthma) is unfair and that local treatment with NS should not be expected to affect asthmatic symptoms during the season. However, a beneficial effect of NS treatment on the lower airways has been demonstrated in a number of studies performed on seasonal and perennial rhinitis.¹⁷⁻²¹ The reasons for the improvement can only be speculated on. One possibility is the restoration of normal conditions in the nose, preventing mouth breathing and direct allergen inhalation. Another possibility is that postnasal drip, spreading the released mediators, directly affects the mucosa of the lower airways, influencing airway inflammation and so resulting in BHR increase. The possibility of certain systemic effects cannot be excluded.

The work of Denburg et al²² indicates that the indirect systemic effect of very low levels of circulating steroid could inhibit hematopoietic processes in the bone marrow, thus affecting inflammatory changes in the distant organ. Local steroids might also exert an indirect effect by interfering with the chain of events following antigen-IgE-antibody coupling at many levels.

There is a whole array of studies showing the effects of steroid treatment in a variety of cells—antigen-presenting cells,²³ T cells,²⁴ mast cells,²⁵ and eosinophils²⁶—and on the production of mediators²⁷ and cytokines²⁸ in both upper and lower airways. The effect of NS treatment on a local factor (eg, IL-5 or eotaxin) that is derived from the affected tissue and that signals the bone marrow could be suggested. Both direct and indirect effects on bone marrow could be possible explanations of the local steroid effects.²² However, though the direct local effect of the drug applied topically will effectively suppress nasal symptoms, the response from the distant organ (the airways) will be measurable only on mild or moderate allergen exposure. Furthermore, high antigen pressure would render its protective effect insufficient. To overcome the effect of exposure on BHR and eosinophil parameters, higher doses of NS or perhaps treatment with oral steroids would be required. Indeed, it seems that a systemic steroid effect is needed to suppress eosinophil functions effectively.

We have confirmed earlier findings of an anti-eosinophilic effect of SIT.^{12,15,29} Natural exposure to inhaled allergen causes an increase in blood eosinophil numbers, ECP levels, and ECA in peripheral blood, nasal secretions, and bronchoalveolar lavage fluid.³⁰⁻³² In our study, pre-season SIT inhibited both migration (ECA) and activation (ECP) of eosinophil granulocytes in rhinitic and asthmatic patients. However, NS treatment prevented a seasonal increase in eosinophil markers only in rhinitic patients, whereas in asthmatic patients the distant effect of NS was insufficient. The data also confirm our earlier findings of the protective effect of SIT against seasonal BHR increase in asthmatic patients. However, SIT lacks that effect on pollen-induced BHR in rhinitic individuals. Consistency between SIT's action on BHR and its simultaneous action on eosinophil numbers and function would indicate association between these phenomena in lower airway inflammation in asthmatic individuals. Nevertheless, the dissociation of the effect in 2 different patient populations might suggest that the mechanisms behind seasonal BHR increase differ in patients with already established BHR and patients with BHR induced only by allergen exposure. Our findings also suggest that the mechanisms underlying the changes in BHR differ from the mechanisms regulating eosinophil functions.

We also conclude that the mechanisms underlying BHR developing after heavy allergen exposure in patients with rhinitis and basically healthy airways might be partially different from those operating in patients with asthma.

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