

Differences in Effects of Omalizumab on Late-Phase Responses to Allergen Challenge in the Skin and Nose at the Time of Basophil Hyporesponsiveness

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TO THE EDITOR

Omalizumab is a mAb therapeutic directed against IgE. It is FDA (Food and Drug Administration) approved for use in allergic asthma (Presta *et al.*, 1993; Strunk and Bloomberg, 2006). It binds IgE at the same site on its Fc domain as the α -chain of the high-affinity IgE receptor (Fc ϵ RI) and blocks the interaction between IgE and Fc ϵ RI on mast cells, basophils, and dendritic cells (Presta *et al.*, 1993; Schulman, 2001; Prussin *et al.*, 2003). As the IgE level decreases with omalizumab, Fc ϵ RI expression on basophils and mast cells are reduced within 7 days for basophils (MacGlashan *et al.*, 1997) and within 56–70 days for skin mast cells (Beck *et al.*, 2004; Ong *et al.*, 2005).

In a recent study, we found that in cat-allergic subjects receiving omalizumab, the acute-phase clinical responses to nasal allergen challenge (NAC) were decreased at a time when blood basophils (6–8 weeks), but not nasal mast cell-mediator responses, were depressed (Eckman *et al.*, 2010). This suggests that some process, other than mast cell secretion, has a part in defining the acute-phase clinical responses of an NAC response. Acute-phase skin test suppression occurred at 14 weeks.

In this different study, we examined the effects of omalizumab on the nose and skin late-phase reactions at the time of basophil, but not mast cell, hyporesponsiveness. The study was a 16-week, double-blind, placebo-controlled trial of 19 cat-allergic adult subjects, who were randomly assigned to receive

either omalizumab or matched placebo in a 1:1 ratio on the basis of the FDA-approved dosing schedule for allergic asthma.

Subjects underwent basophil histamine response (BHR) and prostaglandin D₂ testing, as well as NAC as previously described (Eckman *et al.*, 2010) with three separate challenges of cat allergen (100, 300, and 1,000 BAU ml⁻¹). Late-phase sneeze counts were measured 4, 8, and 24 hours after NAC. Cat allergen-titrated intradermal skin testing (IDST) was performed at two half-log concentrations of allergen solution beginning with either 0.1 or 0.3 BAU ml⁻¹ depending on the cat puncture skin test result. Concentrations were then increased until the average wheal of a single injection was ≥ 15 mm. Late-phase-induced skin induration was measured at 8 and 24 hours. When a subject's cat allergen-induced BHR area under the curve (AUC) decreased to $< 20\%$ of the baseline value or on study day 56 (week 8), whichever occurred first, a second NAC (NAC-2), IDST, and BHR were performed.

No significant differences were present between baseline characteristics (age, gender, cat puncture test size, total IgE, cat-specific IgE, and percentage of subjects reporting mild asthma (FEV₁ $\geq 80\%$)) in the 10 active and 9 placebo subjects who completed the study. The IgE ranges were 53–298 kU l⁻¹ for total IgE, and 1.0–41.5 for cat-specific IgE, for all subjects. Specific to total IgE ratio levels fell into the previously reported atopic

population range of 0.002–35.8% for cat-sensitized individuals and were maintained during omalizumab treatment, as seen previously (Hamilton *et al.*, 2010).

The average day of NAC-2 was day 48 for treatment group and day 65 for placebo. Consistent with our previous study, at NAC-2, the median cat BHR AUC showed a 57% decrease on omalizumab treatment compared with a 21% increase on placebo administration ($P = 0.008$, data not shown). As was seen in our previous study (Eckman *et al.*, 2010), the acute-phase sneezes trended toward a greater decrease from NAC-1 in the treated group compared with placebo. The change from baseline for the treatment group was a median of 12 sneezes (interquartile range (IQR): 1.5–18.5), or 36%, compared with 4 sneezes (IQR: –8.5–11.5), or 4%, for the placebo group. Within the treatment group, the sneezes at NAC-1 were statistically different compared with NAC-2 ($P = 0.01$, two tailed). There were no differences between or within groups at 8 or at 24 hours (Figure 1). Measures of nasal mast cell allergen responses (nasal lavage PGD₂) did not change at the time of NAC-2 (data not shown). For the late-phase nasal reaction, of the 74% of subjects who had late-phase sneezes recorded, no significant change from baseline was seen in the omalizumab treatment group compared with placebo.

IDST flares were similar between groups at baseline at all time points during the baseline NAC-1. The acute skin flare size at NAC-1 was 134.0 mm (IQR: 119.8–146.5) for treatment group and 112.0 mm (IQR: 103.0–136.0) for placebo. There was no difference in acute skin flare changes at NAC-2

Abbreviations: AUC, area under the curve; BHR, basophil histamine response; FDA, Food and Drug Administration; Fc ϵ RI, IgE receptor; IDST, intradermal skin testing; IQR, interquartile range; NAC, nasal allergen challenge

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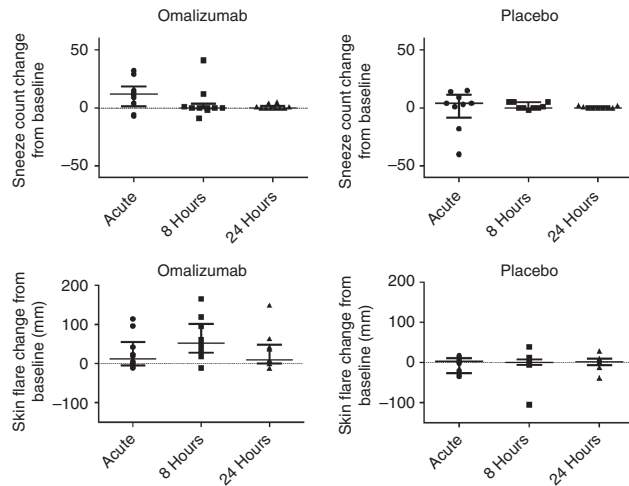


Figure 1. Acute- and late-phase changes in the nose and skin after 48 (omalizumab) and 65 (placebo) days. The change from baseline (nasal allergen challenge (NAC)-1 minus NAC-2) after 48 days of omalizumab treatment, or after 65 days of placebo, is displayed as scatter plots with the medians and interquartile ranges (IQRs) for sneeze counts (upper panels) and intradermal flare size (mm) size (lower panels). Omalizumab-treated subjects showed decreased acute-phase sneeze counts within group ($P=0.01$), but not when compared with placebo. No changes were seen in the late-phase sneeze counts. Conversely, omalizumab-treated subjects' intradermal skin tests showed no changes acutely, but decreased significantly at 8 hours compared with placebo ($P=0.008$). Skin flare size trended toward a decrease at 24 hours.

between treated and placebo groups. At 8 hours, the flare size decreased from NAC-1 to NAC-2 by 52.3 mm (IQR: 27.8–101.4, 54% decrease) in the treatment group, compared with 0 mm (IQR: –6.0–7.3) in the placebo group ($P=0.008$, two tailed). At 24 hours, the flare size decreased by 9.3 mm (IQR: 0–48.3, 38% decrease) in the treatment group, compared with an increase of 1.5 (–1.5) mm (IQR: –7.0–9.3) for the placebo group (10% decrease, Figure 1).

The skin late-phase response decrease at day 48 (range of 27–69 days) is associated with reduced blood basophil allergen response, but not with skin or nasal mast cell allergen reactivity. This was noted in an earlier study, but simultaneous measurements of blood basophil allergen reactivity or parallel nasal allergen reactivity were not performed (Ong *et al.*, 2005; Eckman *et al.*, 2010). This supports the conclusion that a reduction in blood basophil allergen mediator response is linked to the generation of the skin late-phase response, but not in the acute-phase skin reaction.

One explanation for the differences in effects on the late-phase responses between the nose and skin may be the presence of chronic, baseline tissue

inflammation in the nose and not in the skin (Ying *et al.*, 2002; Fokkens *et al.*, 2012). In the absence of basal skin inflammation in our subjects, the acute-phase allergen skin response more closely reflects a pure tissue mast cell response and thus may not be altered in the early weeks of omalizumab therapy. This discordance between acute- and late-phase shifts in allergen challenge models in the nose and skin with omalizumab treatment carries implications for the interpretations of responses to allergen in different tissue compartments.

Written informed consent was obtained via a protocol approved by the Johns Hopkins Hospital Institutional Review Board and the National Institute of Allergy and Infectious Diseases' Data Safety Monitoring Boards. Declaration of Helsinki protocols were followed. This study is registered with ClinicalTrials.gov (registration number NCT01003301). For the CONSORT Flow Diagram, see the Supplementary Material online.

CONFLICT OF INTEREST

SSS has served as a consultant for and has received research support from Genentech and Novartis. The remaining authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/jid>

REFERENCES

- Beck LA, Marcotte GV, MacGlashan D *et al.* (2004) Omalizumab-induced reductions in mast cell ϵ expression and function. *J Allergy Clin Immunol* 114: 527–30
- Eckman JA, Sterba PM, Kelly D *et al.* (2010) Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol* 125: 889–95
- Fokkens WJ, Rinia B, van Drunen CM *et al.* (2012) No mucosal atrophy and reduced inflammatory cells: Active-controlled trial with yearlong fluticasone furoate nasal spray. *Am J Rhinol Allergy* 26: 36–44
- Hamilton RG, MacGlashan DW Jr, Saini SS (2010) IgE antibody-specific activity in human allergic disease. *Immunol Res* 47:273–84
- MacGlashan DW Jr, Bochner BS, Adelman DC *et al.* (1997) Down-regulation of ϵ expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 158: 1438–45
- Ong YE, Menzies-Gow A, Barkans J *et al.* (2005) Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *J Allergy Clin Immunol* 116:558–64
- Presta LG, Lahr SJ, Shields RL *et al.* (1993) Humanization of an antibody directed against IgE. *J Immunol* 151:2623–32
- Prussin C, Griffith DT, Boesel KM *et al.* (2003) Omalizumab treatment downregulates dendritic cell ϵ expression. *J Allergy Clin Immunol* 112:1147–54
- Schulman ES (2001) Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 164:S6–11
- Strunk RC, Bloomberg GR (2006) Omalizumab for asthma. *N Engl J Med* 354:2689–95
- Ying S, Kikuchi Y, Meng Q *et al.* (2002) TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: Comparison with the allergen-induced late-phase cutaneous reaction. *J Allergy Clin Immunol* 109: 694–700

CONSORT 2010 Flow Diagram

