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Invited Review Article

Current status of sublingual immunotherapy for allergic rhinitis in Japan

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AIT, allergen immunotherapy;
SCIT, subcutaneous immunotherapy;
SLIT, sublingual immunotherapy;
AR, allergic rhinitis; JCP, Japanese cedar pollen; JAU, Japanese allergy units;
JSA, Japanese Society of Allergology

ABSTRACT

Japanese cedar pollen (JCP) and house dust mite (HDM) are two major allergens that cause allergic rhinitis (AR) in Japan and the prevalence of AR is increasing. Pharmacothearpy is a commonly used treatment, but the level of patient satisfaction is very low. Allergen immunotherapy (AIT) is the only therapeutic modality that provides not only symptom relief but also quality of life improvement that leads to a high rate of satisfaction. In particular, sublingual immunotherapy (SLIT) is a safe and effective treatment for AR. Here we introduce a large-scale double-blind, placebo-controlled trial of SLIT in Japanese patients using JCP droplets or HDM tablets conducted in Japan. The immediate future of SLIT in Japan is also discussed.

Introduction

Allergic rhinitis (AR) is the most common allergic disease in the world[1] that represents a global health problem. AR was estimated to affect nearly 40% of the Japanese population in a 2008 epidemiological study, which reported an increase in prevalence of about 10% compared with the same epidemiological study conducted in 1998.[2] In particular, the prevalence of Japanese cedar pollinosis (JCP) has increased more than other forms of AR caused by house dust mites (HDM) or pollinosis other than JCP, and continues to rise. AR is not a life-threatening illness; however, it can have a negative impact on quality of life,[3,4] work productivity,[5] learning ability,[6] and sleep.[7] In addition, the onset of AR has preceded the development of bronchial asthma (BA) in many patients according to a preliminary prospective small study.[8] Furthermore, recent reports suggest that AR in preschool children is a predictor for subsequent wheezing onset in school-aged children,[9] and that AR in adults is also a risk factor for asthma in adults.[10]

JCP and HDM are the two major allergens in Japan. Other allergens commonly seen in allergic patients in Japan are cypress pollen, orchard grass, ragweed, mugwort, Birch, and Japanese Alder. The allergenicity of Japanese cedar and cypress allergens is homologous and nearly 70% of JCP-sensitized subjects also respond to cypress pollen.[11] Furthermore, JCP and HDM are a commonly seen combination of polysensitized allergens in allergic subjects, although patients polysensitized to more than three allergens were also recognized. Polysensitized and polyallergic patients are likely to have persistent rhinitis symptoms and their symptoms tend to become serious and intractable.

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Major allergens in Japan

Characteristics of pollinosis

In the spring, large amounts of JCP and cypress pollens disperse in Japan. Because JCP and cypress pollens disperse over several tens to thousands of kilometers, people living in urban areas also suffer from pollinosis. One epidemiological survey has indicated that 26% of the population suffers from seasonal allergic rhinitis caused by JCP and cypress pollen.[2] This is unique compared with other kinds of pollinosis around the world in that the Japanese cedars (JC) and cypress trees that disperse pollen in the spring in Japan are planted forests and not natural ones.

Nearly 70% of the land in Japan is forested, and about 40% of the forests are planted. Seventy percent of these comprise JC and cypress trees that disperse pollen in the spring. JC and cypress trees that were planted as the result of massive afforestation policies after World War II. These planted forests were not harvested because of competition from cheap imported wood.[11] As a result, JC and cypress trees that are 30 years old or over disperse a large amount of pollen every spring.

HDM allergens

HDMs are a major indoor allergen causing AR not only in Japan but also in other areas of the world. *Dermatophagoides pteronyssinus* (DP) and *Dermatophagoides farina* (DF) are commonly distributed HDM throughout the world; however, there is a higher density of HDM allergens in bedclothes in Japan, with a much higher concentration of Dermatophagoides species (Der 1) compared with the United States and Europe.[12] This indicates a large contribution of mite allergens to inducing perennial allergic rhinitis in Japan.

In addition, a longitudinal study suggested that HDM sensitization influences JCP sensitization, i.e., students who were positive for HDM sensitization in the JCP-negative groups in the first grade of primary school developed significantly higher JCP-specific IgE antibody levels compared with HDM-negative students over the 6 years of primary school.[13] However, HDM sensitization did not affect the increase of JCP-specific IgE levels in the initially JCP-positive groups.

Treatment of AR

Management of AR consists of elimination and/or avoidance of environmental allergens, pharmacotherapy, allergen-specific immunotherapy (AIT) and surgical treatment.[2] Among these treatment modalities, AIT induces clinical tolerance, has long-term efficacy, and reduces the reliance on pharmacotherapy. In addition, AIT is the only form of therapy available that can alter the natural course of allergic diseases. As for AIT, subcutaneous immunotherapy (SCIT) has been used over the past century.[2] However, sublingual immunotherapy (SLIT) has been available very recently in Japan. This review article will discuss AIT, especially the current status of SLIT in Japan.

History of AIT in the world and Japan

AIT clinical research was begun more than a century ago by Leonard Noon.[14] It was administered as a subcutaneous injection called SCIT until the sublingual trial was developed in 1986.[15] In Japan, SCIT using non-standardized house dust crude allergen extract began in 1963 and continued until 2015, when the Japanese Allergology Society (JSA) task force developed standardized mite allergen.[16]

JCP crude allergen has been also available since 1969 and was used in clinical practice until 1999. A standardized JCP allergen for SCIT became available in 2000 and has been used in general clinical practice ever since.

The use of SLIT was proposed following surveys describing SCIT-related deaths, leading to increased interest in the safety as well as the risks and benefits of SCIT. SLIT was first introduced in the EAACI guidelines in 1993[17], and was then mentioned as a possible alternative to SCIT in a World Health Organization (WHO) position paper in 1998.[18] SLIT was described as being as effective as SCIT and as having a better safety profile than SCIT in a WAO position paper in 2009.[19] The ARIA guidelines (2001)[20] documented SLIT, and have consistently supported the effectiveness and safety of SLIT throughout subsequent updates. SLIT is currently available in many countries including those in Europe, North and South America, and Asia.

There is an urgent need in Japan to prepare guiding principles for the safe administration of SLIT. The Japanese Rhinologic Society task force prepared clinical questions concerning SLIT and searched literature published between January 2003 and December 2012. Qualifying studies were analyzed and the results evaluated, consolidated and codified. Finally, we presented evidence-based recommendations concerning SLIT in 2012.[21]

A phase III clinical trial on SLIT for JCP was conducted in 2011 and 2012.

A standardized JCP extract for SLIT, Cedartolen® has been available since October 2014. In addition, large-scale phase II/III clinical trials on SLIT tablets, produced by companies overseas, for Japanese patients with HDM-induced allergic rhinitis were conducted by two pharmaceutical companies separately. As a result, the Ministry of Health, Labour and Welfare approved two different SLIT tablets: Miticure® and Actair®. They have been available since June 2015. Consequently, one SLIT extract Cedartolen® for JCP and two SLIT tablets Miticure® and Actair® are available for HDM-induced allergic rhinitis in Japan.

Next, I introduce randomized, double-blind, placebo-controlled large scale trials of the JCP SLIT extract in adult Japanese JCP pollinosis patients and HDM SLIT tablet in Japanese HDM-induced AR, separately.

Efficacy and safety of SLIT extract in patients with JCP

Five hundred and thirty-one patients with JCP, aged 12–64 years, who had had symptoms of JCP for the previous 2 years and JCP-specific IgE levels (ImmunoCAP) of class 3 or higher, were randomized into a Cedartolen® group and a placebo group.[22] Treatments were given for an average of 18 months from October 2010 to April 2012. Treatment began before the start of the pollen season in 2011 and continued to the end of the pollen season in 2012. The primary endpoint was the total nasal symptom and medication score (TNSMSs) during the peak symptom period in the second season. As a result, the TNSMSs during the peak symptom period were significantly lower in the SLIT group than in the placebo group (Fig. 1). There was a 30% reduction compared with the placebo group, suggesting clinically relevant efficacy. At least one adverse event (AE) occurred in 212 of the 266 subjects (79.7%) in the SLIT group and in 189 of the 265 subjects (71.3%) in the placebo group. The most common AEs were mouth edema, throat irritation, headache, oral pruritis and ear pruritus, and most of the AEs were mild and required no treatment. No anaphylactic reactions and no deaths occurred. Treatment-related AEs occurred in 36 subjects (13.5%) in the SLIT group and 14 (5.3%) in the placebo group (Table 1).

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