

Antihistamine premedication in specific cluster immunotherapy: A double-blind, placebo-controlled study

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Background: Specific immunotherapy treatment in allergic diseases involves a risk of systemic side effects. A double-blind, placebo-controlled study was performed in 45 patients allergic to pollen to determine whether pretreatment with loratadine could reduce the number and severity of systemic reactions during the dose-increase phase of cluster immunotherapy.

Methods: The patients received cluster immunotherapy with a standardized birch (*Betula verrucosa*) or grass (*Phleum pratense*) pollen extract adsorbed to aluminum hydroxide. The immunotherapy schedule involved seven visits and 14 injections to reach a maintenance dose of 100,000 standardized quality units. Loratadine, 10 mg, or placebo tablets were administered 2 hours before the first injection at each visit.

Results: A total of 720 injections were given (309 injections in 21 patients receiving loratadine and 411 injections in 24 patients receiving placebo). The median numbers of injections to reach maintenance dose were 15 (range, 14 to 18) in the loratadine group and 16 (range, 14 to 23) in the placebo group ($p = 0.037$). The numbers of patients with systemic reactions were seven (33%) and 19 (79%) in the loratadine and placebo groups, respectively ($p = 0.002$). Twenty-five reductions caused by systemic reactions were observed in the placebo group in contrast to nine in the loratadine group ($p = 0.047$). No life-threatening systemic reactions were observed in either group. Systemic reactions were, however, more severe in the placebo group, mainly because of a significantly higher incidence of urticaria (10 vs 1, $p = 0.022$).

Conclusion: Pretreatment with loratadine seems to reduce both the number and severity of systemic reactions in specific cluster immunotherapy. (*J Allergy Clin Immunol* 1996;97:1207-13.)

Key words: Allergy, immunotherapy, side effects, antihistamine, pretreatment

The clinical efficacy of immunotherapy as a specific treatment of allergy is well documented, but the treatment always involves a risk of side effects.¹ The frequency and severity of systemic reactions (SRs) vary between studies, with SRs in 0% to 100% of patients receiving immunotherapy.^{2,3} The main aim in immunotherapy is to reach optimum clinical effect with as few side effects as possible. Published immunotherapy studies are difficult to compare because of differences in se-

Abbreviations used

BU:	Biologic units
CPT:	Conjunctival provocation test
EAACI:	European Academy of Allergology and Clinical Immunology
LR:	Local reaction
PEF:	Peak expiratory flow
SPT:	Skin prick test
SQ-U:	Standardized quality units
SR:	Systemic reaction

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verity of disease, allergen extract, immunotherapy schedule, and differences in the grading of SRs.²⁻⁸ Reassessment of the "optimal top dose" of standardized extract, the use of conventional slow immunotherapy schedules, and small increments

TABLE I. Patient characteristics at inclusion

Patients	Loratadine group	Placebo group	p Value
M/F (no.)	13/8	17/7	0.526*
Age (yr)			0.864†
Median	30	30	
Range	20-56	23-59	
Allergy (yr)			0.309†
Median	14	15.5	
Range	4-32	4-49	
RC (no.)	21	24	
Asthma			0.258*
None	14	12	
Allergen contact only	1	5	
With or without allergen contact	6	7	
Allergen			0.873*
Birch	11	12	
Grass	10	12	
Specific IgE (no.)			0.941*
ML class 2	5	4	
ML class 3	9	11	
ML class 4	6	8	
ML class 5	1	1	
SPT response (mm)			0.183†
Median	7.5	9.6	
Range	5-13.75	5-13.75	
CPT result (no.)			0.175*
10 ² SQ-U/ml	0	3	
10 ³ SQ-U/ml	4	1	
10 ⁴ SQ-U/ml	12	15	
10 ⁵ SQ-U/ml	5	5	

RC, Rhinoconjunctivitis; ML, Magic Lite.

*Derived by chi square test.

†Derived by two-tailed Mann-Whitney test.

during the induction regimen have been proposed to reduce side effects.² In two rush protocols, premedication with methylprednisolone, ketotifen, and a long-lasting theophylline reduced the incidence of SRs.^{9, 10} Moreover, a very low incidence of SRs has been reported when prophylactic antihistamines were administered before injections.^{11, 12} These studies were, however, neither blinded nor controlled. A reduction in local cutaneous symptoms and urticaria and angioedema was seen in a placebo-controlled, double-blind study of pretreatment with terfenadine in patients allergic to honeybee venom, in contrast to no difference in respiratory and cardiovascular symptoms.¹³ Premedication has not been an accepted practice because of a lack of double-blind, placebo-controlled studies and because of concern

about masking a mild reaction, which with a future injection, could result in a more serious reaction.¹

We performed a double-blind, placebo-controlled study of antihistamine premedication in patients receiving cluster immunotherapy with pollen extracts. The aim of the study was to elucidate whether antihistamine pretreatment would influence the frequency and severity of SRs. Furthermore, we wanted to investigate a possible influence on time lag from injections to SRs and on local reactions (LRs).

METHODS

Patients

Forty-five patients, aged 21 to 59 years, who had had seasonal allergic rhinitis for a median duration of 15 years (range, 4 to 49 years), participated in the study. All patients fulfilled the criteria for immunotherapy according to the Position Paper from the European Academy of Allergology and Clinical Immunology (EAACI).¹ They had severe allergy symptoms in either April and May or May through July, corresponding to the birch and grass pollen seasons, respectively. All patients had a positive skin prick test (SPT) response (wheal diameter ≥ 3 mm) to *Betula verrucosa* or *Phleum pratense*, a specific IgE of class 2 or greater, and a conjunctival provocation test (CPT) result of 100,000 standardized quality units (SQ-U)/ml or less in response to birch or grass pollen allergen. No patients had received immunotherapy within the previous 5 years.

The study was approved by the local ethics committee, and written informed consent was obtained from all patients before admission to the study.

Extracts

The *B. verrucosa* and *P. pratense* extracts for SPT (Soluprick SQ), for CPT (Aquagen SQ), and for immunotherapy treatment (Alutard SQ) were supplied by Allergologisk Laboratorium (ALK, Hørsholm, Denmark). The raw material for the extracts was collected at different places in the United States and Europe. Microscopically verified pollen was dried, defatted, and extracted in isotonic buffer (neutral pH). Subsequently, the extracts were dialyzed and lyophilized (partly purified allergen extract).

The partly purified extracts were standardized relative to an internal standard by a combination of three independent methods: (1) quantitative immunoelectrophoresis for characterization and quantitation of the major allergens, (2) RAST inhibition for total allergenic activity, and (3) SPT on more than 10 clinically allergic patients as a control for biologic activity.¹⁴ Because the biologic activity of the standard in-house preparation (concentration of standard producing the same wheal reaction as 10 mg/ml histamine dihydrochloride, corresponding to 10,000 biologic units [BU])¹⁵ is known from testing a large number of clinically allergic patients, the

potency of the extracts could be calculated. The activity of the extracts was given in standardized quality units. The content of birch pollen major allergen Bet v1 was 23 µg per 100,000 SQ-U (30,000 BU) and the content of grass pollen major allergen Phl p 5 was 25 µg per 100,000 SQ-U (30,000 BU).

The same partly purified extracts of birch and grass were used for the production of Soluprick SQ (10,000 BU/ml, dissolved in 50% glycerol), for Aquagen SQ (freeze-dried), and for Alutard SQ (aluminium hydroxide absorbed, 0.5% phenol). The extracts were distributed in vials and stored at 4° C (39° F) until use, and all extracts were used well before the date of expiration assigned by the manufacturer.

Allergy testing

SPTs were performed with *B. verrucosa* or *P. pratense* (Soluprick SQ, SQ 108 or SQ 225, ALK) in duplicate on the volar side of the forearm according to the recommendations made by the EAACI.¹⁵ The wheal size was measured by the formula: $(D + d) \div 2$, with *D* being the maximum diameter, and *d*, its perpendicular diameter. A mean diameter greater than 3 mm was considered a positive result.

CPTs were performed with extracts of *B. verrucosa* or *P. pratense* (Aquagen, SQ 108 or SQ 225, ALK), diluted in isotonic saline solution on the day of testing. Allergen dilutions were 10-fold (100, 1000, 10,000, and 100,000 SQ-U/ml). The CPTs were performed by applying 1 drop of the diluent in the conjunctival sac and then increasing allergen solutions every 10 minutes until a positive reaction (conjunctival redness and itching) occurred.¹⁶ A reaction of 100,000 SQ-U/ml or less was considered to be positive.

Specific IgE was measured by a immunochemiluminometric method with a solid phase of paramagnetic particles (Magic Lite, ALK) according to the instructions of the manufacturer. A specific IgE class of 2 or greater was considered to be positive.

Patient assignment

The patients were assigned to active treatment with loratadine or placebo tablets by the method of minimization to secure two balanced treatment groups.^{17, 18} The method takes into account numerous variates (different risk factors), and it is possible to assign variates different importance by weighting. On the basis of this method, a computer program made a series of calculations to determine the assignment of the next patient in order to minimize the differences between the groups. In this study six variates were considered to be relevant to secure two equally balanced treatment groups: allergen extract (birch or grass), concomitant asthma, age, specific IgE, and CPT and SPT sensitivity (Table I). The variates were weighted, with 2 for allergen and asthma, and 1 for the remaining risk factors.

Twenty-one patients were assigned to active treatment with loratadine, and 24 patients received placebo tablets.

TABLE II. Schedule for dose increment

Week	Injected dose (SQ-U)
1	10
	100
	1,000
2	2,000
	4,000
3	6,000
	10,000
4	10,000
	20,000
5	30,000
	30,000
6	50,000
	50,000
7	100,000

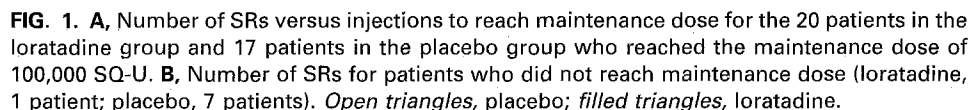
Patient groups were comparable with respect to sex, age, duration of allergy symptoms, specific IgE, and SPT and CPT sensitivity (Table I).

Antihistamine treatment

Loratadine (Claritin; Schering-Plough A/S, Farum, Denmark) is a non-sedating, selective peripheral H₁-receptor antagonist. It is rapidly absorbed after oral ingestion and reaches peak serum concentration after 60 to 90 minutes.¹⁹ In a double-blind treatment schedule, loratadine or identical placebo tablets were administered 2 hours before the first injection at each visit during the dose-increase phase. Patients returned the empty package after each tablet intake. No antihistamine intake was allowed for 4 days before injections.

Immunotherapy

The patients received immunotherapy with either *B. verrucosa* or *P. pratense* pollen extracts (Alutard SQ, SQ 108 or SQ 225, ALK). The practical performance of immunotherapy followed the EAACI Immunotherapy Position Paper guidelines.¹ Before each injection the physician evaluated the patient's condition including peak expiratory flow (PEF) by using a mini-Wright peak flow meter (Clement Clarke International Ltd., Harlow, England), and assessed the patient's suitability for immunotherapy. The clustered induction schedule of the department is shown in Table II. The patients received the injections at 30-minute intervals and stayed in the clinic for at least 30 minutes after the last injection. Dose modifications were made if SRs occurred, with either no increment, or reduction of the dose up to 4 steps. Patients who experienced severe SRs, repeated allergic rhinitis, or inconvenient large LR during cluster immunotherapy were transferred to the department's conventional (one injection a week) schedule. If SRs persistently occurred despite these preventive measures, the patients were excluded from the study.



Statistics

Treatment groups were compared by the chi square test of independence in 2 by 2 tables and by two-tailed Mann-Whitney U test.¹⁸ Comparison of treatment groups at each time point or interval was done by the exact two-sample Wilcoxon rank-sum test (Mann-Whitney).¹⁸ Statistical analyses were performed with the SPSS/PC software package, version 4 (SPSS Inc., Chicago, Ill.).²⁰ Probability (*p*) values of less than 0.05 were considered statistically significant.

Twenty patients (95%) in the loratadine group reached the scheduled maintenance dose and completed the study in contrast to 17 (71%) in the placebo group. The one patient in the loratadine group, who did not complete the study, stopped immunotherapy after five injections with no SR because of lack of time. The seven patients in the placebo group, who did not reach the maintenance dose, stopped immunotherapy after six to 24 injections. All seven patients experienced SRs (1 to 9 SRs, Fig. 1), but only one patient was excluded from the study because of SRs. This patient had

nine SRs during placebo treatment but was able to reach maintenance dose with no SR when pre-treated with antihistamine outside the study. Four patients discontinued immunotherapy during the pollen season. Three did not return because of the time-consuming schedule, and the fourth reached the maintenance dose but was out of the protocol. One person stopped immunotherapy after several dose modifications because of exceeding the time interval, which was caused by upper airway disease. The airway symptoms started after initiation of immunotherapy and disappeared after termination of the immunotherapy treatment. One patient stopped immunotherapy because of pregnancy.

Of the patients who reached the maintenance dose, four in the loratadine group were transferred to conventional immunotherapy during the dose-increase phase, three because of SRs and one because of inconvenient late LR. In the placebo group three patients who completed the study were transferred to conventional immunotherapy, all because of SRs. Of the patients in the placebo group who did not reach the maintenance dose, four were transferred to conventional immunotherapy because of SRs.

The median number of injections for the patients reaching the maintenance dose was 15 (range, 14 to 18) in the loratadine group and 16 (range, 14 to 23) in the placebo group ($p = 0.037$). The number of injections versus the number of SRs until the maintenance dose was reached for individual patients are shown in Fig. 1.

Symptoms and the number of SRs are shown in Table III. No life-threatening (grade 4) SRs were observed, either in the loratadine group or in the placebo group (Table III). SRs were more severe in the placebo group than in the loratadine group, with 28.2% versus 5.9% of the SRs graded as 3 ($p = 0.037$). The grade 3 SRs involved 10 episodes of urticaria and 1 episode of asthma in the placebo group versus 1 case of urticaria in the loratadine group (Table III). The difference in severity of the SRs was reflected in the number of dose reductions caused by SRs, with nine and 25 dose reductions in the loratadine and placebo groups, respectively ($p = 0.047$).

There was a significant difference in the number of patients with SRs, seven (33.3%) and 19 (79.2%) patients in the loratadine and placebo groups, respectively ($p = 0.002$) (Table III). In the loratadine group the maximum number of SRs per patient was seven, as opposed to nine in the placebo group ($p = 0.010$) (Fig. 1). The total numbers of injections were 309 and 411 in the

TABLE III. Number and distribution of injections and systemic reactions

	Loratadine group	Placebo group	<i>p</i> Value*
U+A+RC (no.)	0	3	
U+A (no.)	0	1	
U+RC (no.)	0	3	
U (single symptom) (no.)	1	3	
U (total)	1	10	0.022
A+RC (no.)	2	1	
A (single symptom) (no.)	5	4	
Asthma (total)	7	9	0.946
RC (single symptom) (no.)	9	21	
RC (total)	11	28	0.056
Itching without U (no.)	1	3	0.468
SR (total)	18	39	
Early SR (no.)	5	13	
Late SR (no.)	13	26	
Grading of SR (2/3/4) (no.)	(17/1/0)	(28/11/0)	0.037
Patients with SR (%)	33.3	79.2	0.002
Patients with RC (single symptom) (%)	23.8	33.3	0.482
Patients with A (%)	4.8	25.0	0.062
Patients with U (%)	4.8	25.0	0.062
Total injections (no.)	309	411	
SR per injection (%)	5.8	9.5	0.072

U, Urticaria; A, asthma; RC, rhinoconjunctivitis.

**p* values were derived by the chi square test.

loratadine and placebo groups, respectively. The number of SRs per injection was 5.8% in the loratadine group and 9.5% in the placebo group, but the difference did not reach statistical difference ($p = 0.072$) (Table III).

There was no difference in the percentage of SRs occurring late (72% vs 67% in the loratadine and placebo groups, respectively, $p = 0.214$) (Table III). The time interval from last injection to onset of urticaria symptoms was 30 minutes for the one patient in the loratadine group, whereas in the placebo group the median time was 2 hours after the last injection (range, 5 minutes to 9 hours). The time interval to onset of asthma symptoms ranged from 20 minutes to 24 hours in the loratadine group (median, 6.5 hours) and from 5 minutes to 24 hours (median, 1.6 hours) in the placebo group, with no significant difference.

The LR was significantly smaller in the loratadine group between 30 minutes and 24 hours after the injection (Fig. 2). According to the EAACI Immunotherapy Position Paper guidelines,¹ no increment in allergen dose is recommended if the early LR exceeds 5 cm or if the late LR is greater than 8 cm or inconvenient to the

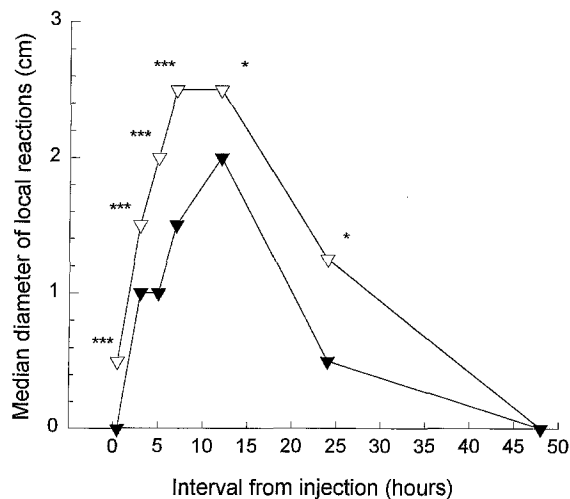


FIG. 2. Median diameter of LR after immunotherapy at different time intervals. Open triangles, Placebo; filled triangles, loratadine. Parameters were assessed by the exact two-sample Wilcoxon rank-sum test (Mann-Whitney). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

patient. No patients had an early LR greater than 5 cm. There was no difference in the number of late LRs greater than 8 cm between the loratadine and placebo groups, with late LRs greater than 8 cm in 6.5% and 9.5% of injections, respectively ($p = 0.144$). Similarly, no difference in the number of dose reductions caused by inconvenient late LRs was seen (8 vs 11, $p = 0.942$). No relation between late LR greater than 8 cm and SRs was observed at the same visit.

DISCUSSION

In this study, the number of patients experiencing SRs was high compared with other studies in which the same top dose of allergen was used. In this study 79% of the patients in the placebo group had SRs compared with 5% and 30% in another grass pollen and house dust mite study, respectively.^{5,7} These studies used a conventional (1 injection per visit) schedule in contrast to our cluster (2 to 3 injections per visit) schedule. An editorial on SRs reported a higher frequency of SRs in studies in which accelerated schedules were used compared with conventional schedules.² When compared with a pollen study in which an accelerated immunotherapy schedule was used, our results are in the same range.¹⁰ The pollen study did not include rhinoconjunctivitis as SR. If we excluded the patients with rhinoconjunctivitis as a single symptom, 50% in our study had SRs compared with 36.2%.¹⁰ The difference could be due to a difference in maintenance dose. In our

study the maintenance dose was 10 times higher than the corresponding top dose.¹⁰ The number of patients experiencing SRs in our study was still high, and the clustered dose-increase schedule should be performed in a specialized allergy department in a hospital, and not in usual office practice.

Pretreatment with antihistamine showed a significant reduction in the number of patients experiencing SRs, from 79% to 33% ($p = 0.002$). It is possible that patients with severe disease are more likely to experience side effects. In our study 12 patients in the placebo group and seven in the loratadine group had concomitant asthma (Table I). However, the difference was not statistically significant ($p = 0.087$ when the status with or without asthma was considered and $p = 0.258$ when the severity of asthma was taken into consideration [Table I]). Furthermore, there was no difference in the number of SRs involving asthma ($p = 0.946$, Table III). The numbers of SRs per injection were 9.5% and 5.8%, respectively, but the difference did not reach statistical significance ($p = 0.072$). This could be explained by the higher number of injections in the placebo group (placebo, 17.1 per patient vs loratadine, 14.7 per patient). The number of reductions caused by SRs was higher in the placebo group (25 vs 9). Furthermore, the SRs were also more severe in the placebo group, and because the number of dose-reduction steps (1 to 4 steps) was dependent on the severity of the SRs, the reductions consequently would be more pronounced, resulting in a higher number of injections.

The numbers of mild systemic reactions (grade 2) were 28 and 17, corresponding to 72% and 94% of total SRs in the placebo and loratadine groups, respectively. The grade 3 SRs involved 28% of the SRs in the placebo group and 6% in the loratadine group. One would expect a higher degree of severe SRs in the loratadine group, if antihistamines did mask the mild reactions, which with future unreduced doses, would result in more serious reactions. This study supports the conclusion that early warning signs of severe reactions are not masked by antihistamine pretreatment.¹¹

Pretreatment with antihistamine did not delay the onset of SRs. Sixty-eight percent of the SRs in this study were late SRs, but the reactions were mostly mild with only three reactions necessitating contacts to medical doctors (three in the placebo group). Other studies have provided data from 0% to 100% late SRs.^{2,3} In our study no SRs were seen after 24 hours. In three studies in which aqueous

extracts were used, no reactions were seen later than 45 minutes (observation time was 12 hours) either in patients without pretreatment or in patients treated with methylprednisolone, ketotifen, and a long-lasting theophylline.^{5, 9, 13} In two studies with depot extracts, SRs appeared after 1.5 to 8 hours in the first study with no information on observation time,⁸ whereas the second study had no late reactions within an observation period of 48 hours.⁷

In a placebo-controlled, double-blind study of pretreatment with terfenadine, 120 mg twice daily, in patients allergic to honeybee venom, a reduction in large LR and itching was seen.¹³ In this study we did not ask about subjective cutaneous symptoms, but there were no differences in reductions caused by large inconvenient LR and no differences in the number of late LR greater than 8 cm in mean diameter between the groups. This study did, however, show a reduction in median size of LR at 30 minutes to 24 hours, but the reductions were small, and the clinical relevance doubtful. The possible role of a large LR as a predictor of a later SR was not investigated in this study, but we did not find a correlation between large LR greater than 8 cm and SRs at the same visit.

In conclusion, pretreatment with antihistamine in specific cluster immunotherapy seems to reduce both the number and severity of SRs. There is no evidence of masking the early warning signs and of delaying the onset of SRs. The future role of antihistamine pretreatment in specific immunotherapy must, however, be established by further studies, involving different dosage regimens and larger groups of patients.

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