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IgE blockade during food allergen ingestion enhances the induction of inhibitory IgG antibodies

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IgE-mediated food allergy is a growing problem with no curative therapy¹. Oral immunotherapy (OIT) has shown promise, but its utility is limited by reactions during treatment and a lack of sustained protection following therapy. IgE antibodies trigger

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hypersensitivity reactions to foods. Their effects, mediated by FcεRI on mast cells and basophils, can be countered by IgG antibodies of shared specificity signaling via the inhibitory Fc receptor, FcγRIIb². OIT induces only modest reductions in specific IgE antibodies but stimulates dramatic increases in inhibitory IgG^{3, 4}.

The use of omalizumab during OIT results in decreased allergic reactions and facilitates rapid dose escalation^{5, 6}. Studies using animals have shown that IgE inhibition during OIT not only blocks acute reactions but also promotes beneficial immunological responses including the induction of inhibitory IgG antibodies⁷. Such observations led us to hypothesize that the use of omalizumab in OIT might result in more effective suppression of allergen-specific IgE while enhancing production of peanut-specific IgG.

To test this hypothesis, we analyzed sera from 34 of 35 subjects who completed OIT in PRROTECT, a multicenter randomized placebo-controlled study of omalizumab in rapid oral peanut desensitization [NCT01781637, www.clinicaltrials.gov]⁸. The study was approved by the Institutional Review Boards of all participating institutions. There were no significant demographic differences between the groups randomized to omalizumab vs placebo. Peanut- and Ara h2-specific IgE and IgG4 levels were similar. Subjects all had high levels of peanut specific IgE (median of 88 kU_A/L placebo, 91 kU_A/L treatment). Patients reacting to ≤50 mg peanut protein were randomized 3.5:1 to receive either omalizumab or placebo for 12 weeks followed by rapid escalation to 250 mg of peanut protein on the first day of desensitization. Over the next 8 weeks, patients underwent weekly up-dosing to a maximum of 2000 mg. Patients continued omalizumab or placebo for a total of 19 weeks, at which time drug was discontinued and OIT was continued. At 52 weeks, a food challenge of up to 4000 mg of peanut protein was performed. Subjects failing to reach the 250 mg dose at 19 weeks were given the option to switch to open-label omalizumab and all but one crossed over to treatment with omalizumab prior to completing OIT. However, all subjects initiated OIT (weeks 12–19) in their originally assigned treatment groups (omalizumab vs. placebo).

As observed previously, subjects on omalizumab advanced more rapidly on their peanut doses in the build-up phase and had fewer reactions⁸. At week 12, subjects in the omalizumab group tolerated a median daily dose of 250 mg, 15 times as much as placebo subjects (15 mg, $p < 0.0001$) (Fig 1A). The increased dose tolerance of the subjects initially randomized to receive omalizumab persisted to the 20 week point with a 25-fold difference between the groups (2000 vs 75 mg median doses) but by 52 weeks there was no significant difference in daily peanut dose between groups. There was also no correlation between enrollment peanut and Ara h2-specific IgG4 levels and initially-tolerated peanut doses, allergic symptoms, reaction severity, or ability to up dose. We reasoned that IgE blockade during that critical early first dose escalation phase might exert a lasting impact on the immunological changes, including peanut- specific IgE levels and inhibitory IgG function, induced by therapy. To assess effects of omalizumab on OIT-induced changes in antibody responses we measured week 52 peanut-specific IgE and IgG4 levels. We also used an indirect basophil activation assay to test inhibitory effects of OIT-induced IgG³. In this protocol, basophils from a non- allergic donor were sensitized using pre-OIT sera, then challenged with peanut antigen. Activation was determined by flow-cytometric quantitation

of CD63. Post-OIT sera were added to these reactions to assess their capacity to suppress activation conferred by pre-OIT sera.

Patients receiving omalizumab exhibited significant reductions in their peanut- and Ara h2-specific IgE, whereas placebo subjects did not (Fig 1B). IgG4 levels increased markedly in all patients (Fig 1C) with no difference in the peanut or Ara h2-specific IgG4 levels between groups. Similarly, when analyzed as percent change, median peanut specific IgE levels decreased over the course of therapy with omalizumab with a significantly greater reduction in subjects randomized to receive omalizumab (Fig 1D) (−30.4% in PN IgE versus −19.15%, $p = 0.0475$). Median Ara h2-specific IgE levels (measured at week 52) decreased over the course of therapy with omalizumab but increased in those initially randomized to receive placebo (Fig 1D) (−37.75% vs +4.9% Ara h2, $p = 0.01$). In contrast to the modest reductions in allergen-specific IgE levels, peanut- and Ara h2-specific IgG4 increased with a significantly greater rise in peanut IgG4:IgE ratio in the omalizumab group than in subjects initially treated with placebo (Fig 1E). Functional consequences of these changes were revealed by the indirect basophil activation assay (Fig 1F) ($P = 0.0014$). We observed a clear enhancement in suppressive activity of sera from subjects originally assigned to the omalizumab group (mean suppression 61%) compared to sera from the placebo group (mean suppression 9%). There was a highly significant relationship between the Log (IgG4:IgE) ratio and percent suppression across all subjects (Fig 1G).

Our findings provide the first evidence that IgE blockade during OIT not only facilitates dose escalation but additionally exerts ~~sustained~~ immunomodulatory effects. Several observations in patients and animal models suggest potential mechanisms. For instance, IgE:FcεRI-activated mast cells and basophils produce cytokines, including IL-4, that polarize T cells towards the Th2 phenotype whereas interference with IgE impairs the ability of these innate immune cells to drive type 2 immune responses⁷. Furthermore, by reducing levels of free IgE antibodies, omalizumab decreases expression of FcεRI on effector cells and increases their threshold for activation^{9, 10}. Thus, it is likely that the innate pool of Th2-polarizing cytokines would be suppressed by omalizumab treatment. This benefit of omalizumab might be further enhanced by the more rapid dose escalation (and hence greater allergen exposure) in treated subjects. Taken together, our observations suggest that effectiveness of OIT is enhanced by implementing strategies to block IgE function or the activation of cells (mast cells and basophils) triggered by IgE antibodies.

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References

1. Renz H, Allen KJ, Sicherer SH, et al. Food allergy. *Nat Rev Dis Primers* 2018;4:17098. [PubMed: 29300005]
2. Malbec O, Daeron M. The mast cell IgG receptors and their roles in tissue inflammation. *Immunol Rev* 2007;217:206–221. [PubMed: 17498061]

3. Burton OT, Logsdon SL, Zhou JS, et al. Oral immunotherapy induces IgG antibodies that act through FcγRIIb to suppress IgE-mediated hypersensitivity. *J Allergy Clin Immunol* 2014.
4. Santos AF, James LK, Bahnson HT, et al. IgG inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. *J Allergy Clin Immunol* 2015.
5. Nadeau KC, Schneider LC, Hoyte L, Borrás I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011;127:1622–1624. [PubMed: 21546071]
6. Schneider LC, Rachid R, Lebovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut- allergic patients. *J Allergy Clin Immunol* 2013;132:1368–1374. [PubMed: 24176117]
7. Burton OT, Noval Rivas M, Zhou JS, et al. Immunoglobulin E Signal Inhibition during Allergen Ingestion Leads to Reversal of Established Food Allergy and Induction of Regulatory T Cells. *Immunity* 2014;41:141–151. [PubMed: 25017467]
8. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2017;139:873–881 e878. [PubMed: 27609658]
9. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεRI expression. *J Allergy Clin Immunol* 2003;112:1147–1154. [PubMed: 14657874]
10. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. *J Allergy Clin Immunol* 2004;114:527–530. [PubMed: 15356552]

Figure 1.

Impact of omalizumab adjunct therapy on OIT-induced changes in allergen-specific immunoglobulins. **A**) *Daily peanut consumption by study subjects*. The daily consumption of peanuts (mg) in subjects in the omalizumab (Om) and placebo (Pl) groups is shown at 12, 20 and 52 weeks. **B**) *Change in specific IgE against peanut or Ara h2 from enrollment (W0) to trial end (W52)*. Each data point represents a single patient, showing the serum IgE (kU_A/L) at enrollment (W0) and conclusion of the trial (W52). **C**) *Specific IgG4 levels ($\mu g/mL$) against peanut or Ara h2 at enrollment (W0) and trial end (W52)*. Each data point represents a single patient. **D**) *Change in specific IgE against peanut or Ara h2 from enrollment (W0) to trial end (W52)*. Each data point represents a single patient, showing the percent change in serum IgE level between pre- and post-OIT sera. Negative values represent a decrease in IgE over the course of OIT. **E**) *Alterations in specific IgG4:IgE ratios, expressed as % change in ratio from pre-OIT to post-OIT*. **F**) *Suppression of pre-OIT (W0) serum-induced basophil activation by post-OIT (W52) serum, and the impact of*

omalizumab adjunct therapy on this suppression ($P = 0.0014$). Placebo (PL)-assigned patients are shown in teal blue, while omalizumab (OL)-assigned patients are in purple. **G)** *Correlation between peanut- specific IgG4:IgE ratios post-OIT and basophil suppression.* The trend line (solid) and 95% confidence intervals (dashed) are depicted from linear regression analysis of the entire study cohort. A-G * $P < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, analysis performed using Wilcoxon rank sum paired t test or Mann Whitney unpaired t test.