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Commentary

Sustained Effect of Immunotherapy for Food Allergy: Breaking Up is Hard to Do

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The majority of clinical trials put emphasis on when and how to start a treatment. The urge for efficacy via raising the dose of the experimental drug must be balanced with concerns for safety and adverse events. The outcome of the treatment may be crucially dependent on the regimen: a careful selection of dosing increments and intervals. Nowhere is this truer than in the field of allergen-specific immunotherapy (AIT) of allergic diseases – a treatment that dates back more than a century [1]. This is often initiated by a dose-increase phase followed by a prolonged maintenance phase of a fixed dose administered at regular time intervals.

But how long should the treatment be continued? There is evidence for giving the treatment for at least 3 years [2], but evidence beyond this is based on a relative few studies. Such studies are inherently difficult to perform, since there is little acceptance from both patients and authorities to perform double-blinded, placebo-controlled trials studies of 3–5 years of treatment followed by observation periods of similar duration. Also, there is a paucity of biomarkers that correlates well with the individual patient's treatment outcome [3].

In many countries, IgE-mediated food allergies seem to have increased dramatically in recent years, and no curative treatment has yet been devised [4]. While many studies have confirmed the efficacy of AIT in inhalation allergy [2], this therapeutic principle is still mostly on the experimental level for food allergy [5]. The often severe and acute response of food allergic patients when exposed to foods or extracts hereof, has forced investigators to consider alternatives to parenteral administration. Oral immunotherapy (OIT) with daily dosages and a gradual dose increase have been described [5,6] as efficient, safe, and patient friendly allowing foods rather than pharmaceutical preparations thereof to be used. Still, the Achilles' Heel of the treatment is the question of sustainability, will the induced tolerance endure when the daily dosing is terminated or just dropped for a period due to lack of compliance, concomitant disease etc.?

This question is addressed in this issue of EClinicalMedicine, where Sandra Andorf and coworkers from a large multicentre group lead by Kari Nadeau at Stanford University, present an interesting study [7] where OIT up-dosing is followed by a six-week period, where two doses (1 and 0.3 g food protein/day) of daily maintenance therapy are compared with discontinuation of treatment in a blinded setup. The study comprises some of the most difficult-to-treat patients, namely multi-allergic children and adolescents, and stands on the shoulders of previous studies from the group, where OIT with multiple foods is initiated under a cover of anti-IgE treatment [4,8]. Based on the primary outcome parameter, which is tolerance of 2 g of food protein for at least two allergenic foods, the continued patients demonstrate an 85% success-rate vs. 55% in the discontinued group. While the patient number is relatively small with sixty subjects reaching the randomized phase, several of the secondary outcomes, such as tolerance of 4 g protein for at least two foods, 2 g for at least three foods etc., confirm the overall trend of the study. Interestingly, the magnitude of the maintenance dose (1 g vs. 0.3 g of food protein per day) seemed to be of lesser importance. Many different foods are in play, and future, larger studies will have to explore potential differences between foods and their potential cross-reactive patterns.

In two ways the study has paved the way for improving the lives of food allergic patients and caretakers: 1) it has confirmed that the cover of omalizumab (a biological which can temporarily neutralize IgE-mediated side effects by complexing free IgE) may allow a parallel up-dosing with several foods in multi-allergic patients, and 2) it has devised method for evaluating the necessary length of the maintenance phase.

There is still some way to go, however. A tolerance of 2 g of food protein is not curing the patients' food allergy. It does, however, put them at a much-reduced risk level, where hidden traces of allergenic foods become much less of a problem in daily life. Moreover, we still do not know how and when to terminate the treatment. The fact that only about half of the patients discontinuing the OIT after 30 weeks met the tolerance criterium suggests that longer time of OIT is necessary for a sustained effect. Also, the experiences with AIT for inhalation allergies would suggest slower kinetics, so further studies are clearly needed to explore whether prolonged maintenance treatment and/or further increased dosing could eventually preserve patients' tolerance for a longer period if not making them perpetually tolerant.

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