

Sublingual Immunotherapy for Japanese Cedar Pollinosis

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ABSTRACT

The prevalence of pollinosis caused by cedar pollen has increased by 10% these ten years of 26.5% in the investigation of 2008 in Japan. The pharmacotherapy is a main treatment tool for pollinosis, and the surgical treatment is not acknowledged to the treatment of pollinosis internationally. Moreover, allergen immunotherapy enters a special treatment method, and is an important therapeutic procedure. The allergen immunotherapy is unique for having possibility of curing allergen specific allergic diseases. However the side effect of allergen subcutaneous immunotherapy (SCIT), such as anaphylaxis is kept at a distance in a medical situation in Japan. Then, a sublingual immunotherapy (SLIT) that was safer than it, developed in Europe for pollinosis induced by grass or ragweed, but not in Japan. As a result, the effect of SLIT was proven in the cedar pollinosis in Japan as high level evidence. A whole body immunity induction is thought in the appearance of the effect, and, in addition, it is necessary to be going to be cleared the accurate mechanism of the effect in the future. Moreover, the development of a special SLIT and the import of an overseas product are needed in Japan.

KEY WORDS

Pollinosis, QOL, SCIT, Sublingual immunotherapy (SLIT)

INTRODUCTION

After Dr Noon begins to appear the conventional allergen specific subcutaneous immunotherapy (SCIT) in 1911, and is continuing treatment method.¹ The effect of SCIT on pollinosis caused by cedar pollen is low though the high therapeutic gain is admitted for the perennial allergic rhinitis in Japan. It is because the effect of SCIT has decreased relatively because this depends on the amount of pollen to which the symptoms of pollinosis and the amount of dispersion increases in recent years or the administering allergen of SCIT is a little. The problem of anaphylaxis in cause that SCIT has not become general treatment though effectiveness is confirmed.² An alternative immunotherapy to change the allergen administering route in Europe and United States to decrease the number of side effects of SCIT is done considerably than before. There are alternative route via the nose, sublingual, and the oral in the method development is not done respectively in Japan as for the double blind test comparison examination though effectiveness has been proven either. Therefore, it explains around sublingual immunotherapy (SLIT) that we are

doing without the relation of the pharmaceutical company in Japan.

DEVELOPMENT IN JAPAN

In SLIT, high effectiveness is shown in Europe, and the few reports of the anaphylaxis have shown in randomized double blind placebo controlled (RCT) comparison examination evaluation.³⁻⁵ It was one asthma case, and it was one diarrhea case in the SLIT 115 cases in three theses. It is recorded that it is not an anaphylaxis though the asthmatic attack is not described detailed. Moreover, that has not arrived importantly though the reaction of one case's near anaphylaxis externals less than ten times of allergen dose administration was observed by a recent report.⁶

To receive a lot of these reports, and to make SLIT adjust to pollinosis caused by cedar pollen from which the amount of the dispersion pollen was thought most, the research was started. We did the ex vivo culture experiment of the first human mouth mucous membrane incised by the time of surgery for analysis of allergen aspiration to the mucosal membrane. The double of the amount of the allergen dose

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Table 1 Allergen administration schedule (increasing dosing)

	1 st week (2 JAU)	2 nd week (20 JAU)	3 rd week (200 JAU)	4 th week (2000 JAU)	5 th week (2000 JAU)
1 st day	1 drop	1 drop	1 drop	1 drop	20 drops
2 nd day	2 drops	2 drops	2 drops	2 drops	
3 rd day	3 drops	3 drops	3 drops	4 drops	
4 th day	4 drops	4 drops	4 drops	8 drops	
5 th day	6 drops	6 drops	6 drops	12 drops	20 drops
6 th day	8 drops	8 drops	8 drops	18 drops	
7 th day	10 drops	10 drops	10 drops	20 drops	

[After sixth week to pollen dispersed season, 20 drops of allergen extract was administered once a week sublingually. After pollen dispersed season, same dose was administered once in two weeks.]



Fig. 1 How to be adapted the allergen extract and bit of bread.

in SCIT is almost the same dose aspirated by SLIT. So SLIT may act as the case of the SCIT is achieved is guessed by over the double dose of allergen at SCIT.⁷

HOW TO DO

The approval of the Nippon Medical School ethics committee was received to the pollinosis caused by cedar pollen patient and it went from some examinations including this basic experiment in SLIT. The allergen for SLIT, standardized Japanese cedar pollen allergen (2000 JAU [Japanese Allergology Unit]/ml, Torii Pharmaceutical, Tokyo, Japan), especially for SCIT products, was used for our SLIT trial. The allergen was able to be put on sublingual by using the bit of bread for the allergen to flow in actual sublingual and so as not to go out, then the allergen was kept to maintain at least for two minutes, and to present the antigen enough to the lymphatic tissue in the mouth.

The allergen administration was every day according the administration schedule from beginning to the forth week. On the first week, 2 JAU of allergen was administered from 1 drop to 10 drops, on the second week, 20 JAU of allergen was administered from 1 drop to 10 drops, on the third week, 200 JAU of allergen was administered from 1 drop to 10 drops, and then on forth week 2000 JAU of allergen was adminis-

tered from 1 drop to 20 drops, as the final dose. On the fifth week twice a week after the sixth week, 2000 JAU/ml was administered to sublingual 20 drops as the final highest dose by once a week (Table 1, Fig. 1). There is tablet allergen for SLIT against grass pollinosis in Europe. There are some different allergen characters between Japanese cedar and grass. We cannot make the tablet allergen for SLIT of Japanese cedar pollinosis caused by its sticky character now.

THE EFFECT AND THE SIDE EFFECTS IN JAPANESE CEDAR POLLINOSIS

The Japanese cedar and cypress pollen dispersion was about 12000 grains, a large amount of dispersion in 2005 for these ten years. The RCT comparison by 60 cases was examined for making the first evidence in Japan. The SLIT group was intentionally low total symptom score (TSS) compared with the placebo (Fig. 2). This RCT of SLIT has shown to have lowered the symptom score more intentionally than the placebo in late pollen season.⁸ SLIT had no significant difference with the drug therapy in the symptom score in the comparison research with the current drug therapy. However, the quality of life (QOL) score evaluated standardized Japanese Rhinitis Quality of Life Questionnaire (JRQLQ), is significantly decreased by SLIT group than placebo group, up to half level of score. QOL deterioration is significantly inhibited by SLIT (Fig. 3).

Moreover, it was confirmed though the side effect was completely fewer. Itchy of the tongue and the mouth when the antigen was administered, the feeling of numbness, nasal secretion increases, itchy of the skin, and hives were admitted at total of frequency of about 10% through the experiment, there were neither an anaphylaxis nor an asthmatic attack.

HOW TO ACT

The mechanism of the effect manifestation is known few up to the present time though the immunity induction of the limited part have some role on most of the effect of SLIT.⁴ The mechanism of action for SCIT have been reported by the reduction of the effector cells^{9,10} and the increase of blocking antibody¹¹⁻¹⁴ in

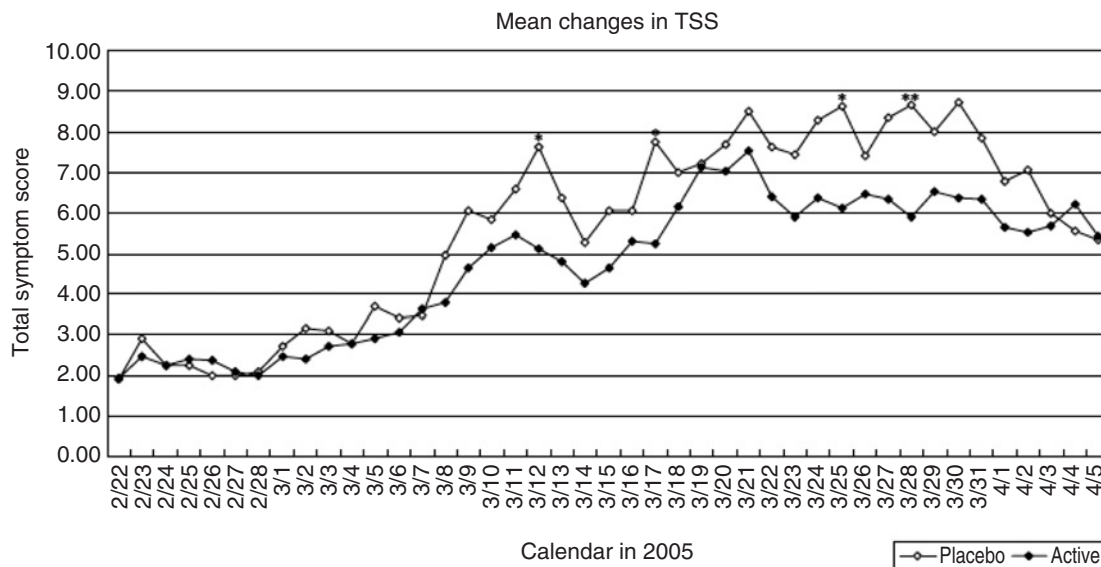


Fig. 2 Mean change of total nasal symptom score by SLIT and placebo group.

the conventional theories ten years ago. Recently, however, it has become widely accepted that SCIT may modify the T cell response to natural allergen because of T cell anergy and/or immune deviation¹⁵⁻¹⁸ and regulatory T cell enhancement.¹⁹

For SLIT in particular, allergen administered to the oral mucosa accumulates in the sub-mandible lymph node, in which the immune response occurs²⁰ and peaks at approximately 2 h after administration.²¹ An increase in stimulation index (SI) of PBMC at the early stage of the SLIT shows that the immunity induction of a sublingual allergen was at least caused in the general reaction.²² It tried to reduce the side effect by reducing the effect throughout the body compared with past SCIT in SLIT. However, it has been understood that this result causes a general immunity induction. One more study of SLIT for Japanese cedar pollinosis was published by Chiba group also expressed the SLIT controlled the general Cry j-specific Th2 clone size.²³ The regulatory T cell enhancement in general by SLIT has reported in some papers recently.²⁴⁻²⁶ So SLIT may act on generally, not just locally. It is necessary to clarify the exact effect mechanism of SLIT from the examination of the regional lymph node etc. by a similar examination that increased the number of cases or a detailed basic examination on animals in near future.

FOR THE FUTURE IN JAPAN

Approximately 15% of the Japanese population is affected by Japanese cedar pollinosis in 2002²⁷ and increase up to 26.5% in 2008.²⁸ The proportion of severe status patients is higher than with grass or ragweed pollinosis, which is the representative condition in other countries. The symptoms of Japanese cedar pollinosis persist for about 3 months, becoming a so-

cial issue. When the amount of pollen increases, patients show more severe symptoms, and the number of severe status patients is greatest in mid-March 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 SCIT for pollinosis treatment, the comments and responses of WHO are that the effect is verified from a lot of RCT comparison examinations.²⁹ However, it is a treatment method to which the medical treatment of Japan is kept at a distance because of the complexity, the possibility of the side effects, the cost and the enforcement under the present situation. The drug therapy is a main current in Japan where the allergy clinic has not been established from these problems for pollinosis. However, the immunotherapy that is fundamental treatment is an important method in the allergy management. The new SLIT shows the effect in pollinosis by cedar pollen was clarified in our examination in Japan. Any QOL fields and items became half QOL deterioration by the placebo in the evaluation using JRQLQ No1. This QOL questionnaire developed in Japan in the symptom score though the difference with the placebo was small in pharmacological treatment.³⁰ SLIT strongly controls the QOL deterioration in pollinosis rather than the symptom score to do effect is thought. Of the local immunotherapy modalities and SLIT is the most effective with a lower incidence of side effects, which complies with the WHO position paper on allergen

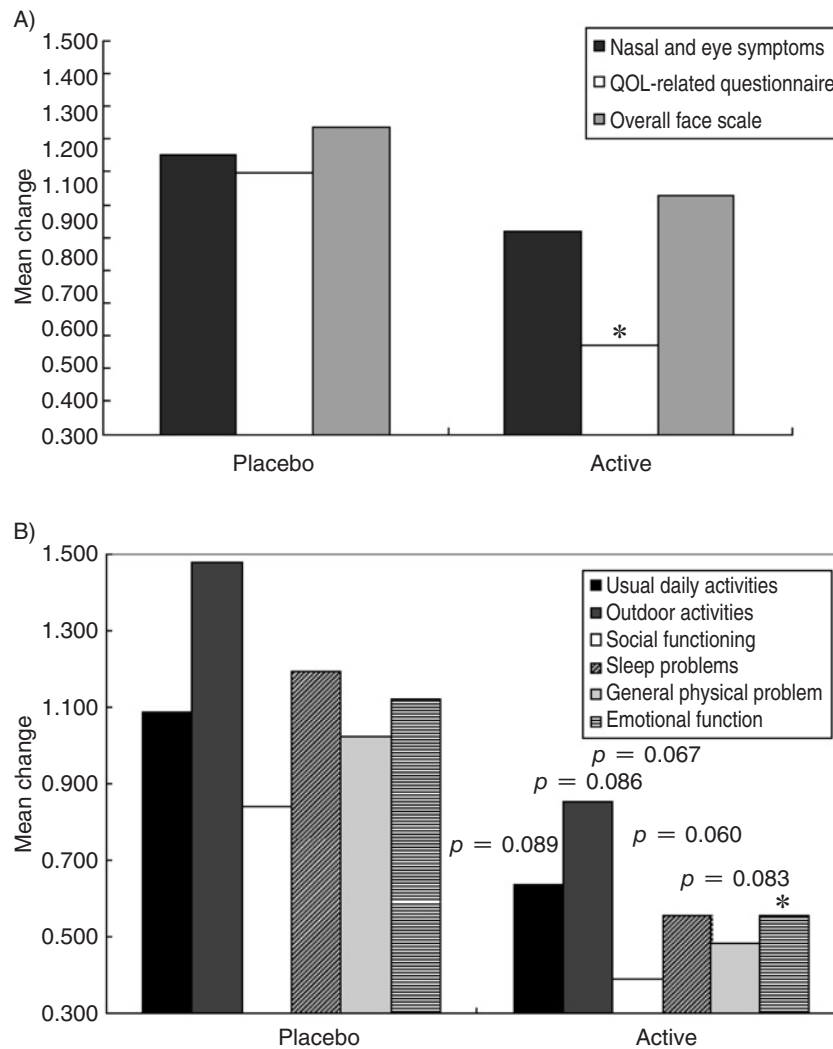


Fig. 3 The mean change of QOL score. **A)**, total QOL scores; **B)**, health related QOL fields.

immunotherapy requiring a new route of administration, such as local immunotherapy, and treatment that does not cause anaphylaxis, such as peptide therapy.³¹

In the comparison of double blinds RCT of the immunotherapy by a SLIT and the SCIT examination, the report is still few.³² As for the level of the side effect frequency and the effect, it is uncertain. The score of the symptom medicine passes low through the pollen dispersion all seasons. This shows that the drug use decreases in SLIT and corresponding to the result of the RCT examination that uses the placebo.³³ It is thought that the effect equal with the drug use is shown, and a SLIT from which the use of the medicine is decreased is useful in economy. In SLIT studies in Japan, 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.

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