

The effects of repeat omalizumab administration on skin test positivity and the assessment of the safety of administration in patients with positive skin tests to mouse antigen

Mathew Varghese, M.D., and Phil Lieberman, M.D.

ABSTRACT

Patients receiving omalizumab for moderate-to-severe allergic asthma were evaluated for the effect of omalizumab administration on immediate hypersensitivity skin test reactions. The existence of a relationship between a positive skin test for mouse antigen and risk for anaphylaxis in patients receiving omalizumab was also investigated. Seventeen patients were skin tested serially to tree, grass, and weed pollens; molds; dust mites; cat and dog allergens; mouse antigen; and cockroaches. Skin tests were performed before the initiation of omalizumab therapy and at each subsequent clinic visit (every 2–4 weeks). At the time of each visit, skin tests were performed immediately before the subcutaneous administration of omalizumab and 20 minutes afterward. A marked reduction in skin test reactivity was noted after the administration of omalizumab. Some of these reductions became more pronounced 20 minutes after administration compared with testing done before administration. There was one mild urticarial reaction 20 minutes after administration in a patient with a positive skin test to mouse antigen. The skin test was positive at the time of this reaction. Omalizumab therapy was continued without further adverse events and the skin test to mouse antigen became negative. In addition, seven other subjects with positive skin tests to mouse antigen have received repeated doses of omalizumab without adverse events. Omalizumab administration results in significant reduction of skin test reactivity to aeroallergens. Furthermore, a positive skin test to mouse antigen does not automatically preclude the use of omalizumab for therapy of moderate-to-severe allergic asthma.

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Key words: Aeroallergen, anaphylaxis, immunoglobulin E, mouse allergy, mouse epitope, omalizumab, skin test reactivity

Immunoglobulin E (IgE) is important in the pathogenesis of asthma. Allergen exposure initiates IgE synthesis and attachment to mast cells; subsequent exposure causes IgE cross-linking on the surface of mast cells and initiates the allergic cascade.¹ The recombinant humanized monoclonal antibody omalizumab (Xolair, Genentech, Inc., South San Francisco, CA) prevents inflammation at the first step by binding and reducing serum-free IgE.² Patients with asthma often exhibit immediate skin test reactions to aeroallergens,^{3–5} which are a measurement of specific mast cell-bound IgE in the skin. Evidence also suggests a direct correlation between free IgE levels and the degree of skin test sensitivity to aeroallergens.³ Because

omalizumab has been shown to lower free IgE levels, we investigated the effect of repeat, consecutive treatments with omalizumab on allergen skin test sensitivity in patients with asthma.

SUBJECTS AND METHODS

Patients with moderate-to-severe asthma who received omalizumab therapy for at least 1 month and had been compliant with the manufacturer's recommended dosing schedule² were eligible for inclusion. This study was clinic based and informed consent was obtained from each patient. All patients were counseled before testing to remain off antihistamines during the study.

Patient charts were reviewed to identify patients who had skin test positivity to specific aeroallergens before initiation of omalizumab. Allergens tested were grass, tree, weed, mold, dust mite, cat, dog, mouse, and cockroach. Skin tests were performed by both epicutaneous and intracutaneous methods, because intradermal or intracutaneous testing may pick up reactions to irritants. Intracutaneous tests were used if initial epicutaneous tests were negative. Epicutaneous tests were performed using a DermaPIK (Greer Laboratories, Lenoir, NC) with extracts obtained from Hollister-

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Address correspondence and reprint requests to Mathew Varghese, M.D., University of Tennessee, Health Science Center, 930 Madison Avenue, Memphis, TN 38163
E-mail address: mvarghese78@gmail.com
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Table 1 Patient demographics (*n* = 17)

Age	12–66 yr
Male patients	<i>n</i> = 8
Race/ethnicity	
White	<i>n</i> = 10
Black	<i>n</i> = 7
Cumulative dose	450–8625 mg
Length of therapy	4–46 wk
Number of injections	2–23
Total serum IgE	30–700+ IU/mL (<i>n</i> = 1; >700 IU/mL*)

*The manufacturer's recommended upper limit for serum IgE.

Stier Laboratories (Spokane, WA) at a concentration of 1:20 w/v. If epicutaneous tests were negative, intracutaneous tests using first a 1:1000 w/v concentration of the allergen at a dose of 0.03 mL were administered. If intradermal skin testing was negative, additional skin testing was done with a 1:500 w/v concentration of the same allergen. Solutions for intracutaneous skin tests were obtained also from Hollister-Stier Laboratories. All skin tests were performed on the volar aspect of the forearms. Skin tests were graded in accordance with Doan and Zeis methodology^{6,7} as follows:

- 0, No reaction or a reaction no different from negative control (normal saline).
- 1+, Erythema <21 mm and larger than negative control.
- 2+, Erythema >21 mm.
- 3+, Erythema and wheal formation without pseudopod formation.
- 4+, Erythema and wheal formation with pseudopod formation.

In addition to saline as a negative control, histamine phosphate (0.275 mg/mL for intracutaneous testing or 2.7 mg/mL for epicutaneous testing) and histamine hydrochloride, 10 mg/mL, were used as positive controls (data not shown).

Skin testing was performed when patients visited the clinic to receive their regular omalizumab dose (every 2–4 weeks), using allergens to which patients had initially tested positive. If the tests were negative, intradermal testing was performed at increasing concentrations. Skin testing was performed at two time points during each visit: (i) immediately before subcutaneous administration of omalizumab and (ii) 20 minutes after administration.

RESULTS

Table 1 presents patient demographics for the 17 enrolled patients. Skin test results for all aeroallergens

tested are presented in Fig. 1, A–D. There was a pronounced decline in skin test reactivity for most patients after several consecutive doses of omalizumab. For many patients, this diminished skin test response was more prominent immediately after the administration of omalizumab compared with the response before administration.

Two patients showed positive skin tests to mouse antigen (epicutaneous only); both reactions were 2+ in nature. One of these patients experienced a mild urticarial reaction after the third dose of omalizumab, which did not require therapy. Omalizumab therapy was continued and no subsequent reactions have occurred. Although the patient's mouse skin test still was positive at the time of the urticarial reaction, her skin test to mouse antigen subsequently became negative. The other subject, with a positive skin test to mouse antigen at the time of initiation of omalizumab therapy, experienced no reaction. This patient's skin test to mouse antigen became negative after three administrations of omalizumab.

DISCUSSION

The decline in skin test reactivity to allergens observed after repeated, consecutive administration of omalizumab supports the findings of other studies.^{8–11} A reduction in IgE bound to mast cells in the skin is most likely a consequence of the known mechanisms of action of omalizumab: decreased concentrations of serum-free IgE and the down-regulation of IgE receptors on mast cells result in decreased binding of IgE molecules to mast cells.^{12–14}

Our results were consistent with those noted previously and confirm that skin test reactivity is markedly diminished by the administration of omalizumab. In addition, we made two further observations during our investigation. First, skin test reactivity is diminished 20 minutes after the administration of omalizumab compared with reactivity determined before administration. We do not have an explanation for this phenomenon but presumably the administration itself acts as a "sump" to bind any remaining IgE antigen combining sites without triggering mast cell degranulation. Second, patients with preexisting sensitivity to mouse antigen(s) might be expected to have an allergic reaction to omalizumab, which is a humanized monoclonal antibody. However, in our investigation, sensitivity to mouse epitope did not preclude the use of omalizumab. There is a caveat in making this statement, because in our series we only found two patients with positive skin tests to mouse antigen.¹⁵

These data were presented previously at the American College of Allergy, Asthma and Immunology meeting and published as an abstract.¹⁶ It should be

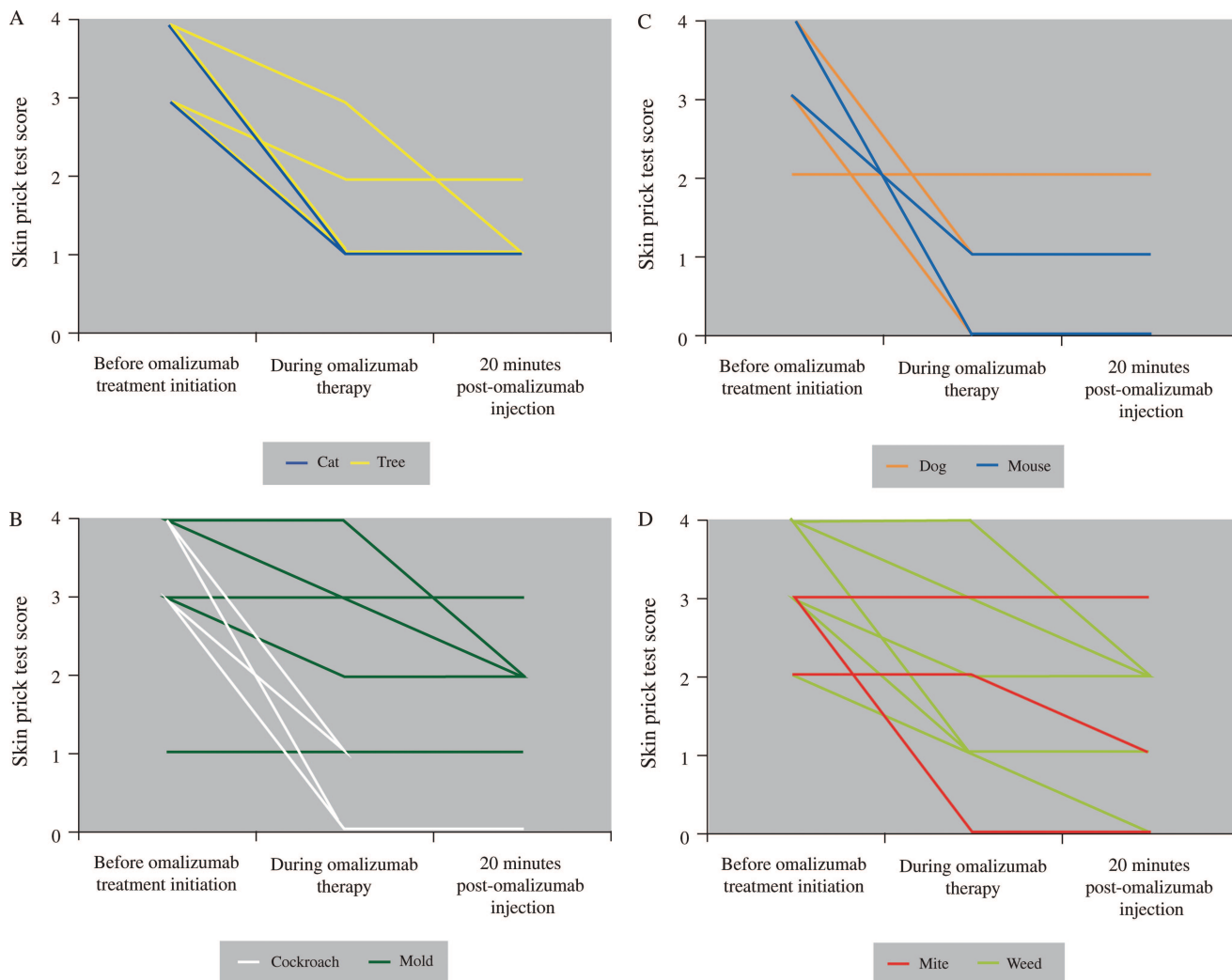


Figure 1. Change in skin reactivity to eight aeroallergens in patients who received several consecutive doses of omalizumab (cumulative dose >1500 mg). Skin test reactivity was scored as 0, no reaction or a reaction no different from negative control (normal saline); 1+, erythema <21 mm and larger than negative control; 2+, erythema >21 mm; 3+, erythema and wheal formation without pseudopod formation; 4+, erythema and wheal formation with pseudopod formation. (A) Skin test reactivity to cat and tree allergens; (B) skin test reactivity to cockroach and mold allergens; (C) skin test reactivity to dog and mouse allergens; (D) skin test reactivity to mite and weed allergens.

noted, however, that since the publication of that abstract, five other patients, who were not part of the original study group but who showed positive skin tests to mouse antigen during routine testing before initiation of anti-IgE therapy, have received anti-IgE without difficulty. These five cases strengthen the conclusion that demonstration of IgE anti-mouse is not necessarily a contraindication to the administration of omalizumab. These findings are also in keeping with an observation by Price and Hamilton, who have reported two anaphylactic reactions to omalizumab, not caused by mouse antigen but rather polysorbate, an excipient in the preparation.^{17,18}

REFERENCES

- Platts-Mills TA. The role of immunoglobulin E in allergy and asthma. *Am J Respir Crit Care Med* 164:S1–S5, 2001.
- Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 108: 184–190, 2001.
- Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 320:271–277, 1989.
- Lin FJ, Wong D, and Chan-Yeung M. Immediate skin reactivity in adult asthmatic patients. *Ann Allergy Asthma Immunol* 74: 398–404, 1995.
- Zimmermann J, Silverman R, and Frieri M. Specific IgE levels in moderate to severe asthmatics in the emergency department. *Ann Allergy Asthma Immunol* 96:P151, 2006.
- Doan T, and Zeis CR. Skin testing in allergy. *Allergy Proc* 14:110–111, 1993.
- Demoly P, Piette V, and Bousquet J. In vivo methods for study of allergy: Skin tests, techniques, and interpretation. In Middleton's Allergy: Principles and Practice, 6th ed. Adkinson NF Jr, Yunginger JW, Busse WW, et al. (Eds). St. Louis: Mosby, Inc., 631–643, 2003.

8. Ong YE, Menzies-Gow A, Barkans J, et al. Anti-IgE (omalizumab) inhibits late-phase reactions and inflammatory cells after repeat skin allergen challenge. *J Allergy Clin Immunol* 116:558–564, 2005.
9. Noga O, Hanf G, and Kunkel G. Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. *Int Arch Allergy Immunol* 131:46–52, 2003.
10. Beck LA, Marcotte GV, MacGlashan D, et al. Omalizumab-induced reductions in mast cell Fc epsilon RI expression and function. *J Allergy Clin Immunol* 114:527–530, 2004.
11. Togias A, Corren J, Shapiro G, et al. Anti-IgE treatment reduces skin test reactivity. *J Allergy Clin Immunol* 101(suppl):S171, 1998.
12. Holgate S, Casale T, Wenzel S, et al. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 115:459–465, 2005.
13. Huang Y-C, Leyko B, and Frieri M. Effects of omalizumab and budesonide on markers of inflammation in human bronchial epithelial cells. *Ann Allergy Asthma Immunol* 95:443–451, 2005.
14. Soresi S, and Togias A. Mechanisms of action of anti-immunoglobulin E therapy. *Allergy Asthma Proc* 27:S15–S23, 2006.
15. Lanier B. Unanswered clinical questions and speculation about the role of anti-immunoglobulin E in atopic and nonatopic disease. *Allergy Asthma Proc* 27:S37–S42, 2006.
16. Varghese M, Lieberman P, Treadwell G, et al. Omalizumab (O) administration reduces symptom scores, medication use, and markedly diminishes skin tests (ST) reactivity. *Ann Allergy Asthma Immunol* 94:110, 2005 (Abs 39A).
17. Price K, Woodard L, Pringle M, et al. Anaphylaxis to omalizumab after 14 months of successful therapy. *J Allergy Clin Immunol* 117:S10, 2006.
18. Price K, and Hamilton R. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 28:313–319, 2007. □

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