

Allergen Immunotherapy for Allergic Rhinitis

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Abstract

Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the 2 forms of desensitization for allergic diseases which are used internationally. Despite the lack of sufficient evidence of the mechanism, SCIT has been used in Japan. When SCIT is performed appropriately, it is effective for allergic rhinitis, as supported by high-level evidence, including the results of meta-analysis. However, its use in Japan has not become widespread due to various problems, including the risk of anaphylaxis. Therefore, attention is being focused on SLIT because it is easier to perform but may be similarly effective and has been extensively discussed and evaluated internationally. Comparison of SCIT and SLIT can only be done with some allergen, which has also been discussed extensively. Many patients and physicians would welcome the use of SLIT in Japan, and its first use against pollinosis due to Japanese cedar pollen is planned for 2014.

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Key words: subcutaneous immunotherapy, sublingual immunotherapy, regulatory T cell, pollinosis

Introduction

Allergic rhinitis (AR) is a typical type I allergic disease in the classical classification of Gell and Coombs and is recognized as a chronic lifestyle disease by the Japanese Ministry of Health and Welfare. It reduces quality of life (QOL) even if it is unlikely to cause death. The recent increase in prevalence has been marked for atopic dermatitis and asthma as well as for AR. It is not possible to achieve advances in the treatment of other diseases if AR (a simple type I allergy) cannot be controlled.

Because AR is caused by specific allergens, immunotherapy is an important form of treatment. However, immunotherapy is not widely used in

Japan because of the risk of anaphylaxis and the high cost. Subcutaneous immunotherapy (SCIT) was first performed by Noon in 1911¹. Therefore, this treatment has been used for nearly a century, and much evidence has been accumulated. The latest evidence about immunotherapy is considered in this editorial.

SCIT

SCIT is a treatment for allergen-specific allergic diseases (**Fig. 1**) which involves the subcutaneous injection of gradually increasing doses of the allergen, with the aim of decreasing the patient's responsiveness. SCIT is mentioned in the "Practical Guideline for Management of Allergic Rhinitis in

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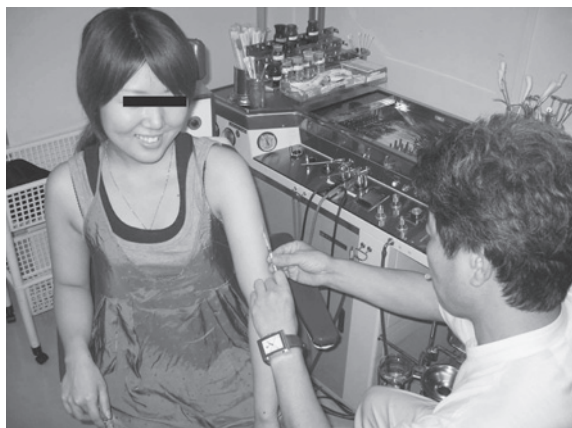


Fig. 1 SCIT.



Fig. 2 SLIT.

Japan 2009"², and in "Allergic rhinitis and its impact on asthma (ARIA)"³, which is an international guideline. The following features of SCIT were described in the immunotherapy opinion book published by the World Health Organization.

1. SCIT can be used for treatment of AR alone or with other methods.
2. SCIT is also effective for allergic conjunctivitis and allergic asthma.
3. SCIT should be performed by an allergy specialist.
4. Only standard allergens should be used.
5. The amount of allergen is increased gradually from a low dose until the maintenance dose is reached.
6. The maintenance dose is usually 5 to 20 μg of allergen per injection.
7. There is a risk of anaphylaxis, and appropriate precautions are necessary in case of emergency.
8. Treatment is generally continued for 3 to 5 years, although the optimum time is uncertain.

Efficacy, Mechanism, and Problems with SCIT

The subjective efficacy rate of SCIT for AR due to house dust (HD) mite is 80%, and the efficacy rate in the United States for the treatment of AR due to ragweed has been reported to be 90% or more⁴. In Japan, an efficacy rate of about 70% has been reported for pollinosis caused by Japanese cedar (JC) pollen, even allowing for seasonal variations in the pollen count. Persistence of the effect after the completion of treatment has been confirmed

internationally⁵.

An efficacy rate of 80% to 90% has been reported for atopic asthma with moderate symptoms^{6,7}. Effectiveness for occupational allergy has also been reported.

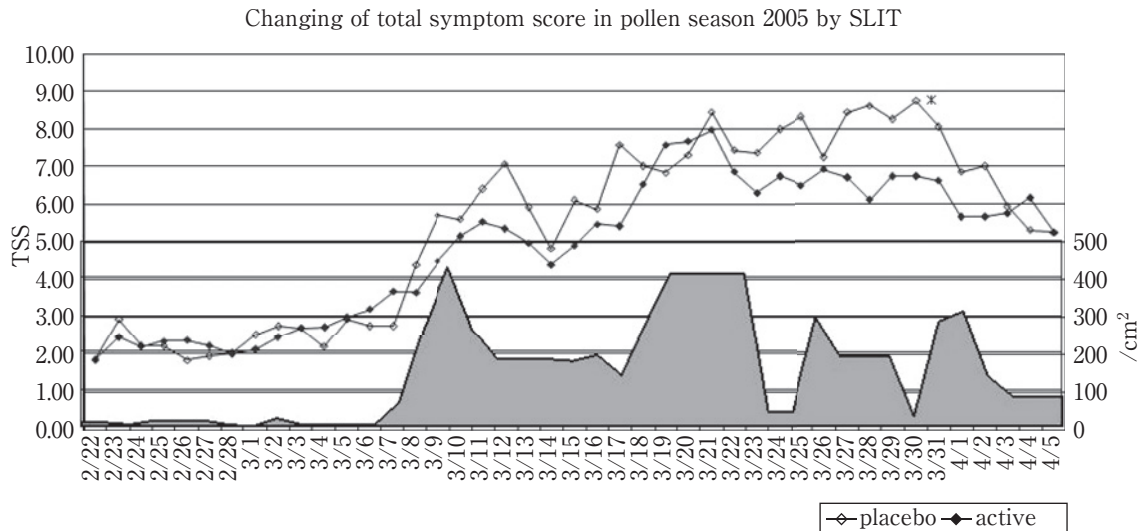
SCIT is not considered effective for skin diseases, and it is not found in the guidelines for standard therapy despite some reports of its effectiveness in foreign countries.

There is considerable evidence for the efficacy of SCIT for bronchial asthma and AR in children⁸. Moreover, if SCIT controls pollinosis in infants, asthma can be prevented⁹. However, the frequency of an exaggerated immune response (anaphylaxis) to SCIT is greater in children than in adults.

Although the mechanism of action of SCIT has not been clarified, SCIT might depend on the suppression of IgE production^{10,11}, production of blocking antibodies¹⁰⁻¹², a decrease of mast cells in nasal mucosa¹³, a decrease of cytokine production (down regulation of interleukin 5 mRNA)¹⁴, and an increase of Th1 cytokines¹⁵.

Thus, induction of tolerance or anergy, alteration of the Th1/Th2 balance, and regulation of T cells^{16,17} may be involved in the immunologic mechanism of SCIT. However, the failure to completely clarify these mechanisms helps prevents the widespread use of SCIT.

The main problem with SCIT is the risk of systemic side effects. We have reported 17 cases of side effects in 1,642 patients with AR who underwent SCIT at the Department of Otolaryngology of Nippon Medical School from 1979



Start of pollen dispersing on February 22th
10,625 pollens/cm²/season by Darham sampler

*: $p < 0.05$

Fig. 3 JC pollen was present at high levels in 2005 (placebo-controlled study). The solid area shows the changes in the pollen count. Open squares represent the total symptom score (TSS) in the placebo group, and solid squares represent the TSS in the group given JC allergen.

through 1990. The clinical records in 5 of these cases were found to be incomplete. If these cases are excluded, the rates of eruptions, respiratory symptoms, and circulatory symptoms were 1% or less in the total patients base, which was 1/10th of the frequency in the total injection base¹⁸.

SCIT and Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) has been reported as an alternative form of immunotherapy. SLIT can affect numerous lymph nodes (oral lymph nodes, Waldeyer ring, and cervical nodes) and is more useful than SCIT because of its simplicity and safety (**Fig. 2**). A clinical trial of SLIT for JC pollinosis was started in our department because its efficacy has often been reported¹⁹.

Two studies have compared the effects by means the double-dummy method, although few comparisons of SCIT and SLIT have assessed efficacy, cost, and other factors. Thirty-six patients with AR and asthma due to house dust mites were evaluated in the first randomized study in 1999²⁰. Symptoms of asthma improved only with SCIT, but symptoms of rhinitis decreased with either SCIT or

SLIT²⁰. However, the asthma symptom score before immunotherapy was higher in the SCIT group than that in the SLIT group. In another study, 58 patients with silver birch pollinosis were randomly assigned to receive SCIT (n=19), SLIT (n=14), or a placebo (n=15). This study was small, but improvement in symptoms was significantly greater with SCIT or SLIT than with placebo but did not differ between the two immunotherapy methods; however, a difference might have been found if more cases were included²¹. Randomization was difficult because these studies had a limited number of subjects who differed in the severity of symptoms.

SLIT is already used widely for the treatment of AR, such as that due to pollinosis, in Europe. SLIT products for general clinical application are available from Stallergenes in France and Alk Abello in Denmark. There have been objections to SLIT in the United States, probably because SCIT used only by allergists. However, a Cochrane cooperative meta-analysis by Wilson showed that SLIT was effective²². In the ARIA 2000 guidelines, SLIT is recommended for AR, conjunctivitis, and asthma due to pollen or mite allergy; these guidelines also clarified that SLIT influences the natural history of allergy in the same

way as SCIT²³. The concept that the mechanism of SLIT involves IgX, which blocks all IgE, has been proposed²⁴. However, a reported has pointed out the problem of presentation bias in a new meta-analysis. As a result, it has been suggested that there was no significant efficacy shown in some of the studies where SLIT was reported to be effective²⁵.

SLIT Research in Japan

Our group at Nippon Medical School began a clinical trial of SLIT for JC pollinosis in 2002²⁰. Moreover, it is that the clinical trial of the doctor initiation was made as a high evidence in our group²⁶ and Chiba University²⁷, also. Our SLIT regimen involved sublingual JC allergen at a dose from 2 Japanese Allergology Units (JAU)/mL to 2,000 JAU/mL, with a daily increase over a 4-week period. The maximum dose (2,000 JAU/mL=20 drops) is administered twice during week 5. From week 6, the same dose is administered once a week through the season.

The level of JC and Japanese cypress pollen was about 12,000 grains/cm², which is high, during a 2005 study in Tokyo²⁶. Sixty patients were randomly assigned to each treatment, and a double-blind placebo-controlled examination was done. In patients with JC pollinosis, SLIT decreased the symptom score and the QOL score more than did placebo, and the improvement was by double rate compared to the placebo, especially in QOL (**Fig. 3**). The effect against JC pollinosis has also been studied by Chiba University and was found to be similar, with a decrease in JC-specific T cell clones in the peripheral blood²⁷. Moreover, Tr1 (which induces regulatory T cells) was induced by SLIT in a study by Nippon Medical School and Mie University. The induction of regulatory T cells is a significant effect of SLIT²⁸.

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