

## EDITORIAL

# Clinical & Experimental Allergy

## Baby – and toddler – steps toward immunotherapy for food allergy

This editorial discusses the findings of the paper in this issue by Martorell et al. [5] pp. 1297–1304.

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Nearly 100 years after the benefit of immunotherapy for respiratory allergies was demonstrated, immunotherapy for food allergies is finally coming into its own. Small studies in the last decade show some success in desensitizing to peanut, milk and egg, although we are far from a uniform safe protocol for clinical use [1–4]. To date, for reasons of safety and practicality, studies of these treatments have generally not focused on the youngest patients, and when they have included younger subjects, they have not reported age-specific results [2, 4]. Theoretically, tolerance may be induced with greater ease in young children because of their immature immune systems. However, they may also be at increased risk of adverse reactions compared with their older counterparts, especially given the difficulties in interpreting early subjective symptoms of a reaction in young children. To complicate matters further, many, if not most, children in the younger age group will have natural resolution of their milk and egg allergies. For these reasons, the report in this issue of the journal by Martorell and colleagues, which addresses some of these questions, is a welcome addition to the literature [5].

Martorell and colleagues describe the results of a randomized controlled trial of milk oral immunotherapy in sixty 2-year-old milk allergic children. Consistent with other reports in older children [1–4], they had good success in desensitizing over approximately 1 year; 90% of those treated with milk oral immunotherapy reached the goal of 200 mL, compared with < 23% in the untreated control group. Moreover, they found that milk-

specific IgE and skin prick size decreased compared with baseline in the treated but not control group [5]. These results are encouraging because they suggest that young children can be desensitized orally to food allergens with as much success as older subjects. Still, many questions remain unanswered.

The most important concern is safety. In the study by Martorell and colleagues, 15% of doses were associated with adverse reactions and a full 47% of subjects had moderate reactions, defined as generalized urticaria, facial angioedema, cough or mild bronchospasm, during immunotherapy. In the vast majority of cases, the therapy could be continued with subjects eventually tolerating larger amounts of milk [5]. However, this rate of reaction, similar to what has been reported in other studies of oral immunotherapy [2, 3, 6], remains troublingly high. For immunotherapy to food allergens to be widely applied in the general allergy clinic, safety will need to be improved.

Several methods show promise in improving safety. Using extensively heated (baked) milk instead of unheated milk could be one way to safely build tolerance to milk. Nowak-Wegrzyn and colleagues at Mt Sinai reported in 2008 that 75% of patients reactive to unheated milk are able to tolerate extensively heated milk [7]. In these patients, introduction of heated milk resulted in increased milk-specific IgG4 and decreased milk-specific skin prick test size after 3 months. This was not done in a clinical trial and prospective controlled data on this approach are not yet available, but it seems likely that, for many patients, baked milk may be a safer and more convenient way to increase milk tolerance than unheated milk immunotherapy. It appears that egg allergy behaves similarly to milk in terms of the difference between extensively heated and intact protein, and that introduction of baked egg may also increase tolerance in many egg allergic patients [8].

But what of the patients who do not tolerate baked milk or egg, or who have other food allergies? The allergenicity of peanut and tree-nut allergens is not reduced by heating,

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and some milk and egg allergic subjects will react to even very small amounts of heated milk or egg. For these patients, other modifications of orally delivered immunotherapy could potentially increase safety, including a slower dose escalation, escalation using sublingual dosing at far lower doses, or the use of medications, such as omalizumab, in conjunction with immunotherapy to decrease symptoms. Studies of these methods are currently in process.

Other important questions regarding immunotherapy for young children relate to the nature of the clinical benefit and whether it changes the long-term trajectory of the disease. Within the field of allergy, we have examples of therapies that do both. When we desensitize to penicillin, for example, we do not expect any long-term benefit. In contrast, with long enough duration of immunotherapy for pollen allergy we expect that there will be long-term immunologic changes that we would call 'tolerance'. One central unknown about oral immunotherapy for food allergy is whether patients are transiently desensitized or truly tolerant. Although several studies are ongoing, there is very little published data about this subject. Buchanan and colleagues took four children who had performed well with egg oral immunotherapy off all egg for 3 months. Of this group, 1/2 (two children) reacted at much lower doses than before withdrawal of therapy, suggesting that at least some oral immunotherapy will lose protection without ongoing exposure [1]. For all food immunotherapy subjects this distinction has implications for the long-term risk of acute reactions, but it is particu-

larly important for the youngest patients, who may have a much greater likelihood of natural resolution of their allergies. Theoretically, a patient who could have been completely milk tolerant without intervention by age 5 might instead be at risk for anaphylaxis at the same age if he misses several days of exposure (because of a stomach illness, for example), and this after a course of treatment to which he had frequent mild-to-moderate reactions.

On the other hand, for some patients it is likely that avoidance actually leads to more severe, persistent allergy, and that oral immunotherapy may lead to long-term tolerance and real resolution of allergy. Animal studies suggest that allergen exposure leads to molecular changes consistent with both desensitization and tolerance. Which of these mechanisms predominates depends on dose, but there is some evidence of overlap [9]. In this study milk-specific IgE decreased in treated, but not control subjects, although this finding has not been universally reported in similar studies. More studies reporting more detailed mechanistic markers will be helpful. Even more reassuring would be long-term studies comparing clinical outcomes for treated and untreated children, and biomarkers to best predict those children who are most likely to require, and benefit from, immunotherapy. Rigorous studies of this kind are difficult, but essential.

Thus, although the results in the report by Martorell and colleagues, as well as those in several other recent reports, are encouraging, key questions remain that must be answered before these methods can be effectively applied to more wide-spread use.

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