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Review

A Guide to Sublingual Immunotherapy in Japan

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Used to treat type I allergies, allergen immunotherapy (AIT) can lead to sustained remission even after treatment cessation. In Japan, sublingual immunotherapy (SLIT) is the only therapeutic option for allergic rhinitis caused by Japanese cedar pollinosis (JCP) and house dust mite (HDM) allergies. Clinical studies have shown that SLIT tablets reduce symptom scores by approximately 30% while maintaining a high safety profile; serious adverse events are rare, and most reactions are mild, local irritations. Japanese multicenter studies have also confirmed the safety of concomitant administration of JCP and HDM SLIT tablets within a five-minute interval. Additionally, JCP SLIT shows cross-efficacy against Japanese cypress pollinosis. While a treatment period of 3–5 years is recommended for long-term efficacy, significant clinical benefits are often observed during the first pollen season. Japan maintains a high adherence rate of approximately 80%, underscoring the importance of proper patient selection and pretreatment education. Thanks to its efficacy, safety, and non-invasive nature, SLIT continues to play a central role in the management of allergic rhinitis in Japan.
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Keywords: allergic rhinitis, Japanese cedar pollinosis, allergen immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy

Introduction

Allergen immunotherapy (AIT) can be used to treat Type I allergies, and if continued for several years its effects can persist after treatment cessation, resulting in long-term remission or resolution. Subcutaneous immunotherapy (SCIT) is a long-established treatment first performed in 1911. Sublingual immunotherapy (SLIT), developed in 1986, is a treatment that is painless and safe to administer and thus more acceptable to patients. This therapy can also prevent new allergen sensitization and development of other allergic diseases (i.e., bronchial asthma). Because conventional subcutaneous injections are associated with high-risk reactions such as anaphylactic shock, AIT injections have not been widely adopted in Japan. SLIT, however, can be safely and easily administered. In Japan, AIT is not a common treatment for allergic diseases; however, SLIT was seen as a viable treatment option after it became available for clinical use. The mechanism by which SLIT exerts its effects is not fully understood, but hypothesized mechanisms include blocking by IgG4 antibodies, a shift from Th2 T cells to Th1 T cells, and immunosuppression due to increased regulatory T cells. These mechanisms likely combine synergistically to enhance the therapeutic effect.

Pharmacotherapy, the most common type of treatment for allergies, is a symptomatic treatment. Although it is effective while treatment is ongoing, symptoms reappear when the medication is stopped. These therapeutic agents are selected on the basis of the patient's symptoms, regardless of the underlying cause. Surgical therapy offers longer therapeutic effects, but it is also a symptomatic therapy. The only curative therapy available at present is AIT, which can lead to long-term remission and even resolution.

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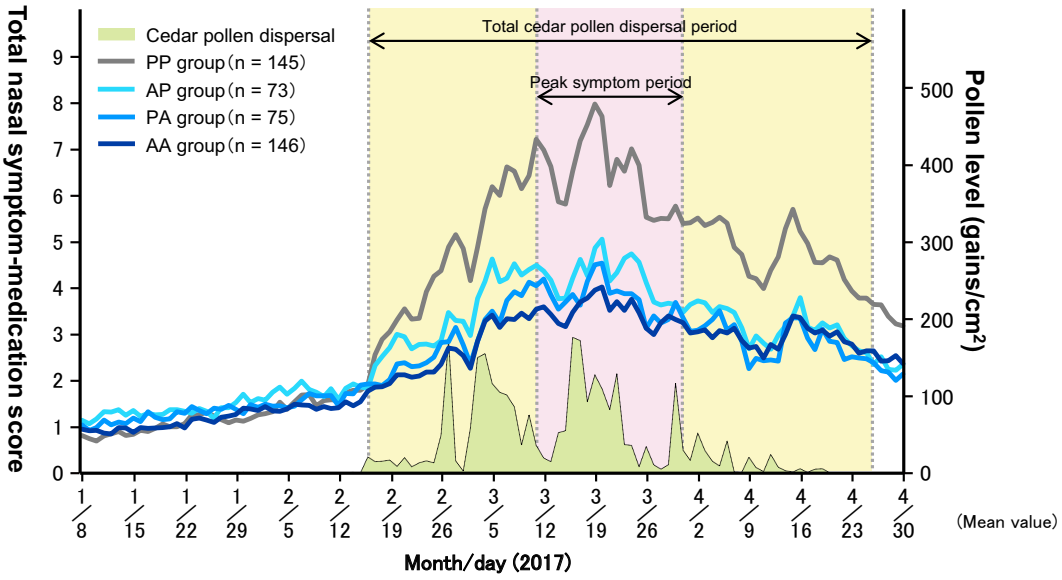

Figure 1 Changes in cedar pollen dispersal levels and total nasal symptom-medication scores[3]
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SLIT in Clinical Practice

The 2024 Practical Guideline for the Management of Allergic Rhinitis in Japan (Revision Ver. 10) recommends administration of SCIT and SLIT in patients with allergic rhinitis/pollinosis, regardless of severity[1]. Caution is required, however, for contraindicated cases and other patients requiring careful administration. In patients with asthma, treatment should be started after a thorough evaluation of lung function.

Efficacy and Safety of SLIT for Japanese Cedar Pollinosis

In 2014, SLIT for treatment of Japanese cedar pollinosis was first released in a liquid form. Two companies released sublingual tablets for the treatment of mite allergies in 2015, followed by the marketing of sublingual tablets for the treatment of Japanese cedar pollinosis in 2018, after a dose-finding study. The sublingual tablet offered a maintenance dose of 2000 Japanese allergyunit (JAU) for Japanese cedar pollinosis. A Phase 3 study found that in its second season of use, SLIT resulted in a symptom score decrease of approximately 30% during the peak pollen period, as compared with placebo. There were no systemic side effects, and the rate of localized side effects—approximately 13%—confirmed a high level of safety[2]. The absence of major side effects suggested that the treatment was safe.

Sublingual tablets for treatment of Japanese cedar pollinosis offer higher allergen doses than would be possible in liquid form. Although a dose-finding study was not performed as part of a clinical trial for the sublingual liquid, a dose-finding study of the sublingual tablets examined three doses—200, 5,000, and 10,000 JAU. The 5,000 JAU dose was significantly more effective than 2,000 JAU. Because the 5,000 and 10,000 JAU doses had similar efficacies, 5,000 JAU, which was 2.5 times the sublingual liquid dose, was selected as the maintenance dose. Although the sublingual liquid resulted in a symptom score decrease of approximately 30% in the second year of use, the sublingual tablets produced a similar result in the first year (**Figure 1**)[3]. These results suggest that the effects appeared more quickly with the sublingual tablet because of the selection of an appropriate therapeutic dose.

Concomitant Therapy for Mite Allergies and Japanese Cedar Pollinosis

The most common causative allergens of systemic allergies and allergic rhinitis in Japan are dust mites and Japanese cedar. The release of sublingual tablets for the treatment of mite allergies in 2015 and Japanese cedar allergies in 2018 increased clinical demand for a combination immunotherapy. Some facilities administered the sublingual tablet for dust mite allergies in the morning and the dose for Japanese cedar pollinosis in the afternoon. After it was confirmed that this method was safe, a Japanese multicenter clinical study was planned to determine optimum concomitant therapy by evaluating the frequency and types of side effects that occurred over a

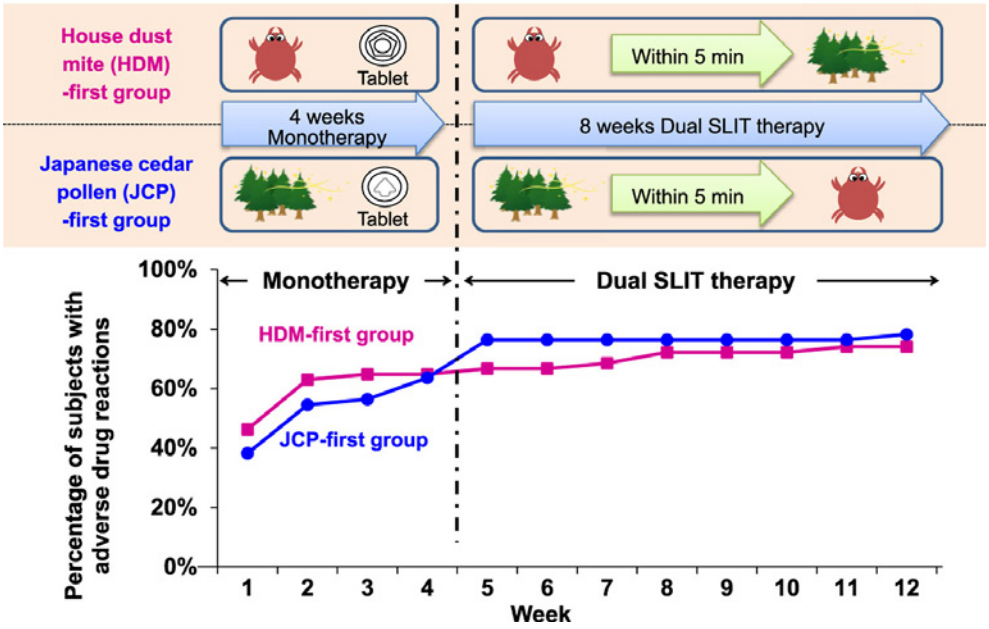

Figure 2 Onset rate of side effects during concomitant use of sublingual tablets for cedar pollen and dust mite allergies[4]

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3-month period. In that study, monotherapy for either dust mites or Japanese cedar pollen was administered for the first month, followed by a concomitant administration period of 2 months during which both sublingual tablets were administered within 5 minutes of each other. A safety evaluation of side effects during the 2-month dual administration period indicated that the frequency of side effects did not differ in relation to which tablet was administered first and that the concomitant administration of the tablets did not cause serious side effects. The side effects that occurred were identical to those noted during monotherapy (**Figure 2**)[4]; therefore, the safety of concomitant administration of both sublingual tablets within 5 minutes of each other was confirmed, providing clinical trial evidence of the safety of this concomitant therapy in Japan.

Continuation of Effects after Treatment Completion

Clinical trials of these sublingual tablets comprised a dose-finding study performed in the first season and verification of the safety of long-term administration in the second and third seasons. To verify the duration of treatment efficacy after treatment completion, no study drug was administered in the fourth or fifth seasons, although monitoring of symptom scores continued. Symptom-medication scores after treatment completion were compared between a placebo and a treatment group, which was subdivided into one-, two-, and three-season treatment subgroups, all of which exhibited significantly decreased symptom-medication scores, as compared with placebo, in the second season post-administration (**Figure 3**)[5]. Although a treatment duration of one season did not result in sufficient treatment effects, some efficacy was achieved, even with a shorter-than-expected treatment period. Before starting this treatment, physicians typically inform patients that a treatment period of 3–5 years is necessary. However, at clinical sites it may be more prudent to have patients undergo treatment for one season and then decide whether to continue immunotherapy based on the effects at that point in time.

Efficacy for Japanese Cypress Pollinosis

Because of a common allergen for Japanese cedar pollen allergies, approximately 70% of patients with Japanese cedar pollinosis exhibit positive results for Japanese cypress–specific immunoglobulin E (IgE) antibodies. Therefore, a large proportion of these cases are complicated by Japanese cypress pollinosis. In Western Japan in particular, where there are large areas of Japanese cypress, more Japanese cypress pollen than Japanese cedar pollen is dispersed. Therefore, when SLIT was administered to patients with Japanese cedar pollinosis who also had Japanese cypress pollinosis, clinicians were very interested in

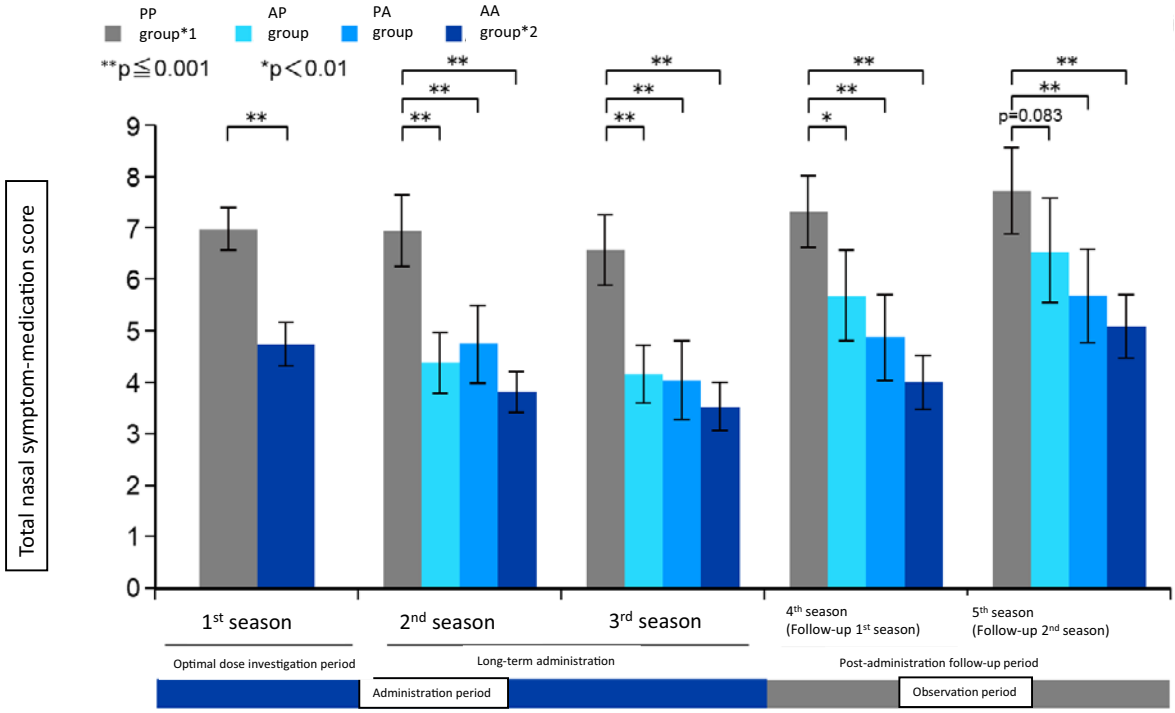

Figure 3 Total nasal symptom-medication scores during the peak symptom period (first through fifth seasons)[5]
Adapted from J Allergy Clin Immunol Pract, Vol. 9, Yonekura S et al., Disease-modifying effect of Japanese cedar pollen sublingual immunotherapy tablets, pp. 4103–16. e14, Copyright (2021) The Authors. Published by Elsevier. Licensed under CC BY-NC-ND.

the extent to which the antiallergenic effects would carry over to symptoms of Japanese cypress pollinosis. However, since the advent of SLIT extract production, it has been difficult to create a product for Japanese cypress pollen, as it was impossible to collect the amount of allergen required for treatment. The situation remains the same today.

To evaluate changes in Japanese cypress pollinosis symptoms during SLIT for Japanese cedar pollinosis, the results of a prior clinical study of sublingual tablets for the treatment of Japanese cedar pollinosis were used to classify patients into two groups on the basis of whether their symptoms did or did not worsen during Japanese cypress pollen season. The results confirmed that in the Kanto region, where the clinical trial was performed, some efficacy was observed against Japanese cypress pollinosis[6,7]. However, as the level of Japanese cypress pollen dispersed each year is lower in the Kanto region, further verification is required to determine whether these results are generalizable to regions with higher levels of pollen dispersion.

Postmarketing Surveillance Results

There have been two reports in Japan of postmarketing surveillance results regarding SLIT for the treatment of dust mite allergies[8,9]. Both reported no serious side effects over a study period of several years and indicated that long-term treatment increased efficacy (**Figure 4**)[9]. While various reasons were provided for discontinuing treatment, most patients who discontinued treatment did so because treatment was deemed effective.

Requirements for Starting SLIT

Physician Requirements

Physicians wishing to administer SLIT in Japan must pass an e-learning course and register both a prescribing and designated emergency medical facility.

Comparison with SCIT

SCIT is administered over the course of several years. It can be started with multiple allergens at once, and once the maintenance dose is reached, only once-monthly treatments are needed. SLIT, however, is only available for Japanese cedar pollinosis and dust mite allergies—it cannot be administered for other allergens. The success of this treatment therefore depends on the patient's ability to take one sublingual dose daily at home. Treatment selection should consider whether the medical facility is easily accessible by the patient (for SCIT, in particular) and whether they can maintain compliance (for SLIT, in

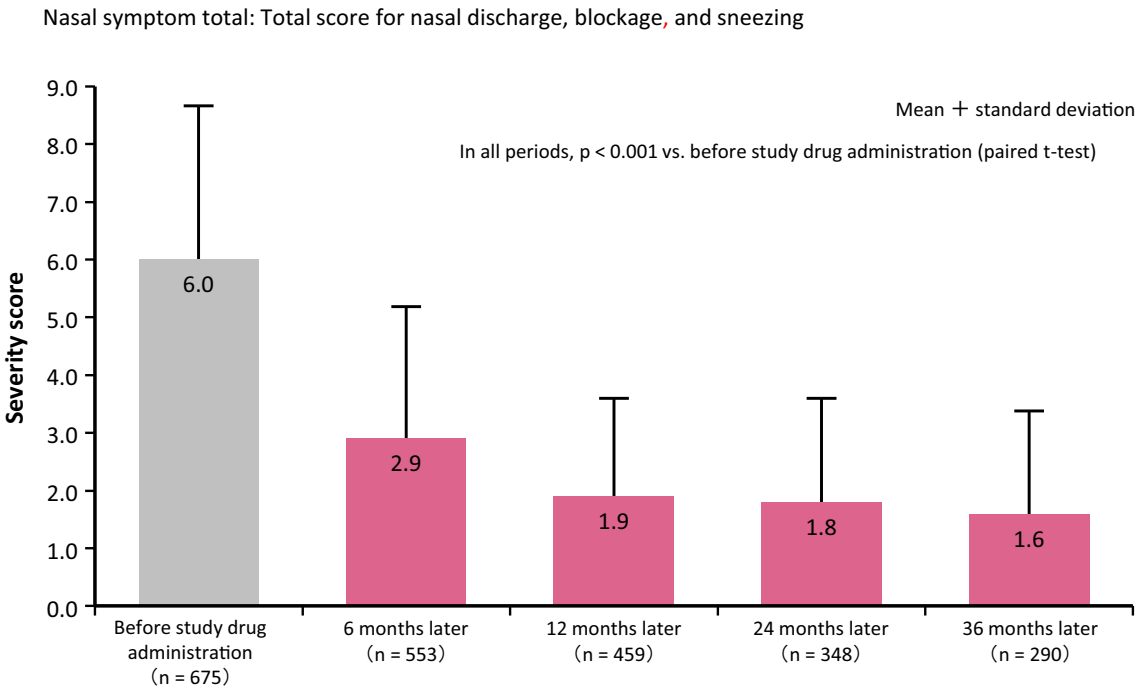

Figure 4 Change in severity of nasal symptoms (nasal symptom total)[9]
Reprinted from Allergy Asthma Proc, Vol. 46, Gotoh M et al., Real-world surveillance of standardized quality (SQ) house dust mite sublingual immunotherapy tablets for 3 years in Japan, pp. 59–69, Copyright (2025), with permission from OceanSide Publications, Inc., U.S.A.

Table 1 Comparison of subcutaneous and sublingual dosing schedules

	Subcutaneous	Sublingual
Threshold testing	Necessary	Not necessary
Starting level (Maintenance dose)	Varies by patient	Unified as a rule
Schedule	Varies by patient	Unified as a rule
Multiple antigens	Treatment can be started simultaneously	Interval of 1 month Administer within 5 min.
Treatment management	Medical institution	Patient

particular), as well as the medical environment itself, whether the patient is prepared for treatment, and their overall condition (**Table 1**).

Patient Selection

Many patients with allergic rhinitis feel that symptomatic treatment is sufficient. Before providing a detailed explanation of SLIT and the frequency of side effects, it is essential to confirm whether they can take a sublingual tablet every day for 365 days. As the daily sublingual doses are the patient's responsibility, subcutaneous, pharmacologic, or surgical therapy may be selected if the patient feels uncertain that they can adhere to this dosage schedule. Cases with contraindications and patients requiring careful administration, as mentioned below, are also considered (**Figure 5**).

Clinical Practice Treatment Methods

The Allergen Immunotherapy Guidebook, by the Japanese Society of Allergology, is a useful reference for real-life methods of administering AIT[10]. AIT is started after careful patient selection (**Table 2**). Although being pregnant at the start of treatment is a contraindication, patients may continue treatment if they become pregnant during the course of treatment.

Unlike SCIT, SLIT does not require determination of treatment initiation doses for each patient—all patients receive the same treatment dose according to the same administration schedule. While the treatment protocol depends on the product used, patients are generally started on a low dose, which is then increased to the maintenance (highest) dose after several days to 1 week.

SLIT has a low risk of anaphylactic shock, and no treatment-related deaths have been reported. Although

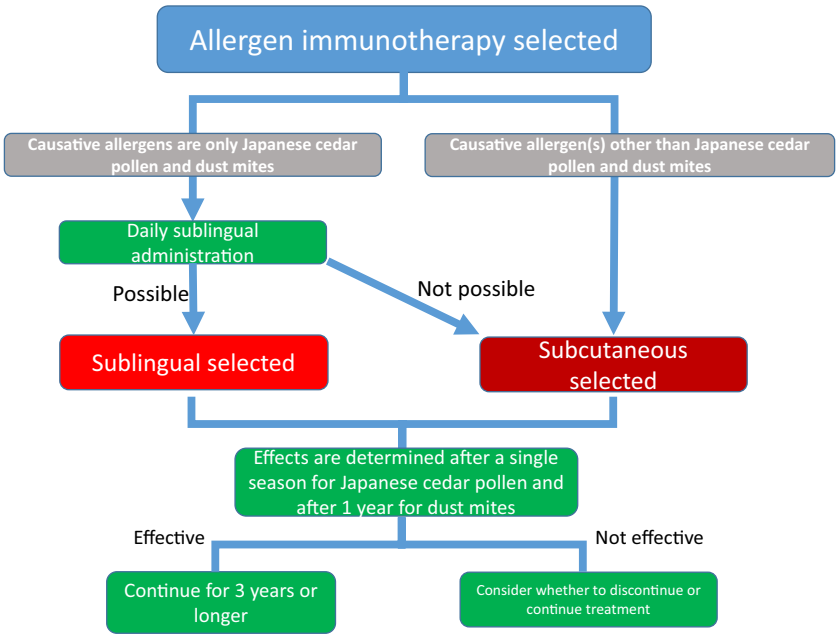

Figure 5 Selection of allergen immunotherapy

Table 2 Contraindications and conditions requiring careful administration of allergen immunotherapy[10]

Contraindications and conditions requiring careful administration:
① Patients using beta blockers
② Patients with %FEV1 <70% or uncontrolled bronchial asthma
③ Patients using systemic steroids or anticarcinogenic agents
④ Patients pregnant at the start of treatment
⑤ Patients with an acute infectious disease
⑥ Patients with a present history, past history, or significant family history of autoimmune disease.
Careful consideration is also required for patients planning to relocate and those for whom regular hospital visits are not possible.

anaphylactic shock has been reported in patients with asthma or food allergies in Japan, the incidence was <0.1%. In most cases, a mild local adverse reaction occurred within 1–2 months after starting treatment. These adverse reactions gradually resolve, and many patients report oral itching, oral edema, or throat irritation. While AIT is ideally administered regularly, it can be paused if the patient is feeling unwell, e.g., if they develop an acute infectious disease.

Response to Side Effects

The results of previous clinical studies and trials indicate that side effects commonly arise within 1 month of first administration. Accordingly, adverse reactions are particularly likely in the first month after starting SLIT, and an appropriate response is required. Most reactions can be controlled with antihistamines. Because the first administration of SLIT for Japanese cedar pollinosis occurs during a season in which there is no allergen exposure, antihistamines can be administered on an as-needed basis for most patients. Dust mite allergens are a year-round exposure, and SLIT is started when symptoms are present; thus, ongoing pharmacotherapy should be continued for the first few months of SLIT. After several months have passed and symptoms have subsided, the pharmacotherapy dose can be reduced.

Treatment Adherence

SLIT adherence outside Japan is poor, and the percentage of patients who successfully continue treatment is extremely low. However, an analysis that used prescription data to determine treatment continuation rates in Japan found that nearly 80% of patients continued treatment without interruption through the first year[11]. This finding indicates that, in Japan, if treatment is appropriately introduced after patients are given a sufficient pre-treatment explanation of the need to continue treatment, there are fewer drop-out cases than in other countries.

Summary

Approximately 10 years after SLIT was made available in Japan, its clinical safety and efficacy have been established. Although SLIT is currently offered for treatment of dust mite and Japanese cedar pollen allergies, future use in the treatment of grass and birch pollen allergies is highly likely. Otorhinolaryngologists regard SLIT as an important treatment option because of its effectiveness for both symptomatic pharmacotherapy and curative therapy.

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