

Oral peanut immunotherapy

How much is too much? How much is enough?

Efficacy of food allergy immunotherapy (FA-AIT) for cow's milk, hen's egg, and peanut at the level of desensitization is established via several small placebo-controlled trials and a number of open-label trials.¹ First approved treatments for peanut allergy are projected to become available soon including oral immunotherapy (OIT). But there is still a discussion which group of patients might profit most of OIT and what amount of maintenance dose to apply.

In this issue of *Allergy*, Reier-Nilsen et al² present the results of the build-up phase of the TAKE-AWAY trial, an open-label controlled, randomized, high-dose peanut OIT trial in 5- to 15-year-old children aiming for sustained unresponsiveness to peanut after 4 years of treatment (Take-Away Food Allergy; Inducing Tolerance in Children Allergic to Peanut, NCT02457416). Seventy-seven children were randomized to either receive peanut OIT (n = 57) or avoidance (n = 20). At baseline, 79% of children in the OIT group reported a history of anaphylaxis and were highly sensitized to peanut (geometric mean of Ara h 2- IgE: 56.2 kU/L [IQR: 37.2; 87.1]), and 42.1% suffered from asthma. Anaphylaxis was confirmed for each one via oral food challenge (OFC). The lowest observed adverse effect level at inclusion was <20 mg peanut protein. Patients on OIT followed a slow, up dosing protocol with biweekly dose increases up to a high maintenance dose of 5000 mg peanut protein. In this issue, the researchers aimed to determine the feasibility of reaching the maximum maintenance dose (MMD) or an individual maintenance dose (IMD) in the OIT group. Only 21.1% reached MMD, 54.4% stayed on an IMD, and 24.5% discontinued. The main reasons for not reaching the MMD were distaste, adverse reactions, and social reasons. None in the control group but 19.4% of patients in the OIT group experienced an anaphylactic adverse event during up dosing.

Despite official statements from North American Societies for Allergy that do not recommend the conduction of OIT outside of clinical trials, a non-neglectable number of community allergists have decided to implement OIT as a treatment option for their patients. The existing body of evidence prompted the European Academy of Allergy and Clinical Immunology (EAACI) to consider OIT "a treatment option in well-defined cases of children with cow's milk, hen's egg or peanut allergy by a team that is experienced in conducting OIT and has access to infrastructure to manage severe acute reactions and provide admission for observation for up to 12 hours."¹ The presented dataset² adds to current knowledge challenging the feasibility of conventional approaches of OIT in clinical routine but also provides information that may support other than high-dose OIT approaches.

Patients with very low reaction thresholds and severe reactions are perceived as those who would profit most from successful and

safe OIT by raising the reaction threshold or even inducing complete tolerance development.

The authors discuss that they enrolled such a group of severely allergic patients compared to other studies. Although the majority of OIT trials included patients with a history of anaphylaxis and/or asthma, there are some aspects that make this cohort special. The authors applied a protocol for OFCs that required the presence of "at least two moderate objective symptoms in one or more organ systems according to PRACTALL consensus report."³ Thus, all children had an anaphylaxis during OFC who might not have had an anaphylaxis during OFC if conventional stopping rules for OFCs were applied. Authors also argue that predominantly patients with a low threshold were enrolled and illustrate that in such a severely affected population, 75% of these patients can reach a maintenance dose that protects from accidental reactions due to cross contaminations but also highlights the low success rate in this group to reach a maintenance dose equivalent to a full serving (21%).

When discussing OIT to food, two parameters are key: the dose and the time. Data from high-dose immunotherapy using 3-10 g, low-dose OIT of <300 mg,⁴ sublingual Immunotherapy with a very low dose of 1-5 mg of peanut protein,⁵ and epicutaneous immunotherapy of (<1 mg)⁶ have been summarized.⁷ There seems to be a correlation between the number and severity of adverse reactions, dropout rates, and the amount of peanut protein applied (Figure 1). The study by Reier-Nilsen et al supports that notion. During the up dosing phase 1, out of five patients experienced an episode of anaphylaxis. Nine of 11 of these anaphylactic episodes occurred at doses >300 mg peanut protein. Seventy-seven percent of the patients experienced distaste as a daily problem. Although not considered a serious adverse event, distaste is a serious issue when trying to consume 20 or more peanuts at maintenance dose. Lack of compliance is a serious safety issue in OIT.

Currently, the dogma exists that higher doses are linked to a higher probability of developing sustained unresponsiveness or tolerance. But data are not consistent, and additional studies that directly compare different doses are needed. Since the primary aim of the still ongoing TAKE-AWAY trial is analysis of the induction of sustained unresponsiveness, results will help to further delineate this hypothesis. It may well be that the length of application is by far more important for tolerance development and low doses with less side effects are the future of oral immunotherapy.

The most significant factor responsible for the reduced quality of life in food allergic patients is the constant fear of having an accidental exposure. OIT-related gain of control and protection often outweighs the increased chance of an allergic reaction due to treatment. For some however, avoidance may be the better choice.⁸ It is

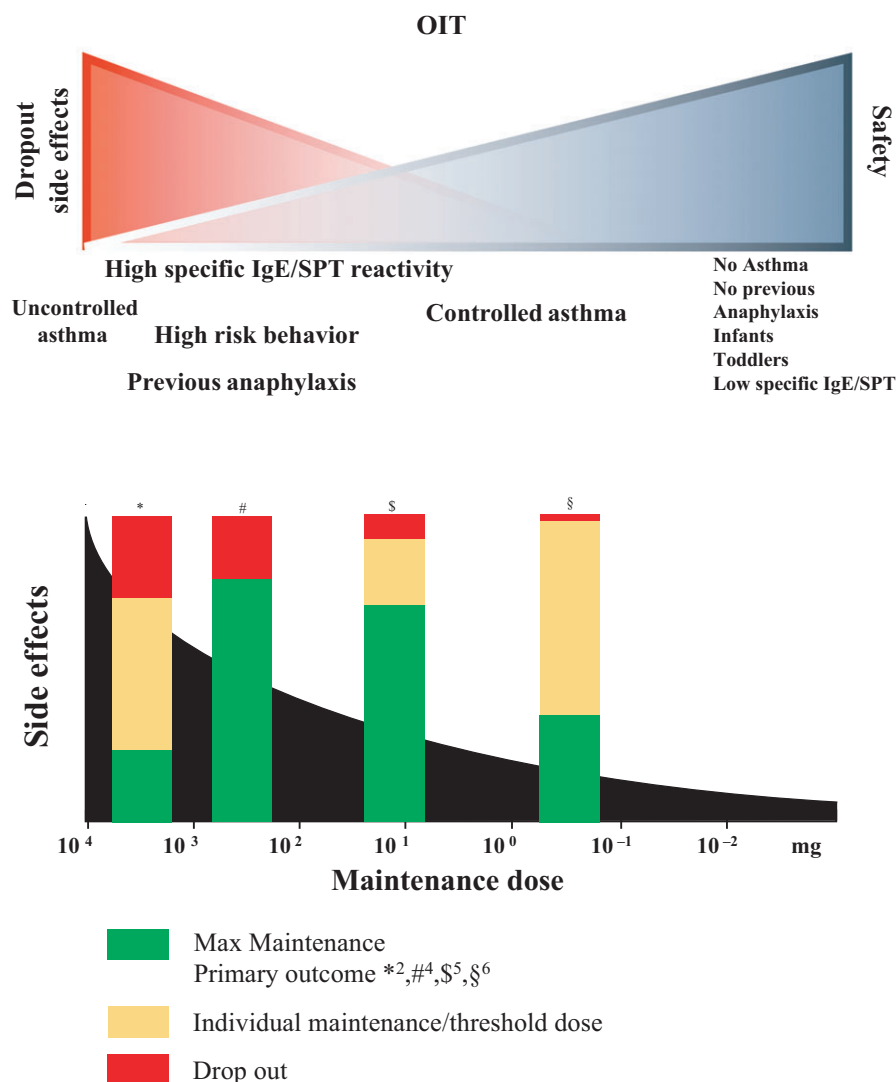


FIGURE 1 Factors contributing to safety of oral immunotherapy (OIT). High-dose OIT is associated with a considerable rate of side effects, which are augmented by a number of risk factors. Low-dose OIT may not lead to the allowance for the introduction of allergen doses equivalent to a normal serving but significantly increases the threshold and allows for a better quality of life and protection from low-level cross-contamination-related allergic reactions. Signs and numbers related to individual studies/data have been retrieved from, *: Ref. 2, #: Ref. 4, \$: Ref. 5, §: Ref. 6)

up to us as allergists to identify those patients who will profit from a treatment and define the aims accordingly. For the very severe cases, aiming for an increase in threshold may be more important than going for the loss of the allergy and risking a treatment failure due to side effects that cannot be tolerated.

New approaches to overcome the limitations of high-dose OIT and allow uncomplicated multi food OIT are demanded. Therefore, co-application of biologicals such as omalizumab allows a better safety profile⁹ and possibly a significantly lower rate of treatment failures. Moreover, novel treatment options such as hypoallergenic variants of allergens, allergen preparations that include potential pro-tolerogenic adjuvants, or peptide immunotherapy may improve the safety and efficacy profile of OIT.

In conclusions, the manuscript of Reier-Nilsen elegantly shows the efficacy of OIT with regard to desensitization, but more importantly raises concerns whether high-dose OIT has the potential, in its current version, to be applied as a standard treatment for food allergy. This applies in particular for patients who are highly sensitized, with a low threshold and a history of anaphylaxis.

CONFLICTS OF INTEREST

Thomas Eiwegger is involved in the conception and conduction of several investigator-initiated oral immunotherapy trials and is site principal investigator of a DBV-sponsored clinical trial on epicutaneous immunotherapy. Dr. Blumchen reports on non-financial support from Novartis, honoraries from Novartis, HAL Allergy, Aimmune Therapeutics, and Thermo Fisher and grants from Aimmune Therapeutics, "Foundation for the treatment of peanut allergic patients (bea Stiftung)," and "The Berlin Sparkasse Foundation for Medicine."

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