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Conflicts of interest

This author discloses the following: Dr Kaplowitz consults for GlaxoSmithKline, JNJ, Pfizer, Takeda, and Daiichi Sankyo pharmaceutical companies. The other authors disclose no conflicts.

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IgG and EoE: Too Soon for a Paradigm Shift Away From IgE



Dear Editor:

It is with great interest that we read the study by Clayton et al which documents a scarcity of esophageal IgE antibodies and lack of response to omalizumab (monoclonal anti-IgE antibody), contrasting this with the abundance of esophageal and food-specific serum IgG4 antibodies.¹ The authors boldly contend that EoE in adults is not mediated by IgE but rather by IgG4 antibodies, and cautiously raise the possibility that IgG4 antibodies may have potential as a diagnostic tool in place of an elimination diet. It is the implications of the claims relating to, and the broader significance of, IgG4 antibodies that concerns us most.

Serum IgG4 antibodies to common food antigens were detectable in disease-free controls as well as those with EoE, although were elevated to a greater degree in the latter group. This finding is similar to a study that demonstrated elevated specific IgG4 antibodies in patients with IBS as well as healthy controls.² What has never been established is the significance of quantitative and qualitative changes in antibody levels and, of particular relevance to EoE, levels in atopic individuals (who by definition have elevated IgE antibodies to common environmental and food antigens, and have a tendency to develop allergic disease).³

It is possible, as the authors propose, that antigen-specific IgG4 antibodies may represent the development of immune tolerance, as suggested by multiple previous

studies of immunotherapy in which a rise in their circulating levels correlates with successful treatment and suppression of IgE antibodies.⁴ The contention that children with previous classical IgE-mediated food allergy may later develop EoE to the same food antigen also supports this hypothesis and has been recorded recently.⁵ However, the study by Clayton et al used disease-free controls, rather than those with other atopic disease and does not examine aeroallergen sensitization. Thus, it could be argued that, rather than demonstrating a clinically relevant entity, they have merely documented the quantitative rise in IgG4 to food antigens typical of atopic individuals.

Esophageal IgG4 antibodies were demonstrated to be greatly increased in those with EoE compared to healthy controls, and the hypothesis that these antibodies may be causally involved was discussed. We apply similar cautions to the interpretation of this finding, which could be reasonably viewed as a non-specific inflammatory response until such time as a similar study that documents a difference between those with, for example, reflux esophagitis and EoE is performed. The finding of elevated IgG4 in tissue or secretions has been documented in other inflammatory disease states, such as atopic rhinitis, chronic sinusitis as well as ulcerative colitis.^{6,7}

Clayton et al propose that IgE is not important in the pathogenesis of EoE, citing the lack of response to omalizumab and the abundance of IgG antibodies. However, it should be pointed out that no attempt was made to locate IgE antibodies in this study, and that the poor response to omalizumab has previously been recorded.⁸ IgE antibodies bound to mast cells have been found in esophageal specimens from children and adolescents with EoE as old as 16 years⁹ in contrast to the findings of this study. A diminished role of IgE antibodies, compared to IgG antibodies has been proposed in classical atopic disease previously defined by their presence, and thus any attempt to cast EoE as an IgG4-mediated condition should be met with caution, or viewed within the ever expanding pool of knowledge relating to eosinophilic disease.¹⁰

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Reply. We agree with Philpott et al, that the mechanism for eosinophilic esophagitis (EoE) remains unclear, and that IgE antibodies are usually present and could play an important role, particularly in the early stages of the disease. However, one must clearly distinguish causal mechanisms from disease markers. Immunity is complex, with many seemingly redundant pathways. The only way to prove that a mechanism induces an immune response is to block it and see what happens. IgE depletion by omalizumab had no effect on symptoms or tissue eosinophil counts in our trial of mostly adult subjects. Philpott et al, correctly note that this is in agreement with the Rocha et al study,¹ which we cited.² However, our double-blind placebo-controlled trial of 30 subjects (which was called for by Rocha et al) is stronger evidence than an open-label, uncontrolled study of 2 subjects.

We also agree with Philpott et al, that showing esophageal mast cell IgE depletion is a crucial confirmation of treatment effect. Contrary to their statement, we did it! (See Supplementary Figure 2 of our article.²) We agree that the failure of omalizumab might not apply to pediatric or recent onset EoE, and that occasional IgG4-negative, IgE-mediated adult cases might happen, as stated in our discussion.

We do not “boldly contend” that adult EoE is mediated by IgG4 antibodies. We stated: “Although IgG4 immune complexes could be causal, we have no evidence to support that over other potential mechanisms.” It remains highly plausible that EoE is entirely T-cell mediated. Also, as hypothesized for IgG4-related disease,³ activated B cells could activate or promote the survival of pathogenic target-food-directed memory Th2 cells.

Oral immunotherapy for food allergies, in which the goal is a tolerance-inducing IgG4 immune response, causes EoE in 2.7% of patients.⁴ While inconclusive, this certainly hints that IgG4, or the inflammatory pattern that induces IgG4 plasma cells, could play a role in EoE.

That IgE is not directly causal in most adults with EoE would not preclude the possibility that it could be a useful marker indicating the trigger foods. However, results of allergy-test-directed food elimination diets have varied widely; a recent meta-analysis found allergy-test-directed

food elimination diets inferior to six-food elimination and elemental diets, with 45.5%, 72%, and 91% overall response rates, respectively.⁵ More work is needed to accurately predict the trigger foods for an individual patient. It is plausible, although unproven, that IgG4 serology might be useful in addition to or in place of IgE.

We agree with Philpott et al, and so state in our paper, that our IgG4 serology findings must be interpreted cautiously and do not prove any practical clinical utility for such testing. IgG4 food reactivity is present even in some normal controls; false positives among atopic patients will likely be problematic. However, regardless of the control results, the presence of food-immunoreactive IgG4 in EoE has two implications: (1) IgG4 blocking antibodies are often present and might help explain the false negative allergy skin testing for trigger foods that is common in adult EoE, and (2) combined with particulate IgG4 immunostaining, it suggests that IgG4 immune complexes might be present, potentially activating cells (like eosinophils) lacking the inhibitory FcγR2b receptor. As stated above, the clinical significance of this hypothetical pathway is unproven.

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