



IgG₄ in eosinophilic esophagitis: perpetrator, accomplice or bystander?

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Comment on: Rosenberg CE, Mingler MK, Caldwell JM, *et al.* Esophageal IgG₄ levels correlate with histopathologic and transcriptomic features in eosinophilic esophagitis. *Allergy* 2018;73:1892-901.

Received: 07 September 2018; Accepted: 24 September 2018; Published: 30 September 2018.

doi: 10.21037/aoe.2018.09.03

View this article at: <http://dx.doi.org/10.21037/aoe.2018.09.03>

Eosinophilic esophagitis (EoE) is a T-helper type 2 (Th2) mediated disease characterized by an eosinophilic dominant esophageal inflammatory response that is thought to promote esophageal remodeling and reduced esophageal caliber leading to vomiting, dysphagia, chest pain, food impaction and decreased health-related quality of life (1). The cellular and molecular processes that underlie the pathophysiology of EoE are not yet fully understood, however a combination of environmental and genetic factors interwoven with host immunity is thought to drive the clinical manifestations of disease (2-5).

The demonstration of histologic and clinical improvement following elemental and elimination diets has led to the concept that food allergens and IgE are important contributors to the pathogenesis of EoE (6-10). This is further supported by the demonstration that EoE individuals have increased incidence of IgE-mediated food sensitization and levels of food specific IgE (11-13). However, elimination of foods based upon skin prick testing (SPT) or elevated serum IgE levels and anti-IgE therapy (omalizumab) have had limited success (14-17).

Recent clinical datasets have revealed a link between IgG₄ and pediatric and adult EoE (17-19). Notably, investigators have demonstrated increased levels of serum IgG₄ and esophageal IgG₄⁺ plasma cells (PCs) in EoE patients compared to control individuals. Assessment of cow's milk protein specific IgG₄ antibodies in a pediatric EoE cohort has revealed serum IgG₄/IgE ratios to be >10,000 in EoE patients and, following adjustment for age

and milk consumption, high titers of IgG₄ to CM protein strongly correlated with EoE with an odds ratio of >20 (19). IgG₄ is considered to be an anti-inflammatory antibody as it possesses a short hinge and low Fab arm flexibility, can undergo a process termed "Fab arm exchange" which precludes cross-linking of identical antigens, and has a low affinity for the Fc gamma activating receptors (20,21). So the link between elevated levels of IgG₄ and EoE was somewhat surprising and led to the speculation that EoE may be an IgG₄-associated disease. However, how IgG₄ contributes to EoE pathogenesis remains unclear.

A recent case-control study by Rosenberg *et al.*, published in the journal *Allergy*, examined the role of IgG₄ in pediatric patients with EoE (22). The authors revealed a relationship between immunoglobulin levels, in particularly IgG₄, and histologic and transcriptomic profiles of esophageal biopsy samples from EoE (n=17) and control (n=19) pediatric patients. Moreover, the authors observed increased levels of IgM, IgA, IgG₁, IgG₂, IgG₃ and IgG₄ in esophageal tissue of patients with EoE compared to controls. Most striking, the esophageal IgG₄ levels in EoE patients were 22-fold higher than that observed in control individuals. No significant differences in esophageal IgE levels were observed in patients with EoE compared to control individuals.

To analyze of the relationship between IgG₄ levels and EoE severity the authors employed the validated EoE histology scoring system (EoEHSS) (23). Rosenberg and colleagues revealed that levels of IgG₄ in esophageal tissue correlated with mean histologic grade and stage in

pediatric EoE. Notably, the strongest correlation was with basal zone hyperplasia (BZH) and esophageal eosinophilia. Transcriptional analyses of cytokine levels revealed a correlation between esophageal interleukin (IL)-4, IL-10 and IL-13 mRNA levels and IgG₄, but there was no association with transforming growth factor beta (TGF- β). IL-4 and IL-13 are known Th2 cytokines that induce B-cell class switching promoting production of IgE and IgG₄ (24,25). On the other hand, IL-10 which is produced at high levels by regulatory T cells (Treg) as well as eosinophils and enhances production of IgG₄ as opposed to IgE (26-28). Comparison of esophageal IgG₄ levels with gene expression in EoE using the EoE Diagnostic panel, a panel of 96 EoE genes (29), revealed a significant correlation with 62 genes that are involved in the biological processes including epithelial barrier, cell adhesion, inflammation, ion channels, chemokines/cytokines as well as proliferation. It would be interesting to know whether the observed increased levels of other immunoglobulins were associated with EoE severity and transcriptome profile to determine whether this was specifically related to IgG₄ or a general phenomenon related to increased inflammatory disease. Despite this, the positive correlation with the inflammatory pathways and observed histologic link suggests that IgG₄ may play a pro-inflammatory role contributing to the ongoing inflammation and esophageal epithelial remodeling in EoE.

Recently there has been a number of studies evaluating esophageal immunoglobulin levels in EoE patients (17-19). In an adult EoE cohort, investigators reported increased IgG₄ levels in esophageal tissue samples from patients with EoE compared to controls, however, levels of IgM, IgA, IgG₁, IgG₂, IgG₃ were not different between groups. Mohammad and colleagues reported increased IgG₄⁺-plasma cells (PC) in a pediatric EoE cohort compared with age- and sex-matched controls (18). Notably, IgG₄⁺-PC levels did not correlate with esophageal eosinophilia or therapeutic outcomes. Similarly, Schuler *et al.* (19) reported high sera CM-specific IgG₄ in a pediatric EoE cohort compared to controls. However, they did not observe any relationship between CM-specific IgG₄ levels and disease remission following CM elimination diet (19). Rosenberg and colleagues did not observe significant differences in esophageal IgE levels in EoE compared with controls. This would be in contrast to previous reports demonstrating heightened levels of IgE and IgE-PCs in esophageal biopsy samples in EoE compared with controls (12,13,19,30). In a randomized, double-blind, placebo-controlled trial of

adults with EoE given an antibody against IgE (omalizumab) investigators reported that treatment with anti-IgE (omalizumab) did not alter symptoms or esophageal eos/HPF compared with placebo treatment (17) suggesting that EoE may not be an IgE-mediated disease process. It is important to note that Rosenberg *et al.* report that the ratio of IgG₄ to IgE was 10:1 in control subjects and was 224:1 in patients with EoE. Consistent with this, Schuyler *et al.*, observed a similar increase in the CM-specific sIgG₄/sIgE ratio in pediatric patients with EoE (19). The discrepancies between these studies related to IgG₄ and IgE association with disease severity and therapeutic outcomes maybe reflective of differential roles for IgG₄ between pediatric and adult EoE or a differential contribution during the natural history of disease where IgE-mediated processes are involved in the initial disease course and then transition to primarily IgG₄-associated disease.

There were some limitations with this study. Firstly, the authors only analyzed n=17 non-EoE controls and n=19 EoE individuals and the small sample size is underpowered to evaluate the relationship between different treatment modalities impacts on IgG₄ levels. Furthermore, EoE individuals were selected without regard to atopic status, treatment status and it was not specified whether patients underwent or undergoing PPI trial which could impact the immunological and histologic outcome measurements. Furthermore, there was no exploration of the food sensitization status of those individuals in the control group. A future case-control study evaluating the levels of esophageal immunoglobulins in the setting of food sensitization could be of value. Furthermore, all the patients were of Caucasian descent which may influence the generalizability of these findings to broader populations.

Despite these limitations, the study by Rosenberg and colleagues adds further weight to the emerging concept of a role for IgG₄ in EoE. However, there are many unanswered questions including (I) whether heightened IgG₄ levels is just an epiphenomenon in EoE patients related to the elevated CD4⁺ Th2 and eosinophilic response or whether IgG₄ directly contributes to disease pathogenesis or (II) what is the predictive value of IgG₄/IgE ratio to EoE disease state and responsiveness to treatment modalities? Questions that will only be fully answered by additional clinical studies in both pediatric and adult EoE cohorts.

Acknowledgments

Funding: This work was supported by NIH R01 AI073553, R01

DK090119, Department of Defense W81XWH-15-1-0517 and Food Allergy Research Education (FARE).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Esophagus*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aoe.2018.09.03>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aoe.2018.09.03

Cite this article as: O'Shea K, Hogan SP. IgG₄ in eosinophilic esophagitis: perpetrator, accomplice or bystander? *Ann Esophagus* 2018;1:14.