

Original article

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How long does the effect of birch pollen injection SIT on apple allergy last?

Background: Recent studies showed that injection specific immunotherapy (SIT) with birch pollen extract greatly reduces or cures the associated apple allergy in a large proportion of birch pollen-allergic patients. However, the long-term efficacy of SIT for apple allergy has not been assessed.

Objective: To evaluate the duration of the effect of injection SIT with birch pollen extract on apple allergy in birch pollen-allergic patients.

Methods: Thirty birch pollen-allergic patients showing both the clinical disappearance of apple allergy and a negative SPT with fresh apple at the end of their injection SIT course were followed-up at 12-month intervals from 6 months after SIT was stopped. Apple tolerance as well as SPT was assessed on all occasions. Fifty-seven birch pollen-allergic subjects without apple allergy and not submitted to SIT regularly followed-up for the onset of oral allergy syndrome (OAS) were used as controls.

Results: The overall prevalence of OAS after 30 months of follow-up did not differ between patients and controls. Although most patients became re-sensitized to apple by SPT over time, > 50% of them were still able to tolerate eating the fruit at the 30-month follow-up visit.

Conclusion: Although most patients show a 'natural', gradual propensity to apple re-sensitization (a consequence of prolonged and repeated inhalation of birch pollen responsible for primary sensitization?), the clinical effects of injection SIT on food allergy seem rather long lasting.

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Key words: apple allergy; birch pollen allergy; food allergy; oral allergy syndrome; specific immunotherapy.

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Accepted for publication 28 January 2003

In most patients with birch pollinosis, primary pollen sensitization is followed by the onset of oral allergy syndrome (OAS, defined as immediate itching with or without angioedema in the mouth and throat) caused by the ingestion of fresh fruit and vegetables as a consequence of cross-reactivity between pollen and food allergens (1–3). Apple allergy is very frequent in these subjects due to the high homology between Mal d 1, the major apple allergen, and the major birch pollen allergen, Bet v 1 (4–6). The finding that most allergenic epitopes of the apple are present in birch pollen (3, 5) has led to investigation of the effects of specific immunotherapy (SIT) with birch pollen extracts on food allergy in patients with birch pollinosis. Probably due to differences in populations studied, doses given, and route of administration, these studies have produced rather contrasting results (7–9). In a recent study carried out in this allergy center (9) 84% of patients submitted to injection immunotherapy with birch pollen extract reported a significant reduction in or the total disappearance of apple allergy, and in most cases the clinical effect was associated with a marked reduction or the total disappearance of skin reactivity to fresh apple as

well. The present study aimed to assess the long-term effects of injection SIT with birch pollen extract on apple allergy.

Patients and methods

Patients

The study was carried out on 30 adults (M/F 10/21; mean age 42.6 years, range 16–60 years) with a history of birch pollen allergy and typical OAS induced by apples who showed the complete disappearance of apple-induced symptoms and a negative SPT with fresh apple at the end of their SIT course. All had undergone injection SIT with a commercial depot aluminum hydroxide-adsorbed birch pollen extract (Allergopharma, Reinbeck, Germany) for 30–52 months (mean 39.0 months) that was stopped at the beginning of March 1998, 1999, and 2000 in 7, 13, and 10 cases, respectively, at which time the follow-up period began. Immunotherapy had been administered following a perennial schedule in all cases and patients were maintained on an optimal dose of pollen extract at 3-week intervals as previously described (9). Some patients (see Table 1) who decided to stop the SIT treatment after as little as 30 months due to work troubles but who tolerated apple and showed a negative SPT with fresh apple were included as well.

Table 1. Patient's characteristics and follow-up data

Patient	Sex/age	Before SIT		SIT duration (month)	End SIT (year)	6-month follow-up		18-month follow-up		30-month follow-up		42 month follow-up	
		SPT	OAS			SPT	Challenge	SPT	Challenge	SPT	Challenge	SPT	Challenge
1	F/46	3+	Yes	42	1998	Neg	Neg	Neg	Neg	3+	Positive		
2	F/40	4+	Yes	40	1998	Neg	Neg	Neg	Neg	3+	Positive		
3	M/34	3+	Yes	36	1998	2+	Positive						
4	F/59	4+	Yes	31	1998	Neg	Neg	Neg	Neg	Neg	Neg	2+	Neg
5	F/30	4+	Yes	39	1998	Neg	Neg	Neg	Neg	2+	Neg	3+	Positive
6	F/39	3+	Yes	30	1998	Neg	Neg	3+	Positive				
7	F/60	3+	Yes	40	1998	Neg	Neg	Neg	Neg	2+	Neg	2+	Neg
8	F/35	2+	Yes	30	1999	Neg	Neg	Neg	Neg	Neg	Neg		
9	F/43	3+	Yes	36	1999	Neg	Neg	Neg	Neg	Neg	Neg		
10	F/48	3+	Yes	32	1999	Neg	Neg	Neg	Neg	ND	Lost		
11	M/47	3+	Yes	39	1999	Neg	Neg	Neg	Neg	3+	Neg		
12	M/47	3+	Yes	28	1999	2+	Neg	3+	Neg	4+	Positive		
13	F/45	3+	Yes	42	1999	2+	Neg	2+	Neg	2+	Neg		
14	F/43	3+	Yes	40	1999	Neg	Neg	Neg	Neg	Neg	Neg		
15	F/42	3+	Yes	40	1999	Neg	Neg	Neg	Neg	Neg	Neg		
16	F/37	4+	Yes	40	1999	Neg	Neg	4+	Positive				
17	M/55	4+	Yes	40	1999	Neg	Neg	Neg	Neg	Neg	Neg		
18	M/51	3+	Yes	40	1999	Neg	Neg	3+	Positive				
19	F/33	4+	Yes	36	1999	Neg	Neg	3+	Neg	3+	Neg		
20	F/16	4+	Yes	42	1999	Neg	Neg	4+	Positive				
21	F/45	2+	Yes	40	2000	Neg	Neg	2+	Neg				
22	F/47	4+	Yes	38	2000	3+	Positive						
23	F/43	3+	Yes	52	2000	Neg	Neg	Neg	Neg				
24	M/28	3+	Yes	42	2000	3+	Neg	3+	Neg				
25	M/52	3+	Yes	40	2000	Neg	Neg	3+	Neg				
26	F/39	3+	Yes	40	2000	2+	Neg	2+	Neg				
27	F/50	2+	Yes	54	2000	2+	Positive						
28	M/42	3+	Yes	36	2000	2+	Neg	3+	Neg				
29	M/54	3+	Yes	30	2000	Neg	Neg	Neg	Neg				
30	M/28	4+	Yes	40	2000	4+	Neg	4+	Neg				

Neg, Negative; ND, not done; Lost, patient lost for follow-up.

Patients were encouraged to reintroduce the apple into their normal diet and to record whenever OAS relapsed. Follow-up visits were all carried out in September/October, starting 6 months after SIT was stopped and then at 12-month intervals up to 42 months. During the follow-up visits patients were thoroughly interviewed and underwent SPT with fresh apple. Moreover, open oral challenges with fresh apple (see below) were carried out as well in all those who did not report OAS relapse. The follow-up was stopped in patients reporting a relapse of their apple-induced OAS.

Skin tests

In order to avoid the variability caused by differences in allergenicity between apple strains (10), all skin tests were carried out using fresh Golden Delicious apples by the prick-prick technique, using 1 mm tip disposable prick lancets. All skin tests were carried out in duplicate. Readings were taken after 15 min. Wheals whose mean diameter was < 50, 50–100, 100, or > 100% of the wheal induced by histamine 10 mg/ml were graded as negative, 2+, 3+, and 4+, respectively.

Oral challenges

All patients not reporting OAS relapse on the follow-up visit underwent oral challenges with fresh Golden Delicious apples.

Patients were asked to chew about 10 g of fresh apple (including peel) for 1 min and then to spit it out. The appearance of itching in the mouth and/or throat during the following 15 min was considered a positive test.

Specific IgE measurements

Pre-SIT and post-SIT birch pollen-specific immunoglobulin E (IgE) were measured in 24 and 9 cases, respectively, by an immunoenzymatic assay (Allercoat, Kallestad, Germany); levels were expressed as arbitrary units per milliliter (AU/ml). Pre-SIT and post-SIT apple-specific IgE was measured in 12 and 10 patients, respectively, by CAP system (Pharmacia, Uppsala, Sweden); levels were expressed in kilounits per litre (ku/l).

Control population

A group of 57 adults (M/F 22/35; mean age 36.5 years) with birch pollen allergy but without OAS included in a previous study (11) was used as control population. Thirty-six of these subjects were positive and 21 negative on SPT with fresh Golden Delicious apple at the time of the first visit, when follow-up was started. Patients were asked to maintain their dietary habits, and were periodically controlled (every other month in most cases) for the onset of OAS (11). No control subject had undergone SIT yet when the follow-up

study was carried out. Birch pollen-specific IgE levels were measured before the start of the follow-up period.

As a previous follow-up study already demonstrated that birch pollen-allergic patients with OAS not submitted to SIT do not show any tendency to a spontaneous reduction or a disappearance of OAS (9), a control group of patients with OAS not submitted to SIT was not included in the present study.

Statistical methods

Owing to their skewed distribution, specific IgE levels were analyzed by nonparametric means, using Spearman's rank correlation test. Proportions were compared by two-tailed chi-square test with Yates' correction. Probability (*P*) values <0.05 were considered statistically significant.

Results

Patients' characteristics, duration of immunotherapy, and follow-up data are presented in Table 1. Although all patients reported a significant benefit on respiratory allergic symptoms after SIT, skin prick test (SPT) with birch pollen extract were unchanged or only slightly reduced (data not shown). At the 6-month follow-up, 27 of 30 (90%) patients were still apple-tolerant, but seven of them showed a positive SPT with fresh apple. All three subjects who reported a relapse of apple-induced OAS showed a positive SPT. All 27 remaining patients attended the 18-month follow-up visit; 23 of 27 (85%) were still OAS-free (i.e. tolerated the ingestion of the apple without any problem), but nine of them had become positive on SPT with fresh apple. All four patients who reported a relapse of apple allergy were positive on SPT. To date, 14 patients attended the 30-month follow-up visit. Eleven (78%) were still OAS-free, but five of them had become positive on SPT with fresh apple. All three subjects who reported a relapse of apple allergy were positive on SPT. Of three patients who attended the 42-month follow-up, two could still tolerate the apple, but both were positive on SPT. The remaining subject was also positive on SPT with fresh apple.

Oral allergy syndrome relapses were preceded or associated with a relapse in skin reactivity in all cases and were in no way associated with SIT duration, age, sex, and pre- or post-SIT birch pollen-specific IgE or apple-specific IgE (data not shown). The overall trend of apple-induced OAS and skin reactivity to apple from 0 to 30 months is presented in Table 2.

Control population

Twenty-five of 57 (44%) controls developed OAS during the follow-up period (after on average 11.8 months; range 1–60 months). Thirty-two (56%) control subjects were still OAS-negative after 18.3 months of follow-up (range 4–84 months). Twenty-three of 25 (92%) control subjects who developed OAS were positive on SPT with fresh apple at the start of the follow-up period. In contrast, 13

Table 2. Challenge test and SPT results 6, 18 and 30 months after the end of SIT

Time after SIT (mo)	No. without OAS (%)	No. with Negative SPT (%)
0	30/30 (100)	30/30 (100)
6	27/30 (90)	21/30 (70)
18	23/30 (76)	14/30 (47)
30	11/21 (52)	6/21 (29)

mo, months.

Table 3. Birch pollen- and apple-specific IgE levels before and after SIT course

Patient	Birch pollen-specific IgE (AU/ml)		Apple-specific IgE (KU/l)	
	Pre-SIT	Post-SIT	Pre-SIT	Post-SIT
1	8.36		3.37	
2	0.88			
3	10.43			
4	16.00	<0.35	1.90	<0.35
5	17.00	1.20	1.50	3.40
7	>17.5		0.50	8.00
8	15.70	12.20	1.80	2.30
9	10.30	4.85	18.50	10.70
11	5.00		1.12	
12	5.71	4.26	2.21	1.91
14	3.80			
15	2.58			
16	17.50	9.15	4.20	27.70
17	>17.5			
18	12.20	4.40	0.60	2.70
19	>17.5	11.30	4.30	3.30
20	7.22			
21	4.97			
22	14.20			
25	7.90			
26	2.90	1.30	0.80	0.50
27	3.95			
29	10.40			
30	9.65			

of 32 (41%) remained OAS-free (*P* < 0.001). Altogether, 23 of 36 (64%) vs two of 21 (10%) controls positive or negative on SPT with apple developed OAS during the follow-up period, respectively (*P* < 0.001). The mean birch pollen-specific IgE levels were 11.9 (median 11.5) AU/ml in patients who developed OAS and 6.7 (5.5) AU/ml in those who did not develop OAS (*P* < 0.001).

Comparison between patients and controls

The overall prevalence of OAS was nearly identical in patients and in the control populations after 30 months of follow-up [10 of 21 (48%) vs 25 of 57 (44%), respectively; *P* = NS]. Patients showed a significantly higher prevalence of OAS than the subset of controls showing negative SPT with fresh apple at the beginning of the follow-up period [10 of 21 (48%) vs two of 21 (10%), respectively; *P* < 0.025]. In contrast, controls showing a positive SPT with fresh apple at the beginning of the follow-up period

showed a higher prevalence of OAS than patients [23 of 36 (64%) vs 10 of 21 (48%), respectively], but the difference did not reach statistical significance.

Not surprisingly, pre-SIT birch pollen-specific IgE levels in patients' sera did not statistically differ from those found in sera from controls who developed OAS [average 10.0 (median 10.0) AU/ml vs 11, 9 (11.5) AU/ml, respectively] but were significantly higher than those observed in controls who did not develop OAS [6.7 (5.5) AU/ml; $P < 0.01$].

Discussion

While the long-term effect of SIT on allergic respiratory symptoms has been extensively investigated (12, 13), this is the first study that tried to evaluate the long-term efficacy of SIT with a pollen extract on a pollen-related food allergy. As this study was carried out on a selected population characterized by the total disappearance of both clinical symptoms and skin reactivity to the apple at the end of the SIT course, results might not be valid for the whole population of patients with birch pollen allergy and apple-induced OAS (9). However, the selection of such an 'anergized' population was essential to avoid bias caused by variability in serial skin testing, and grading of OAS severity in subjects with residual apple-induced oral itching and/or skin reactivity. Follow-up visits were all carried out in fixed, restricted periods in order to minimize bias caused by seasonal fluctuations in birch pollen-specific IgE levels. The use of open, unblinded food challenges might have introduced potential bias.

However, the extreme sensitivity to heat and oxidation of the main cross-reacting allergen (Mal d 1) would have made it very difficult to carry out double-blind placebo-controlled food challenges without substantial loss of allergenic activity of the food. Moreover, all patients had reintroduced the apple into their normal diet at the end of the SIT course, and spontaneously reported a relapse of OAS or a lasting tolerance at the follow-up visits.

As expected (9) birch pollen-specific IgE levels were reduced in most cases at the end of the SIT course, and some patients showed an increase in apple-specific IgE (Table 3). The reasons for this discrepancy are unclear, but this finding confirms that changes in specific IgE levels are not related to the clinical outcome in patients undergoing SIT (14). In contrast, the serological investigation confirmed the prognostic value of birch pollen-specific IgE levels for the development of OAS (11).

Although, in many cases, apple allergy showed a 'natural' tendency to recur after SIT was stopped (perhaps as a result of prolonged and repeated exposure to birch pollen responsible for primary sensitization), several patients were still able to eat apples without any problem and still showed a negative SPT as long as 30 months after the end of injection immunotherapy course. Interestingly, the prevalence of OAS in the study population after 30 months of follow-up was higher than that observed in a subset of controls negative on SPT with apple but lower than the other subset of birch pollen-allergic controls showing a positive SPT with apple. Altogether this study shows that, at least in some patients, pollen SIT can exert a rather long-lasting effect on pollen-associated food allergies.

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