

Editorial

Effects of birch pollen SIT on apple allergy: a matter of dosage?

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The efficacy and long-term effect of injection allergen-specific immunotherapy (SIT) in the treatment of respiratory allergies have been established by a number of studies and are generally accepted (1, 2). Recent findings suggest that the clinical effect of SIT relies essentially on two main immunological mechanisms, namely immune-deviation (a shift towards a Th1 immune response) possibly mediated by IL-12, the strongest inducer of Th1 responses known (3), and immune tolerance induced by IL-10, an immunosuppressive cytokine (4). SIT is presently not accepted as a treatment for food allergies, and allergen avoidance remains the only way to prevent potentially life-threatening reactions in patients sensitized to foods. Yet, curing food allergies by SIT probably remains the secret dream of many clinical allergologists. Some experimental attempts to desensitize peanut-allergic patients proved effective although, probably because of the lack of proper allergen standardization, both the 'build-up' phase and the maintenance protocol were associated with an unacceptably high rate of adverse systemic reactions (5, 6). The pollen-food allergy syndrome shows some advantageous features that make it a unique opportunity to evaluate the effect of SIT on food allergies. First, the risk of adverse reactions is minimal as SIT is carried out using the same well-standardized and safe pollen extracts that are widely used in thousands of allergic patients. In the pollen-food allergy syndrome, it is pollen that causes primary sensitization (7), and food allergy results from the immunological cross-reactivity between allergens in pollen and plant-derived foods (8–11); several lines of evidence suggest that virtually all allergenic epitopes of foods are present in pollen (8–10, 12). Secondly, because of the extreme lability of the relevant proteins, allergic symptoms induced by foods are generally mild and limited to oral allergy syndrome

(OAS), a fact that allows food challenges to be performed without the fear of exposing patients to severe or even life-threatening allergic reactions (13).

In the present issue of *Allergy*, Bucher et al. analyze the effect of 1 year of injection SIT with birch pollen extract in a group of birch pollen-allergic subjects with OAS induced by apple or hazelnut. Notably, most patients studied were not monosensitized to birch pollen, which means that at least part of them were probably sensitized both to Bet v 1 and to other cross-reacting allergens, particularly profilin. After 1 year of immunotherapy, the patients showed an increased rate of skin reactivity to fresh apple, but 87% of them (*vs* only 8% of controls) could tolerate a significantly higher amount of offending food. However, as the average amount of apple/hazelnut tolerated by SIT-treated patients remained relatively small (32 g) Bucher et al.'s conclusion is that SIT has only limited effects on OAS. Only six other studies dealt with the effects of injection SIT (with birch pollen in four studies, and different pollens in two) on food allergy in patients with pollen-food allergy syndrome before. Moller (14) observed a reduction of food-induced reactions in 43% of his birch pollen-allergic pediatric patients *vs* 14% of controls but, because of the lack of a statistically significant difference between the study groups, concluded that SIT is not effective in reducing birch pollen-related food allergies. Herrmann et al. (15) noted an improvement of food allergy in 45% of patients submitted to injection SIT with birch pollen extract. More recently 41 of 49 (84%) adults monosensitized to birch pollen reported a significant reduction or the total disappearance of their apple-induced OAS after 1 year of injection SIT (16); the clinical effect was associated with a marked reduction or with the total disappearance of skin reactivity to fresh apple and was rather long-

lasting (17). Further, Bolhaar et al. (18) observed a reduction of apple allergy in 60% of their birch pollen-allergic patients after as short as 1 year of injection SIT; moreover, they noted a decrease of skin reactivity to apple, hazelnut, and Mal d 1 in >60% of patients. Finally, two studies reported good results from injection SIT with pollens other than birch in patients sensitized to the plant pan-allergen profilin (19, 20). Notably, skin test with fresh fruits represents an extremely sensitive means to assess food hypersensitivity in patients with pollen-food allergy syndrome (13, 21); moreover, it seems unlikely that the use of open rather than double-blind, placebo-controlled challenges in some of those studies may have biased the results (22).

Altogether, the results of these studies seem to suggest that injection SIT with pollen extracts influences reactivity to foods in patients with pollen-food allergy syndrome; this fact is not particularly surprising as this type of food allergy is due to cross-reacting allergens. On the contrary, it is more surprising that in some studies SIT led to a resolution of the respiratory allergy but had little or no effect on the associated food allergy. Some data seem to suggest that the total amount of cross-reacting allergen administered by SIT, particularly the amount contained in a single maintenance dose, may be the pivotal factor influencing the effect of pollen SIT on cross-reactivity to foods. During the SIT course, the maintenance dose may correspond either to the maximum tolerated dose that does not elicit side-effects (23), or to the maximum dose suggested by the producer of the extract (this frequently corresponds to 1.0 ml of the final vial). In the latter case the maintenance dose given per shot depends on the concentration of the allergen that, because of the differences in standardization methods employed by various producers, may change from one product to another (24). During the last years, the major allergenic proteins of the most important respiratory allergens have been identified, and both monoclonal and polyclonal antibodies specific for these proteins have been developed (25). As a result, it is now possible to measure the concentration of a major allergen in mass units. Based on the content of purified major allergens the 'optimal dose' seems to range between 5 and 20 µg (23). The concentration of the major pollen

Table 1. Concentration of Bet v 1 in the final vial of some birch pollen extracts for injection SIT as declared by the producers

Brand name	Standardization	Bet v 1 (µg/ml)	Source
Alutard	100 000 SQ/ml	12.3	ALK-Abello
Pangramin	1000 STU/ml	22.5	ALK-Abello
Retard	5000 UT/ml	20.0	Allergopharma*

*Dr Oliver Cromwell, Allergopharma, Reinbeck, Germany; personal communication.

allergen, Bet v 1, in the maintenance vial of some widely used commercial extracts for injection SIT is shown in Table 1. As the clinical effect of SIT is dose-dependent (23), it seems unlikely that two birch pollen extracts containing 12.3 or 22.5 µg/ml of Bet v 1, respectively, may produce the same degree of immune tolerance/immune deviation and, hence, a similar clinical effect. Interestingly, Bucher et al., as well as Moller (14) and Bolhaar et al. (18), employed the extract containing the lowest concentration of Bet v 1 among those shown in Table 1 to treat their patients. In another study (15), the extract used was not specified, but a pre-seasonal administration schedule was used; clearly, the total dose of allergen given during SIT is much lower if a pre-seasonal rather than a perennial schedule is adopted. In the remaining study, an extract containing 20 µg/ml of Bet v 1 was given to the majority of patients using a perennial administration schedule (16). Notably, the best response of apple allergy to SIT was observed in this last study.

In summary, available data suggest that injection pollen SIT may effectively reduce not only respiratory symptoms but also hypersensitivity to plant-derived foods in patients with pollen-food allergy syndrome. To this end, adequate doses of the primary sensitizing airborne allergen must be administered; as previously noted (14), it is possible that, at least in some patients, doses needed to induce an appreciable effect on the associated food allergy are higher than those sufficient to improve substantially pollen-related symptoms. Along with oral challenge, SPT with fresh apple seems useful in assessing the degree of desensitization induced by SIT.

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