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# Prophylactic Sublingual Immunotherapy for Japanese Cedar Pollinosis

**Kazuhiko Takeuchi** *

*Department of Otorhinolaryngology, Head & Neck Surgery, Mie University Graduate School of Medicine, Mie, Japan*

***Corresponding author:** Kazuhiko Takeuchi, Department of Otorhinolaryngology, Mie University Graduate School of Medicine 2-174 Edobashi, Tsu, Mie 514-8507, Japan, Tel: 81-59-231-5028; Fax: 81-59-231-5218; E-mail: kazuhiko@clin.medic.mie-u.ac.jp

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## Introduction

Japanese cedar pollinosis is an allergic disease specific to Japan as Cryptomeria japonica grows only in Japan. The prevalence is estimated to be 26.5% and this has increased by 10% in 2008 compared with 1998 [1]. This seasonal allergic rhinitis can develop even in the elderly and takes a chronic course [2]. Once people develop this pollinosis, remission rarely occurs.

Sublingual immunotherapy is much safer than conventional percutaneous immunotherapy. This is the only treatment available which can completely cure the disease. A randomized, placebo-controlled, double-blind study has revealed that sublingual immunotherapy is both effective and safe for the patient with this pollinosis [3]. Only recently, standardized Japanese cedar pollen extract became available for Japanese clinicians to use for sublingual immunotherapy in a daily clinical practice.

It is believed that approximately twenty percent of asymptomatic subjects sensitized to this pollen develop symptoms annually [4]. Therefore, prevention of the development of cedar pollinosis in the asymptomatic, sensitized subjects is very important. A randomized, placebo-controlled, double blind trail was carried out in 2012 and 2013 in multiple facilities in Japan in a group lead by Dr. Okamoto, Chiba University. The purpose of this trial was to see if sublingual immunotherapy could prevent the development of pollinosis in sensitized subjects who have no history of pollinosis.

Yamanaka et al. reported a clinical result of this trial which was conducted in Mie University in 2012 and 2013 [5]. 17 subjects participated in the study in each year. In 2012, there was no significant difference in the ratio of symptom development between the sublingual immunotherapy group and the control group. However, in 2013, the ratio of the development of pollinosis in the sublingual immunotherapy group was significantly lower than that of the placebo group, which clearly indicates the efficacy of sublingual immunotherapy for the prevention of pollinosis development [5].

The reason why the efficacy differed in the two years is no clear, but there are some possibilities. The total amounts of pollen scattered during this season in this area, were 7,031 and 16,578 grains/cm$^2$ during 2012 and 2013 pollen seasons, respectively. The effect of prophylactic immunotherapy might have clearly been seen in the year when we had more pollen. Another possibility is that the participants who did not respond to the immunotherapy had been omitted in the study in the year 2013.

It is believed that IL-10 is critical for the induction of specific T cell tolerance. The increment in lL-10 production by monocytes, B cells and T cells during immunothearpy may influence effector cells involved in allergic responses. Thus they have looked at changes of the percentage of IL-10-producing T cells, B cells and monocytes before (December) and after (April) the immunotherapy [5]. The percentage of circulating IL-10 producing T cells and IL-10 producing monocytes significantly increased in the SLIT group in 2012 [5]. However, the number of IL-10 producing B cells remained unchanged [5]. The percentages of circulating IL-10 producing T cells and IL-10 producing B cells significantly increased in the sublingual immunotherapy group in 2013 [5]. The percentage of circulating IL-10 producing monocytes did not change in the sublingual immunotherapy group, but it significantly decreased in the placebo group [5].

Increased IL-10 production by sublingual immunotherapy might have caused energy in peripheral T cells, and regulated specific IgE and IgG4 production towards normal IgG4-related immunity [6]. Decreased percentage of IL-10 producing monocytes in the placebo group in 2013 might reflect the natural course of sensitized asymptomatic subjects who develop the pollinosis symptoms for the first time. The fact that the percentage of circulating IL-10 producing monocytes did not change in the sublingual immunotherapy group indicates the capability of sublingual immunotherapy to prevent the decrease of the percentage of IL-10 producing monocytes. So they concluded that prophylactic SLIT was effective in preventing development of pollinosis and IL-10 producing T cells, B cells and monocytes play important roles in the mechanism of SLIT for the prevention of pollinosis in asymptomatic and sensitized subjects [5].

They also examined the ratio of specific IgE against total IgE (sIgE/tIgE) and found that those who developed pollinosis in the SLIT group had a significantly higher sIgE/tIgE ratio [5]. This is in accord with the report by Fujimura et al. that patients with low sIgE/tIgE ratios were more responsive to SLIT in treatment for Japanese pollinosis [7]. On the other hand, the report by Di Lorenzo et al. reported a contrary result [8]. They reported that a high sIgE/tIgE ratio was associated with an effective response in sublingual and subcutaneous immunotherapy [8]. The reason of this discrepancy is unclear and the importance of sIgE/tIgE ratio as a biomarker for immunotherapy should be investigated in the future study.

Another possible biomarker for prophylactic immunotherapy is micro-RNAs (miRNAs). miRNAs are a class of short single-stranded RNA molecules that silence gene expression in the posttranscriptional stage. miRNAs may mediate allergic immune responses. Trying to investigate the miRNA alteration in asymptomatic subjects sensitized to Japanese cedar pollen under prophylactic SLIT, Hou et al. measured the changes in serum miRNAs by real-time quantitative polymerase chain reaction to see if SLIT had effects on profiles of circulating miRNA [9].

They found that serum hsa-miR-223 was significantly up-regulated in postseason compared with preseason samples [9]. The hsa-let-7b was significantly down-regulated more in postseason than in preseason samples from the placebo group, but not in the SLIT group [9]. Since alterations in miRNA expression occurred in asymptomatic, sensitized subjects during cedar pollen season, miRNA can be a biomarker for immunotherapy.

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