

Clinical effects of immunotherapy on Japanese cedar pollinosis in the season of cedar and cypress pollination

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Abstract

Because of cross-allergenicity between *Cryptomeria japonica* (Japanese cedar) and *Chamaecyparis obtusa* (Japanese cypress) pollens, many Japanese cedar pollinosis patients have symptoms during the cypress pollination season. Therefore, the effect of immunotherapy (IT) specific for Japanese cedar pollinosis must be evaluated not only in the cedar season but also in the cypress season. Eight out of 16 patients with cedar pollinosis who received IT and the same number not receiving IT (non-IT) were studied. Nasal and ocular symptoms and medication(s) prescribed were classified from score 0 to 4 and score 0 to 3, respectively. The sum of these scores was used as the symptom-medication score (SMS). IT with Japanese cedar pollen extract reduced the daily SMS not only in cedar but also in the cypress pollination season, but not significantly. However, after the season, the mean SMS in the IT group tended to be lower than that in the non-IT group ($P < 0.1$). In conclusion, IT was useful as well as concomitant medications also in the cypress season, and considered to shorten the long-drawn symptoms persisting after the season. © 1997 Elsevier Science Ireland Ltd.

Keywords: Immunotherapy; Japanese cedar pollinosis; Pollination; *Cryptomeria japonica*; *Chamaecyparis obtusa*

1. Introduction

Pollen of *Cryptomeria japonica* (Japanese cedar), which accounts for a large part of the Taxodiaceae family, is scattered from February to March and that of *Chamaecyparis obtusa* (Japanese cypress), which belongs to the Cupres-

saceae family, is scattered from March to April. Both pollens are important allergens causing pollinosis in spring in our country. Because of cross-allergenicity between the Taxodiaceae and the Cupressaceae pollens [1–3], many cedar pollinosis patients continue to have allergic symptoms even after the cedar pollen season which is followed by the cypress season. About 70% of cedar pollinosis patients were positive for cypress pollen when tested by RAST and those positive for

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cypress RAST were likely to have long-drawn symptoms until the end of April or May [4]. Therefore, it is necessary to evaluate the symptoms of cedar pollinosis patients not only in the cedar season but also in the cypress season.

Herein, we investigated the effect of immunotherapy (IT) with Japanese cedar pollen extract on the prevention of allergic symptoms in the IT and non-IT groups of patients with cedar pollinosis in the season of high cedar and cypress pollen counts, in the prevailing year, 1993.

2. Materials and methods

2.1. Subjects

The subjects were eight out of 16 patients with cedar pollinosis who received IT and the remaining eight patients not receiving IT. All patients in the IT and non-IT groups had histories of seasonal rhino-conjunctivitis in spring and were positive for Japanese cedar in the intradermal skin test and CAP-RAST. Seven out of eight patients in the IT group and seven out of eight patients in the non-IT group showed positive CAP-RAST for Japanese cypress. Sera from five out of eight patients in the IT group and four out of eight patients in the non-IT group were reacted with the extract of pine, oak, alder, elm, orchard grass or house dust mite. There was no significant difference between the two groups of patients in terms of age, age of onset, period of disease, severity of symptoms, CAP-RAST class for Japanese cedar or Japanese cypress and serum IgE level (Tables 1 and 2). The mean duration of IT in the IT group was 7.1 ± 0.8 years ranging from 4 to 11 years. The patients in the IT and non-IT groups resided in the country or city with little influence of air pollution, and six of the eight patients in each group lived less than 5 km from our hospital, that is, the pollen counting site. Therefore, the amount of pollen exposure in the two groups of patients was not markedly different.

Table 1

Clinical characteristics of immunotherapy (IT) and control groups of patients

	IT group	Non-IT group
No. of cases	8	8
Sex (m:f)	0:8	1:7
Severity of symptoms prior to study		
Severe	7	7
Moderate	1	1
Mean age (years)	46.6 ± 2.8 (37–61)	47.8 ± 3.6 (34–61)
Mean age of onset of pollinosis (years)	32.9 ± 3.3 (22–49)	34.5 ± 4.1 (18–48)
Mean duration of pollinosis (years)	13.8 ± 1.9 (8–24)	13.3 ± 1.8 (6–22)
Mean duration of immunotherapy (years)	7.1 ± 0.8	—

There was no significant difference between the two groups (two-tailed *t*-test). Data indicates mean $\pm$ S.E. and parenthesis shows range of item.

2.2. Method of immunotherapy

It was designed as previously described [5], briefly, starting with 0.02 ml of aqueous extract of Japanese cedar pollen (Torii and Co., Tokyo, Japan) at 1/10 concentration of threshold in the intradermal skin test, it was increased by 50% and administered once a week. The maintenance dose was 0.5 ml of the aqueous extract of 1:1000 (w/v) dilution every 4 weeks in general. However, this concentration was individually adjusted according

Table 2

Serum IgE levels and IgE antibodies specific for the pollen of Japanese cedar or Japanese cypress in two groups of patients

	IT group	Non-IT group
Serum IgE level (U/ml)	88.2 ± 44.0	186.1 ± 82.5
IgE antibodies specific for Japanese cedar (CAP RAST class)	4.13 ± 0.23	3.88 ± 0.23
IgE antibodies specific for Japanese cypress (CAP RAST class)	2.38 ± 0.38	2.25 ± 0.37

No statistical significance was seen between serum IgE levels and specific IgE antibody titers (two-tailed *t*-test). Data indicates mean $\pm$ S.E.

Table 3
Scoring system for symptoms on diary cards

Symptoms	Grade of symptoms for score				
Sneezing	None:0	Mild:1 (1–4)	Moderate:2 (5–9)	Severe:3 (10–29)	Violent:4 (>30)
Runny nose	None:0	Mild:1 (1–4)	Moderate:2 (5–9)	Severe:3 (10–29)	Violent:4 (>30)
Stuffy nose	None:0	Mild:1	Moderate:2	Severe:3	
Itchy eyes	None:0	Mild:1	Moderate:1	Severe:2	

The symptoms in two groups of patients were recorded in their diary cards. Parenthesis indicates the range of frequency of their sneezing attack or blowing nose in a day.

to the diameter of focal swelling, to be less than 5 cm, 20 min after subcutaneous injection.

2.3. Estimation of symptoms and medications

Nasal and ocular symptoms described in the patient's diary cards were classified according to the previous report [5] as follows: sneezing and runny nose represented from score 0 to 4; stuffy nose appeared from score 0 to 3; itchy eyes were expressed as score 0 to 2 (Table 3). Patients in IT and non-IT groups were concomitantly treated with medicine(s) to relieve their symptoms to the approved level. The medicine(s) prescribed were also classified from 0 to 3 (Table 4). We used either mequitazine, ketotifen, oxatamide or azelastine hydrochloride as oral-antihistamines, and naphazoline nitrate twice a day as nasal drops, and flunisolide twice a day as focal steroids. The sum of these scores was used as the symptom-medication score (SMS). No medication to prevent the allergy itself was administered before the pollen season.

Table 4
Scoring system for medications on diary cards

Medications	Scores
Oral-antihistamines	
Once a day	1
Twice a day	2
Nose drops (excluding focal steroids)	1
Focal administration of steroids	2
Oral-antihistamines and focal steroids	3

The prescribed medications in two groups of patients were recorded in their diary cards.

2.4. Sampling and count of pollens

Pollen floating in the environment around Hisai city was sampled using Durham's pollen sampler on the roof of Tsu National Hospital and counted as grains per cm².

3. Results

Fig. 1 shows the daily averages of every 5-day counts of pollen from various trees and grasses during February, March, April and May in 1993. Total pollen counts of the Taxodiaceae and the Cupressaceae were 6211 per cm² and 6096 per cm², respectively, in a high pollination year, 1993. The pollen counts in 1993 were less than that in 1991, but markedly higher than those in the corresponding period during these 7 years. The other tree pollens such as pine and oak or the grass pollens were scattered from April to May and alder pollen was scattered from February to May in our area.

SMS and pollen counts of the Taxodiaceae and the Cupressaceae were shown by daily averages of every 7 days during 16 weeks from February 5 to May 27 (Fig. 2). Alterations of the SMS in the two groups corresponded to those of the pollen season, that is, the first peak of the mean SMS in both groups was observed when the Taxodiaceae showed marked pollination in the week from March 5 to 12 and the second peak of mean SMS in both groups was seen in the week of April 16 when the Cupressaceae pollen dispersed. The mean SMS in the IT group was lower than that in

POLLEN COUNTS/cm²/DAY
(MEAN OF 5 DAYS)

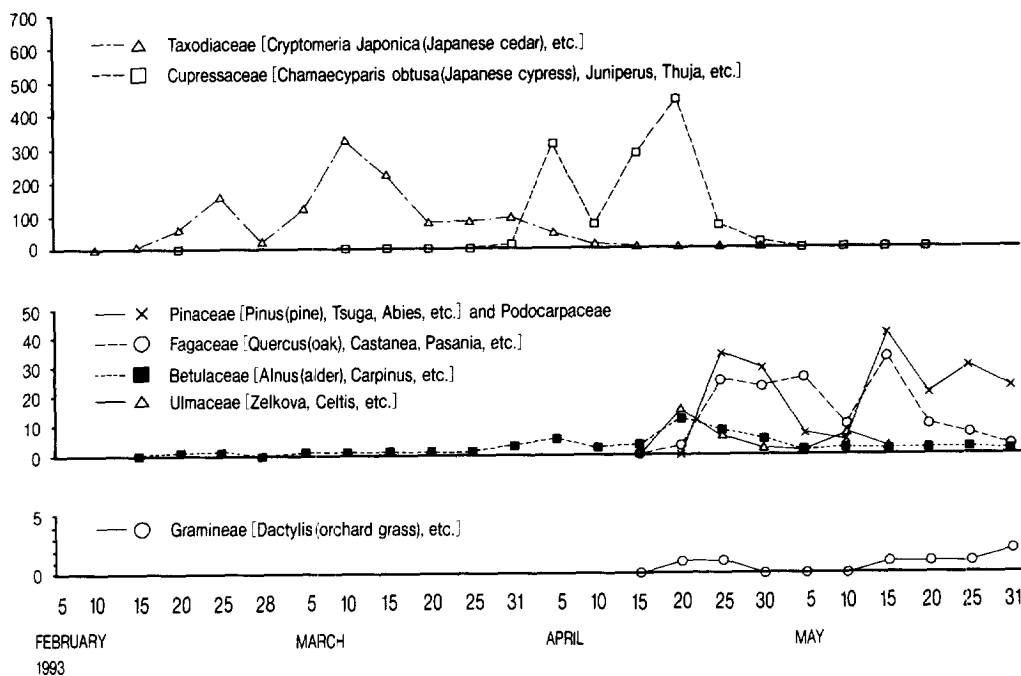


Fig. 1. The counts of airborne pollen from various trees and grasses during the study period.

the non-IT group throughout the study period. The effect of IT in improving the symptoms in patients was examined by comparing the mean SMS in the IT group with that in the non-IT group in the season of cedar (from February 12 to March 25), cedar-cypress (from March 26 to April 8), cypress (from April 9 to April 29) and after season (from April 30 to May 27) (Fig. 3). In cedar, cedar-cypress and cypress season, no significant difference was detected in the mean SMS between the IT and non-IT groups. However, after the season, the mean SMS in the IT group tended to be lower than that in the non-IT group ($P < 0.1$). Then weekly means of daily averages of scores of symptoms and medication in the IT group were similarly compared with those in the non-IT group in the same period as above (Table 5). There was no significant difference between the two groups in either period in the scores of sneezing, runny nose or itchy eyes. The mean score of

stuffy nose in the IT group was significantly lower than that in the non-IT group after the season, and the mean medication score in the IT group was significantly lower than that in the non-IT group in the cedar-cypress and cypress season.

4. Discussion

Several control studies revealed that IT successfully reduced the severity of clinical symptoms caused by allergic pollens, such as grasses, ragweed, mountain cedar and birch [6]. However, a satisfactory result has not been reported in the specific IT for Japanese cedar pollinosis [7,8].

The effect of IT specific for Japanese cedar pollinosis is very difficult to evaluate. Cedar pollinosis patients complain of a wide variety and severity of symptoms, because over a ten-fold difference in the total pollen counts of the Taxodi-

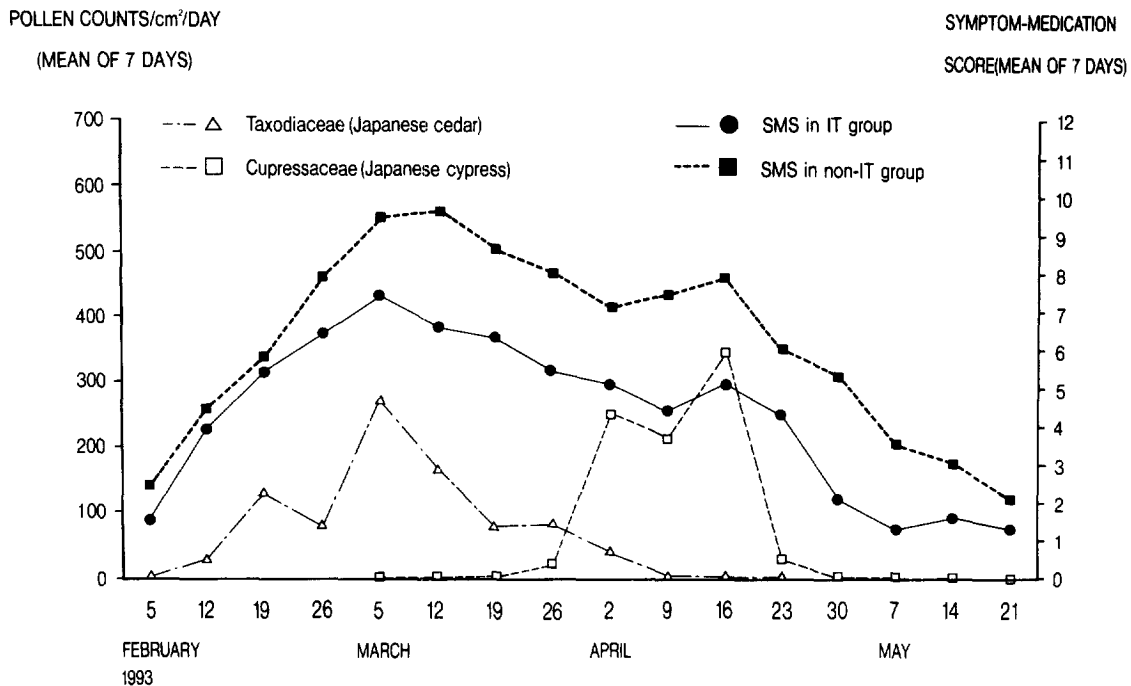


Fig. 2. Daily averages of SMS in two groups of patients from February to May. The SMS is represented as the sum of symptom and medication scores estimated in Tables 3 and 4. Solid line indicates the daily averages of SMS in the IT group and broken line shows those in the non-IT group. SMS in the IT group tended to be lower than that in the non-IT group throughout the study period.

aceae and the Cupressaceae is observed year by year. Therefore it is difficult to compare the symptoms before and after IT in each individual. Secondly, the concomitant use of medicine to relieve their symptoms in a prevailing year, such as 1991 or 1993 might interfere with the evaluation of IT. Finally, since many cedar pollinosis patients also may have symptoms during the cypress season because of cross-allergenicity between the Taxodiaceae and the Cupressaceae pollens [1–3], the influence of the cypress pollen count and duration of pollination should be taken into account to evaluate their symptoms. To eliminate these possibilities and for appropriate comparison, control patients having clinical characteristics and symptoms similar to those in the IT group of patients were selected as a non-IT group in this study. Furthermore, the mean SMS in these groups were compared in both cedar and cypress seasons and after the season, and medication scores were ana-

lyzed to evaluate the symptoms of the patients in addition to symptom scores. Moreover the same proportions of patients having a positive reaction to other allergic pollens, such as oak and alder in the IT and non-IT groups were likely to exclude the implication of these pollens to influence the symptoms of the patients in this study.

In the present study, there were no significant differences in the mean SMS between the IT and non-IT groups in the cedar season, which was in agreement with recent reports [7,8]. However, the SMS in the IT group tended to be lower than that in the non-IT group after the season, because of significantly low score of stuffy nose in the IT group. Pollinosis patients might still have symptoms after the season because of exposure to pollen on the ground or remaining in house dust after airborne cedar and cypress pollen had disappeared [9]. Therefore evaluation of symptom after the season was important as well as during the

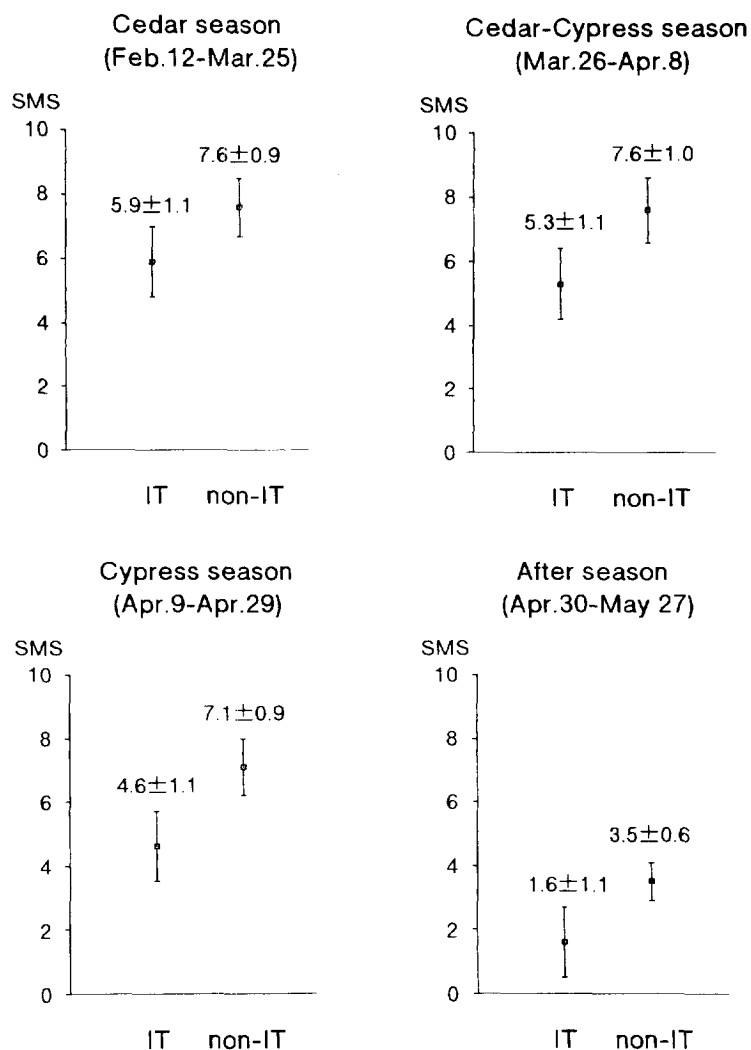


Fig. 3. Means of the daily averages of SMS in the IT and non-IT groups in cedar, cedar-cypress, cypress pollen season and after the season. Data indicate mean $\pm$ S.E. No significant difference between the IT and non-IT groups was seen in the mean SMS in any season, but the mean SMS in IT group tended to be lower than that in the non-IT group after the season ($P < 0.1$).

season, because the long-drawn symptoms after the season might be a disadvantage to each patient. Naito et al. [10] reported that in the season of high Japanese cedar pollen count, the values of mean nasal airway resistance remained elevated for 2 months after the season, and exposure of a large quantity of Japanese cedar pollen could construct non-specific nasal hyper-reactivity, and it might be a cause of long-drawn nasal symptom.

From our present study, we supposed that IT was effective for stuffy nose because of restraining non-specific hyper-reactivity of nasal mucosa owing to a large quantity of pollen antigen explosion during a season. In other words, IT could restrain the allergic reaction itself more effectively than various medications, then it could reduce the non-specific hyper-reactivity so called 'priming effect' proposed by Connell [11].

Table 5

Mean of the daily averages of symptom scores and medication scores in IT and non-IT groups in cedar, cypress and after season

			IT group	Non-IT group
Cedar season (Feb. 12–Mar. 25)	Symptom scores	Sneezing	1.46 ± 0.37	1.77 ± 0.23
		Runny nose	2.02 ± 0.37	2.19 ± 0.39
		Stuffy nose	0.79 ± 0.21	0.96 ± 0.24
		Itchy eyes	0.63 ± 0.14	0.77 ± 0.07
	Medication scores		1.19 ± 0.31	1.92 ± 0.31
Cedar–cypress season (Mar. 26–Apr. 8)	Symptom scores	Sneezing	1.25 ± 0.34	1.56 ± 0.29
		Runny nose	1.81 ± 0.45	2.31 ± 0.48
		Stuffy nose	0.69 ± 0.19	1.13 ± 0.31
		Itchy eyes	0.50 ± 0.19	0.56 ± 0.15
	Medication scores		1.00 ± 0.28*	1.94 ± 0.31*
Cypress season (Apr. 9–Apr. 29)	Symptom scores	Sneezing	1.13 ± 0.32	1.54 ± 0.32
		Runny nose	1.38 ± 0.44	2.17 ± 0.44
		Stuffy nose	0.83 ± 0.25	1.08 ± 0.25
		Itchy eyes	0.38 ± 0.16	0.38 ± 0.16
	Medication scores		0.88 ± 0.30*	1.83 ± 0.30*
After season (Apr. 30–May 27)	Symptom scores	Sneezing	0.41 ± 0.22	0.84 ± 0.18
		Runny nose	0.66 ± 0.41	1.03 ± 0.26
		Stuffy nose	0.03 ± 0.03*	0.59 ± 0.19*
		Itchy eyes	0.06 ± 0.06	0.06 ± 0.04
	Medication scores		0.41 ± 0.26	0.91 ± 0.20

Data indicate mean ± S.E. The mean medication score in IT group was significantly lower than that of non-IT group in cedar–cypress and cypress season, and the mean score of stuffy nose in the IT group was significantly lower than that of the non-IT group after the season (* $P < 0.05$ using two-tailed t -test).

The effect of IT on cedar pollinosis was equivalent to anti-allergic drugs at least in the cedar–cypress or cypress season because the mean medication score in the IT group was significantly lower than that in the non-IT group in the season. However, we concluded that the effect of IT under the present condition was not yet satisfactory.

Finally, the purity of extract from Japanese cedar pollen is one of the most important factors regulating the effects of IT. The major allergen of Japanese cedar pollen, sugi basic protein (SBP) with a molecular weight of 40 000, has been characterized by immunochemical techniques [12], and indicated to be Cry j 1. The Cry j 1 concentration in the aqueous extracts of Japanese cedar pollen allergen commercially available was too low, and there was a dispersion with the lot [13]. Recently the amount of Cry j 1 in the extracts of Japanese cedar pollen allergen has been standardized. We previously reported [14] that the commercially

available extract contained only a small amount of the major allergen and the patients receiving IT produced specific IgG antibodies against other proteins with low molecular weight contained in the extract together with the major allergen. These findings may explain the low effectiveness of IT on Japanese cedar pollinosis.

Ide [15] reported that the sequence of 7 N-terminal amino acids of Cha o 1 which was a major allergen of Japanese cypress was identical to that of Cry j 1, and participated in the cross-allergenicity between Cry j 1 and Cha o 1. Furthermore, he reported that IgE antibodies in the serum of 84% of the Japanese cedar pollinosis patients was combined with Cha o 1. In the present study, because IT with the Japanese cedar pollen extract had some effects also in the cypress season, the IgG antibody, particularly IgG4 antibody produced against the major allergen of Japanese cedar pollen might also have reacted with that of Japanese cypress pollen. Whether or not the specific IgG4

antibodies help improve the symptoms of patients remains unknown, but the reactivity between Cha o 1 and IgG4 antibodies in addition to IgE antibodies in the serum of cedar pollinosis patients who received IT with the Japanese cedar pollen extract is of interest.

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