

Sublingual Immunotherapy for Japanese Cedar Pollinosis

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ABSTRACT

Background: Although subcutaneous immunotherapy may cure allergic diseases, it is not commonly used in Japan because of the pain and risk of anaphylactic shock. Sublingual immunotherapy (SLIT) overcomes these limitations and although it is the most advanced form of local immunotherapy for clinical application, it is not used in Japan nor has it been extensively studied.

Methods: After obtaining approval from the Ethics Committee of Nippon Medical School and informed consent from five patients with cedar pollinosis (one man, four women; age range, 38–66 years), administration of a therapeutic extract was started in July 2001 or later (mean treatment period, 13.4 months). The clinical efficacy of SLIT and its influence on the quality of life, as measured by the Japanese Allergic Rhinitis QOL Standard Questionnaire, and the incidence of side effects were evaluated in 2003.

Results: Between February and April the mean severity score was 1.44 in the patients undergoing SLIT and 1.86 in the patients undergoing pharmacotherapy, and the respective mean QOL total scores during the season were 3.82 and 10.0. Neither systemic nor local side effects occurred during SLIT.

Conclusions: SLIT is safe and effective for Japanese cedar pollinosis.

KEY WORDS

allergic rhinitis, Japanese Allergic Rhinitis QOL Standard Questionnaire (JRQLQ), Japanese cedar pollinosis, quality of life, sublingual immunotherapy (SLIT)

INTRODUCTION

Subcutaneous injection immunotherapy is a painful procedure and has the risk of anaphylactic shock as a side effect, which is why it is not commonly used in Japan. To overcome these limitations, patients in Europe and the United States can undergo local immunotherapy in which the antigen is administered to the nasal, intestinal or tracheal mucosa, and of these, sublingual immunotherapy (SLIT) is the most advanced clinical application. Placebo-control studies of SLIT against house dust,^{1,3} grass,^{4,7} weeds⁸ and *Parietaria*^{9,10} have demonstrated a marked improvement in clinical symptoms after immunotherapy compared with placebo, and a significantly lower incidence of side effects than with injection immunotherapy. In Japan, immunotherapy consists of subcutaneous injection only and local immunotherapy is not used in clinical practice. Other than our pilot study,¹¹ SLIT has not been investigated in Japan. In the pre-

sent study conducted in 2003 we evaluated the clinical efficacy of SLIT, its influence on the quality of life (QOL) and the incidence of side effects in patients with cedar pollinosis.

CLINICAL SUMMARY

SUBJECTS

After the protocol was approved by the Ethics Committee of Nippon Medical School and informed consent was given by five patients with cedar pollinosis (one man, four women; age range, 38–66 years (Table 1)), administration of a therapeutic extract was started.

The main antigen was cedar and none of the patients had other allergic diseases or double sensitization with other antigens that would influence the evaluation of the treatment response during the cedar pollen season. Treatment was started in July 2001 or later, and clinical efficacy was evaluated in April 2003 (mean treatment period, 13.4 months).

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Table 1 Profile of patients

	SLIT	Pharmacotherapy
Age (mean)	47.3	45.0
Sex		
female	4	4
male	1	1
Duration of SLIT (mean)	13.4 months	
Severity		
Mild	0	0
Moderate	2	4
Severe	3	1

Table 2 Schedule of sublingual administration

	1 st week 1 : 50000	2 nd week 1 : 5000	3 rd week 1 : 500	4 th week 1 : 500
1 st day	1 drop	1 drop	1 drop	20 drops
2 nd day	2 drops	2 drops	2 drops	
3 rd day	3 drops	3 drops	4 drops	
4 th day	4 drops	4 drops	8 drops	
5 th day	6 drops	6 drops	12 drops	20 drops
6 th day	8 drops	8 drops	16 drops	
7 th day	10 drops	10 drops	20 drops	

The pharmacotherapy group consisted of five patients with cedar pollinosis who consulted the outpatient clinic of the Department of Otorhinolaryngology at Nippon Medical School Hospital during the same period (one man, four women ; age range, 36–53 years (Table 1)).

METHODS

Japanese cedar antigen extract (1 : 20) (Hollister-Stier Laboratories LLC, Spokane, WA, USA) was diluted prior to use, but because it is not standardized, there are no data about its major allergen content. In our preliminary study, the concentration of the major Japanese cedar pollen allergen, Cry j 1, was regarded as being 7.7–16.5 µg/ml.¹² Crumbs containing the antigen extract were placed under the tongue for approximately 2 min and then spat out ('sublingual spit-out'). The subjects attended the outpatient clinic, weekly from week 1 to week 3 and then fortnightly from week 4 of treatment, where they obtained the therapeutic extract and administered it at home in increasing doses (Table 2).

Clinical Symptoms (Nasal Symptom Score)

Nasal allergic symptoms were evaluated from patient diaries and symptom/severity scores were calculated according to the Japanese Practice Guideline for Allergic Rhinitis (4th edition).¹³ The most severe status was scored as 4, severe status as 3, moderate status as 2, and mild status as 1 (Table 3).

Medication Score

In the drug therapy group, the various medications were also scored according to the guideline¹³ as follows : first- or second-generation antihistamines and mast cell stabilizers, 1 point ; topical steroids, 2 points ; vasoconstrictor or anticholinergic nasal drop preparations, 1 point ; antihistaminic eye drop preparations, 1 point ; steroid eye spray preparations, 2 points ; the period during which the dose is increased, 0.5 points ; the maintenance dose, 1 point ; and mixed preparation of an antihistaminic agent and betamethasone, 3 points (Table 4).

Evaluation of QOL

We evaluated changes in the subjects' QOL during the cedar pollen season using the Japanese Allergic Rhinitis QOL Standard Questionnaire (JRQLQ ; 2002),¹⁴ which has three parts : (I) nasal/ocular symptoms, (II) 17 questions about QOL and (III) a comprehensive evaluation (face scale).

The QOL questions investigated issues in six domains ('daily life', 'outdoor life', 'social life', 'sleep', 'fatigue' and 'emotion'), such as 'interference with study, work, or housework', 'lack of concentration', 'decline in thinking power', 'inconvenience with reading and newspapers', 'debilitating memory loss', 'interference with outdoor activities such as sports, picnic, etc', 'limitation on going out', 'interference with social activities', 'interference with conversation/telephone conversation', 'embarrassment from presumed public attention', 'sleep disorder', 'feeling of weariness', 'fatigue', 'nervousness', 'frustrated', 'gloominess' and 'lack of satisfaction with daily life'. Responses were evaluated using five grades.

PATHOLOGICAL FINDINGS

In 2003, the amount of cedar pollen in Chiyoda-ku, central Tokyo, was 3,622 grains/cm², which was similar to the annual average (according to a survey conducted by the Bureau of Public Health Tokyo Metropolitan Government).

CHANGES IN CLINICAL SYMPTOMS (NASAL SYMPTOM SCORE)

As shown in Table 5 the mean symptom scores in the SLIT group for sneezing, nasal discharge, nasal obstruction, and ocular symptoms between February and April were 1.07, 1.30, 0.56, and 0.39, respectively. All scores were highest in March and rapidly returned to the February values in April. The respective mean symptom scores in the pharmacotherapy group were 1.07, 1.76, 1.01, and 0.80 (Table 5). All scores were highest in March, as in the SLIT group, but in April there was a prolonged interval until symptoms were relieved.

The mean severity scores between February and April were 1.44 in the SLIT group and 1.86 in the pharmacotherapy group (Table 6).

Table 3 Criteria for symptom score and severity score

Grade	No. of sneezing attacks per day	No. of nose blows per day	Nasal obstruction
Most severe (4 points)	>20	>20	Complete (all day)
Severe (3 points)	11–20	11–20	Severe (considerable amount of mouth breathing required)
Moderate (2 points)	6–10	6–10	Marked (frequent mouth breathing)
Mild (1 point)	1–5	1–5	Present (no mouth breathing)
No symptoms (0 point)	0	0	None

Table 4 Criteria for medication score

1 st , 2 nd generation anti-histamines, mast cell stabilizers	1 point
Topical steroids	2 points
Decongestant, anti-cholinergic agents	1 point
Ocular anti-histamines	1 point
Ocular steroids	2 points
Specific immunotherapy	
During step up	0.5 points
During maintenance dose	1 point
Oral steroids and anti-histamines	3 points

CHANGES IN THE MEDICATION SCORE

The mean medication scores between February and April were 0.21 in the SLIT group and 1.85 in the pharmacotherapy group (Table 7).

CHANGES IN THE QOL

The mean QOL total scores during the pollen season were 3.82 in the SLIT group and 10.0 in the drug therapy group (Table 8).

SIDE EFFECTS

Neither systemic nor local side effects occurred during SLIT.

DISCUSSION

The mechanism of action for SLIT, or for conventional allergen immunotherapy, is still unclear, but for allergen-specific immunotherapy, reduction of effector cells^{15,16} and blocking antibody^{17–20} have been the conventional theories. Recently, however, it has become widely accepted that immunotherapy may modify the T cell response to natural allergens because of T cell anergy and/or immune deviation.^{21–24} For SLIT in particular, allergen administered to the oral mucosa accumulates in the submandibular lymph node, in which the immune response occurs²⁵ and peaks at approximately 2 h after administration.²⁶ Of the local immunotherapy modalities, SLIT is the most effective with a lower incidence of side effects, which complies

with the WHO position paper on allergen immunotherapy requiring a new route of administration, such as local immunotherapy, and treatment that does not cause anaphylaxis, such as peptide therapy.²⁷ However, only subcutaneous immunotherapy is used for Japanese cedar pollinosis and other than our pilot study,¹¹ and the present report, SLIT is an unknown treatment.

Approximately 13% of the Japanese population are affected by Japanese cedar pollinosis²⁸ and the proportion of severe status patients is higher than with grass or ragweed pollinosis, which are the representative conditions in other countries, and the symptoms persist for about 3 months, becoming a social issue. When the amount of pollen increases, patients show more severe symptoms, and the number of severe status patients is greatest in mid-March (late season) when the pollen count reaches its peak. Substantial antigen exposure enhances the antigen-antibody reaction in the airways (airway hypersensitivity), which is the mechanism involved in severe pollinosis, and immunotherapy with antigen-specific effects may control the exacerbation of the symptoms in the latter half of the cedar pollen season by inhibiting antigen-related enhancement of nasal mucosal hypersensitivity. In the present study, SLIT both inhibited the exacerbation of symptoms in the latter half of the season and reduced their severity throughout the season. Furthermore, there were neither local nor systemic side effects, as reported elsewhere for other antigens.

SLIT for cedar pollinosis is a new therapy and in the future SLIT may be indicated for patients with nasal allergy caused by other allergens such as house dust mites or animal dander through improvement of the administration schedule and establishing the dose at which the most potent effects are achieved. Therefore, a multicenter study involving a large number of patients should be conducted.

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Table 5 Monthly mean change in symptom score

		Feb.	Mar.	Apr.	Mean of 3 months
Score of sneezing	Pharmacotherapy	0.44	1.35	1.36	1.07
	SLIT	0.84	1.48	0.87	1.07
Score of nasal discharge	Pharmacotherapy	1.02	2.19	2.00	1.76
	SLIT	0.91	1.79	1.16	1.30
Score of nasal obstruction	Pharmacotherapy	0.48	1.37	1.15	1.01
	SLIT	0.31	0.86	0.49	0.56
Eye symptom score	Pharmacotherapy	0.46	1.14	0.76	0.80
	SLIT	0.26	0.68	0.21	0.39

Table 6 Monthly mean change in severity score

		Feb.	Mar.	Apr.	Mean of 3 months
Severity score	Pharmacotherapy	1.14	2.25	2.13	1.86
	SLIT	1.11	1.92	1.26	1.44

Table 7 Monthly mean change in medication score

		Feb.	Mar.	Apr.	Mean of 3 months
Medication score	Pharmacotherapy	1.49	1.90	2.13	1.85
	SLIT	0.07	0.43	0.12	0.21

Table 8 Monthly mean change in QOL score

		Feb.	Mar.	Apr.	Mean of 3 months
QOL score	Pharmacotherapy	6.0	16.8	7.2	10.0
	SLIT	1.67	5.8	3.82	3.82

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