Subcutaneous immunotherapy with birch pollen extract for patients with pollen-food allergy syndrome

To the Editor,

Pollen-food allergy syndrome (PFAS) is an allergic disease caused by a cross-reaction between pollens and vegetable foods. Patients with PFAS usually present with oral symptoms such as oral discomfort and sore throat upon ingesting raw fruits and vegetables, which is referred to as oral allergy syndrome (OAS). However, some patients with PFAS may develop systemic symptoms and require restriction of processed foods often have trouble in their dietary lives.1,2 Some of them develop systemic symptoms upon ingesting soybean and are often placed on a restricted diet at home and school.

In this study, subcutaneous immunotherapy with birch pollen extract (Birch SCIT) was introduced in patients with PFAS and soybean allergy.

We recruited 6 Japanese patients with PFAS (mean age 9.5 years, interquartile range (IQR) 6-10 years) who had experienced non-oral symptoms such as abdominal pain, skin erythema, and respiratory symptoms upon ingesting some soy foods and required soybean restriction in the school lunch program (Table1). All of them had specific IgE antibody titers of class 3 or higher against alder and birch, and class 2 or

higher against Gly m 4, but did not necessarily develop allergic rhinitis to birch pollen. Birch Mix for injection (ALK-Abello, Inc. USA) contained red birch and white birch and was used for Birch SCIT.3

Birch SCIT was introduced by rush subcutaneous immunotherapy with the Birch Mix solution (Birch rSCIT). In the maintenance phase, the antigen dose of 1: $2x10^2$ (w/v) in 0.05 ml was administered once a month in the outpatient clinic.

An oral food challenge (OFC) test with soy milk (protein content 3.5%) was performed before and 1 year after initiating Birch SCIT. The initial amount of soy milk OFC was 1 ml, and the amount of soy milk was gradually increased to 200 ml. Intake status of processed soybean foods, sprouts, and apples were evaluated by interview before and 1 year after Birch SCIT initiation. The restriction of soybean in the school lunch program was confirmed on the school life management instruction sheet.

We obtained an approval regarding the use of the imported Birch Mix for injection from the Yao Municipal Hospital Ethics Committee (YMH-H28-17). Written informed consent was obtained from the parents regarding participation in the study and reporting of study results. This study was approved by the Yao Municipal Hospital Ethics Committee (YMH-051820-85).

Ingestible amount of soy milk, and specific IgE antibody titers were examined before and 1 year after initiating Birch SCIT using the Wilcoxon signed rank test. The

39difference was considered significant if p was less than 0.05.

40 A total of 11 Systemic Reactions (SRs), including 8 skin symptoms and 3 41respiratory symptoms, were observed in 8 of 68 injections (11.8%) in the rapid 42escalation phase. Four of 6 patients (67%) showed the SRs in the rapid escalation phase. 43In Patients 1, 2, 4, and 5 who showed the SRs in the rapid escalation phase, the dose 44was gradually increased to $1:2x10^2$ (w/v) in 0.05 ml by the conventional method in the 45outpatient clinic.

46 The median ingestible amount of soy milk was 1.5 ml (IQR, 1.0 to 2.0) before the 47treatment and significantly increased to 150 ml (IQR, 100 to 200) 1 year after initiating 48Birch SCIT (p = 0.04). One year after initiating the treatment, Patients 1, 2, and 6 were 49able to ingest the target amount of 200 ml soy milk. Patients 3,4 and 5 were able to 50ingest up to 50 ml, 10 ml and 20 ml of soy milk 1 year after initiating the treatment (Fig 511).

52 The specific IgE antibody titers to birch, alder, and Gly m 4 did not change 53significantly before and 1 year after initiating Birch SCIT.

54 One year after initiating the treatment, all patients were free from dietary 55restriction of soybean intake in their school lunch programs (Table 2).

56 Of the patients who needed restriction of apple intake before the treatment, Patient 576 was able to ingest apples without restriction, whereas Patients 1, 2, 4, and 5 were able

58to ingest them partially 1 year after initiating the treatment (Table 2).

59 Allergen-specific immunotherapy (AIT) is expected to be effective in treating 60PFAS, which is unlikely to heal spontaneously after its onset. However, the efficacy of 61AIT with pollen extract to PFAS has differed greatly in various reports, and its 62evaluation has not been established.[4-8]

63 This is the first report specifically evaluating soy milk intake of therapeutic effect 64on PFAS with Birch SCIT. The median intake of soy milk was significantly increased, 65and all patients were able to ingest soybean without restriction in their school lunch 66programs 1 year after initiating Birch SCIT. Birch SCIT could be suitable for patients 67with PFAS associated with soybean allergy.

68 The efficacy of AIT with Bet v1, the major birch pollen allergen has been 69evaluated with apple OFC in some studies.[4-6] However, the method for apple OFC used 70in these studies differed greatly in the amount of apple intake and the definition of 71symptoms. In the study using 10 g apple OFC, AIT with Bet v 1 showed significantly 72more improvement of OAS than the control group.[4] In the other study using whole apple 73OFC, AIT with Bet v 1 did not show improvement of OAS compared with the control 74group.[5] AIT with Bet v 1 by OFC with increasing amount of apple (1 to 128 g) resulted 75in an increase in the average tolerated quantity from 12.6 to 32.6 g apple after 1 year.[6] In

our study, all patients were able to ingest apples partially or completely. The efficacy of apple intake with Birch SCIT could be expected depending on the target setting of each patient.

The antigenic homology between the components in the Birch Mix solution and Japanese birch and alder pollen is unknown. The Birch Mix containing the red and white birch is not an extract preparation with a standardized antigen; therefore, the amount of antigen in this solution is unknown. The target antigen dose of Birch SCIT to achieve sufficient efficacy with AIT has not been established.[9] In our study, the desired therapeutic effect was obtained with the maintenance dose of $1:2x10^2$ (w/v) in 0.05 ml, but the incidence of SRs was 67% in the rapid escalation phase, indicating that the protocol for Birch rSCIT needs further improvement.

The limitation of this study is that it is not a randomized controlled trial. In addition, this study was conducted with a small number of patients at a single facility. Few children have difficulty in soybean intake with PFAS; thus, a multicenter collaborative study will be necessary in the future.

In conclusion, our findings indicate that Birch SCIT should be taken into account in patients with difficulty in ingesting soy foods, and having trouble in dealing with soybean in the school lunch program.

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There are no conflicts of interest related to this paper.

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164**Figure Legend**

165Figure 1. Ingestible amount of soy milk by OFC before and 1 year after Birch SCIT

166initiation

167In the Birch SCIT group, the median ingestible amount of soy milk was significantly

168increased 1 year after initiating Birch SCIT.

169* $p < 0.05$

170OFC; oral food challenge

171Birch SCIT; subcutaneous immunotherapy with birch pollen extract