



Guest editorial

Oral food immunotherapy and iatrogenic eosinophilic esophagitis: an acceptable level of risk?

Given the perplexing increase in food allergy during the past 10 to 15 years, there has been tremendous interest in offering new treatment options other than the standard-of-care approach of identification, avoidance, and emergency therapy. In the absence of new pharmaceuticals that target mechanisms of sensitization, tolerance, and immune cell activation or treatment of symptoms after exposure, the most pioneering work has been performed in the area of food allergen-specific immunotherapy performed under the direct guidance of the allergist. Because preliminary trials of injection immunotherapy to food were associated with an unacceptable systemic reaction rate,¹ modalities such as oral, sublingual, or transcutaneous food desensitization are being explored with oral food desensitization or oral immunotherapy (OIT), the method currently attracting the most clinical research interest.^{2–4} More than 40 studies of OIT to a variety of food allergens have been reported. The studies involve mostly pediatric but also some adult patients, using a variety of study designs and with varying sample sizes. Despite some promising efficacy outcomes, many studies report significant adverse events, including not only systemic reactions that require epinephrine administration but also cutaneous, respiratory, and gastrointestinal symptoms, and notable dropout rates.⁵

The identification of newly diagnosed eosinophilic esophagitis in patients undergoing food OIT has been recognized in numerous OIT studies. In this issue of the *Annals*, Lucendo et al⁶ report a systematic review and meta-analysis to attempt to address the association between OIT and eosinophilic esophagitis with the available data. Using a reference search strategy that encompassed OIT studies in which at least one case of eosinophilic esophagitis was reported, the investigators identified 12 publications (8 being abstracts only) for analysis. This report included data from 711 patients undergoing OIT to peanut, egg, cow's milk, or wheat, with most of the patients being children, in retrospective studies, randomized clinical trials, or case reports. On the basis of this available data set, the investigators calculate a 2.72% (95% confidence interval, 1.7%–4.0%) prevalence of eosinophilic esophagitis in patients with IgE-mediated food allergy undergoing specific food OIT. Because of the study design, individual studies of OIT were excluded from the meta-analysis if no cases of eosinophilic esophagitis were reported; this 2.72% figure may overestimate the overall prevalence. The OIT studies not reporting eosinophilic esophagitis, either because there was no eosinophilic gastrointestinal disease or because eosinophilic esophagitis was not

considered, were not included. This bias is recognized by authors and confirmed by their use of a funnel plot analysis that suggested that studies reporting a lower incidence or no association of eosinophilic esophagitis with OIT were absent. On the other hand, gastrointestinal symptoms are not uncommon with food OIT. Because eosinophilic esophagitis can only be definitively diagnosed with an invasive procedure (endoscopy with biopsy), it could be argued that the true prevalence of eosinophilic esophagitis in patients enrolled in food OIT trials is underestimated.

Because a meta-analysis is derived from a summation of studies, the robustness of its conclusions is only as strong as the underlying data that are combined in the analysis. In addition, the inclusion of divergent study protocols makes a meta-analysis less reliable. Thus, it is not necessary to emphasize that this study, in which only 4 of 12 studies were full text and only 1 of 12 studies that met inclusion criteria was a randomized clinical trial, is not likely to be the definitive or final answer to this question. An adequately powered randomized clinical trial of food OIT in which specific surveillance for the adverse event of eosinophilic esophagitis is included during an appropriate observation period may yield a different outcome.

However, these data are useful in suggesting that the association of OIT, and by extension any food-specific immunotherapy, and eosinophilic esophagitis may not be such a rare or idiosyncratic event. Because endoscopic surveillance is not typically performed before initiating food OIT, it is unknown whether eosinophilic esophagitis associated with OIT is due to the unmasking of preexisting, lower-grade esophageal eosinophilia vs the initiation of new esophageal disease. Given that the duration of food OIT required to induce a remission from anaphylactic sensitivity, if even this is achievable, has not been determined, it is certainly possible that the duration of food OIT may be found in the future to be associated with the risk of developing eosinophilic esophagitis. To date, most of the gastrointestinal symptoms related to food OIT have apparently remitted after cessation of OIT, but it is possible that food OIT could serve as an initiating trigger of an esophageal inflammatory process that establishes itself independently from its initial food trigger. The possibility that a food allergic patient discontinuing OIT because of intolerance or adverse events might be left with 2 diseases (food anaphylactic sensitivity and new eosinophilic esophagitis) may remain a question resolved only after a large number of patients have undergone this treatment procedure.

It is also of interest that a therapy (food OIT) that targets an IgE-mediated disease (anaphylactic food sensitivity) could contribute to the pathogenesis of a disorder of food sensitization (eosinophilic esophagitis) where food specific IgE may be involved but may also

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be dispensable.⁷ Given the reported efficacy of elemental and food elimination diets in the treatment of eosinophilic esophagitis, it is expected that food sensitization must occur at some point in the pathogenesis of the esophageal disease.⁸ However, animal models of eosinophilic esophagitis and some human data suggest that the route of sensitization may occur not only from gut exposure to food allergens but also from sensitization via the airways or even skin.⁹ Indeed, in some animal models, gastrointestinal food exposure is inadequate to initiate esophageal eosinophilia.¹⁰ As the increase in the recognition and prevalence of eosinophilic esophagitis as a unique entity roughly tracks the increasing prevalence of food allergy, one wonders why there is not more overlap between these 2 conditions and whether a critical checkpoint mechanism can be identified in the broad context of atopic disease that controls IgE-dependent vs IgE-independent food sensitization.

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