

# Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy

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## ABSTRACT

*Anti-IgE therapy with omalizumab, a recombinant humanized monoclonal antibody, has anti-inflammatory effects in allergic asthma and rhinitis. Although omalizumab has been exceptionally safe, reactions after its administration have been reported. The goal of this study was to assess two patients who experienced apparent anaphylaxis after omalizumab administration. Two cases of apparent anaphylaxis after omalizumab administration are reported with diagnostic evaluation using skin testing and unique IgE and IgG anti-omalizumab serological assays. At the time of evaluation, both atopic asthmatic patients had total (free and bound) serum IgE levels of 199 kIU/L (100% free) and 200 kIU/L (80% free and 20% bound), respectively. Epicutaneous skin tests to omalizumab were negative at 150 mg/mL of omalizumab in both subjects and the nonexposed negative control subject. Intradermal skin tests were positive at 0.15 mg/mL in subject 1 and negative at 1.5 mg/mL of omalizumab in subject 2 and the control subject. Intradermal testing to polysorbate produced significant wheal/flare reaction in subject 2 but not in the negative control subject. Serological assays for IgE or IgG antibodies reactive with omalizumab were negative. The in vitro and in vivo immunologic data support the conclusion that the adverse reactions experienced by two patients after omalizumab administration after more than a year of successful omalizumab therapy for asthma were likely anaphylactoid in nature. Polysorbate, an excipient in omalizumab, is known to cause similar reactivity to other medicines and is the most likely cause of these reactions.*

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Systemic anaphylaxis that manifests as shock, bronchospasm, urticaria, and/or gastrointestinal distress is traditionally defined mechanistically as small quantities of foreign antigen cross-linking antigen-specific IgE bound to mast cells through FcεR1. This results in histamine and serotonin release and production of other vasoactive and inflammatory mediators such as platelet-activating factor (PAF) and leukotrienes.<sup>1</sup> Anaphylactoid reactions result in the same release of mediators but are caused by nonspecific activation of mast cells independent of specific IgE. Omalizumab, a humanized monoclonal IgG<sub>1</sub>-κ directed against the Cε3 region of human IgE, both reduces free IgE levels in serum and decreases FcεR1 expression on mast cells, basophils, and dendritic cells. This leads to a down-regulation in the number of inflammatory effector cells such as T cells and eosino-

phils in target organs.<sup>2</sup> Successful omalizumab therapy has shown clinical benefit in patients with allergic asthma and rhinitis and should, in theory, protect them against IgE-mediated anaphylaxis. However, a non-IgE-mediated anaphylaxis has been described in mice involving larger antigen quantities cross-linking antigen-specific IgG bound to macrophages through low-affinity FcγRIII. The mechanism is believed to involve the release of PAF, which then induces the smooth muscle contraction and increased vascular permeability, leading to anaphylaxis.<sup>1</sup>

In an early study of omalizumab safety involving 225 children with allergic asthma, 4.9% reported urticaria, almost all of which resolved spontaneously or with antihistamines.<sup>3</sup> No anaphylactic events, adverse reactions suggestive of serum sickness, or immune complex formation and no anti-omalizumab antibodies were detected after a maximum of 52 weeks of omalizumab administration. In this study, we describe two patients who experienced adverse reactions minutes after omalizumab administration after more than a year of uneventful treatment. Both individuals experienced apparent clinical responses to omalizumab before these reactions with decreased asthma morbidity and a reduced need for steroids. Serum tryptase was negative in both cases, thus raising the possibility of an IgG-dependent macrophage-mediated reaction. However, an intradermal skin test to omalizumab was pos-

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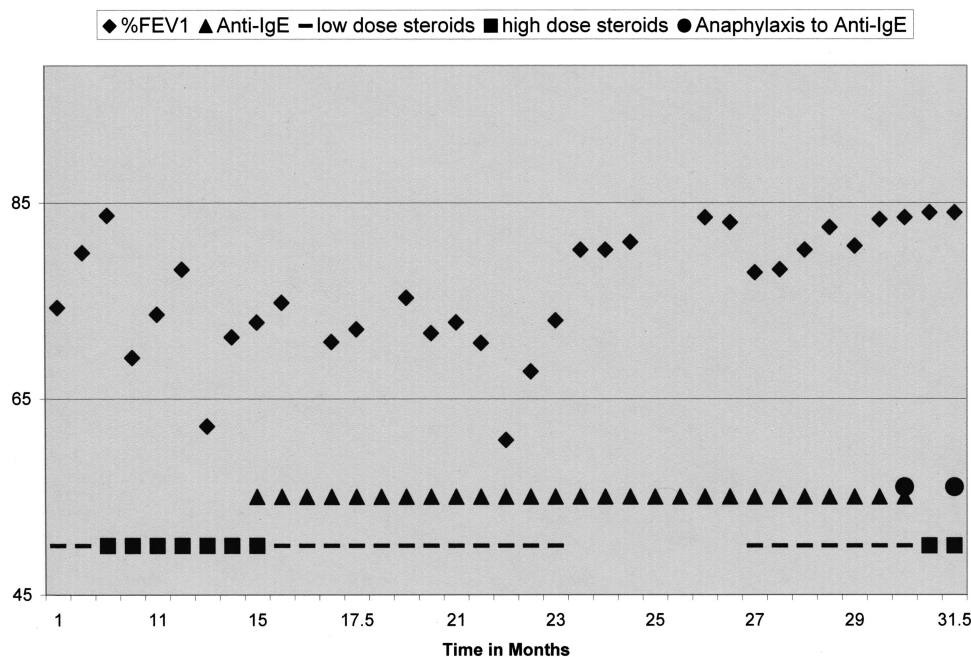


Figure 1. Longitudinal changes in subject 1's %FEV<sub>1</sub> and steroid use before and during omalizumab therapy.

itive in one of the two cases, suggesting a possible IgE-mediated reaction. We developed a panel of serological assays to evaluate these patients for the presence of IgG and IgE antibodies reactive with omalizumab. These assays clarified the *in vivo* skin test results and led to the conclusion that these adverse reactions were most likely anaphylactoid in nature rather than IgE or IgG anti-omalizumab mediated.

## METHODS

### Clinical Evaluation of Patients

**Subject 1.** At the 27th bimonthly 300-mg omalizumab administration, a 56-year-old white woman with controlled conditions of asthma, hypothyroidism, gastroesophageal reflux, and sleep apnea developed itching and redness within 5 minutes at both 150-mg s.c. omalizumab administration sites. Rapid generalized itching, chest tightness, and a sense of impending doom were described by the patient who was hypotensive and tachycardic. Epinephrine (0.3 mL, 1:1000) was given intramuscularly into the thigh, followed by 0.1-mL doses s.c. into each abdominal injection site. Oxygen, a bolus of 500 mL of normal saline, 10 mg each of chewable cetirizine and montelukast, and 40 mg of intramuscular methylprednisolone were administered. The patient recovered hemodynamically within 15 minutes and did not require further treatment. She was discharged hours later with no further sequelae. The patient's asthma had been well controlled during the previous 7 months by environmental avoidance of her pollen, dust, mold, and pet triggers; using preventative omalizumab and montelukast, and intermittent use of

controlling low-dose 100/50 fluticasone DPI in combination with salmeterol and little rescue levalbuterol based on her peak flow action plan (Fig. 1). Six months after her reaction to omalizumab, the patient developed ocular angioedema and generalized pruritus after using eye drops containing polysorbate.

**Subject 2.** After the 13th monthly 300-mg omalizumab administration, a 50-year-old white woman with asthma and gastroesophageal reflux developed head and neck itching, flushing, and oral angioedema with chest tightness and audible wheezing. These symptoms occurred 10 minutes after the administration of two 150-mg s.c. injections of omalizumab. The patient's asthma had been well controlled during the previous 6 months with environmental avoidance of her pollen, dust, mold, and pet triggers; preventative omalizumab and zafirlukast, 20 mg b.i.d.; controlling beclomethasone HFA, 40–80 µg daily; and little rescue levalbuterol based on her peak flow action plan (Fig. 2). The initial response to 0.3 mL (1:1000) of epinephrine, 10 mg of chewable cetirizine, and 1.25 mg of nebulized levalbuterol was immediate. There was no evidence of swelling or erythema at the injection sites and no hemodynamic instability. However, the cutaneous and respiratory symptoms continued to return over the next month, requiring two hospitalizations during the 1st week after the initial reaction with repeated intramuscular epinephrine injections and prolonged use of i.v. H<sub>1</sub>/H<sub>2</sub>-blockers and steroids, as well as nebulized levalbuterol 1.25 q.1–2 hours on day 4 after the initial reaction.

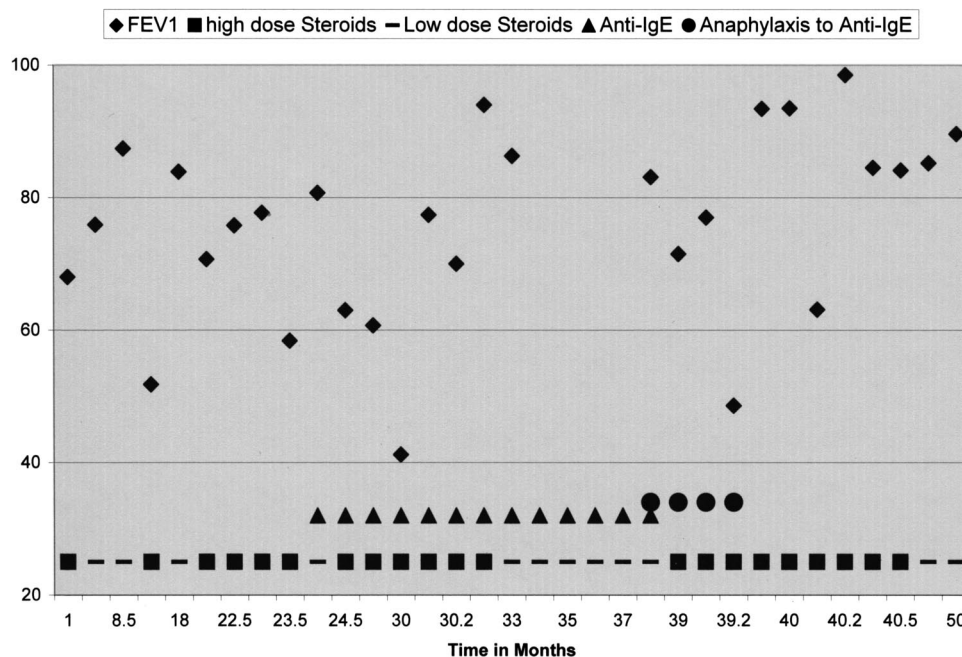


Figure 2. Longitudinal change in subject 2's %FEV<sub>1</sub> and steroid use before and during omalizumab therapy.

### In Vivo Provocation Testing

Epicutaneous testing with omalizumab was performed at full strength (150 mg/mL), and intradermal testing was performed at a 1:1000 (0.15 mg/mL) and 1:100 (1.5 mg/mL) dilution of omalizumab in saline using previously published methods.<sup>4</sup> Subjects 1 and 2 were skin tested 4 and 6 weeks, respectively, after their anaphylactic reaction. Skin testing was simultaneously performed in the same non-omalizumab exposed control in both cases. Saline was used instead of sterile water for injection as recommended in the package insert because preliminary skin tests with omalizumab reconstituted in sterile water for injection produced false positive intradermal skin test results (7 mm wheal and 10 mm erythema) in the non-omalizumab exposed control subject at the dilute 0.15-mg/mL concentration. Ten months after the last omalizumab treatment, skin test reactivity in subject 2 was performed to full strength polysorbate at the epicutaneous and to a 1:100 dilution in saline at the intradermal level.

### Serological (In vitro) Testing

A total serum IgE (free and bound), total free IgE, and multiallergen screen were performed using the ImmunoCAP system (Phadia AB, Uppsala, Sweden) in which its accuracy is known to not be compromised by the presence of therapeutic levels of omalizumab in the serum.<sup>5</sup> The free IgE was measured using a research enzyme immunoassay<sup>6</sup> that uses a labeled  $\alpha$ -Fc $\epsilon$ R1 as its detection reagent for free (non-omalizumab bound) IgE.

**IgE and IgG Anti-Omalizumab Immunoassays.** For the IgE assay, two detection reagents were selected. The biotinylated form of the  $\alpha$ -chain of the high-affinity IgE Fc receptor (Fc $\epsilon$ R1- $\alpha$ -biotin; Heska Corp., Ft. Collins, CO) would be expected to only bind any human IgE that bound to omalizumab *via* its Fab region. Any IgE bound directly by insolubilized omalizumab was not detected by Fc $\epsilon$ R1- $\alpha$ -biotin. To verify that omalizumab was insolubilized on the microtiter plate, biotin-conjugated mouse monoclonal anti-human IgE Fc was used as a second IgE detection reagent. This reagent is known to bind to IgE that is bound by omalizumab.<sup>6</sup> Because the IgG and IgE anti-omalizumab assays were simultaneously performed, the binding of human IgE by solid-phase omalizumab provided a positive control for the presence of immunoreactive omalizumab on the microtiter plates used in both assays.

In the IgE antibody assay, microtiter plates were coated with omalizumab in PBS (10  $\mu$ g/mL; 16 hours; 4°C). Purified polyclonal human IgE was coated directly on 4 wells of the plate as a positive control. Plates were then blocked and washed and human sera (1:2 or greater) were incubated at 23°C (1 hour). After a PBS buffer wash, bound human IgE antibody was detected with either biotin-conjugated Fc $\epsilon$ R1- $\alpha$  or biotin-conjugated mouse monoclonal anti-human IgE Fc (clone HP6061; EMD Biosciences, La Jolla, CA; 1 hour; 1  $\mu$ g/mL). After a PBS wash, streptavidin-horseradish peroxidase detected bound biotin (1 hour; 23°C; 1  $\mu$ g/mL) and plates were developed with ABTS-H<sub>2</sub>O<sub>2</sub>. The optical density at 405 nm was read at 15 minutes in a microtiter plate reader. Negative IgE antibody results

Table 1 Epicutaneous and intradermal skin test results with omalizumab\*

| Skin Tests   | Wheal/Flare (mm)          |         |                          |           |                          |      |
|--------------|---------------------------|---------|--------------------------|-----------|--------------------------|------|
|              | Epicutaneous<br>150 mg/mL |         | Intradermal<br>150 µg/mL |           | Intradermal<br>1.5 mg/mL |      |
|              | Control                   | Case    | Control                  | Case      | Control                  | Case |
| Subject 1    |                           |         |                          |           |                          |      |
| Histamine    | 5/5 (+)                   | 5/5 (+) | 20/40 (+)                | 20/45 (+) | ND                       | ND   |
| Saline       | 0/2                       | 0/4     | 5/0                      | 5/0       | ND                       | ND   |
| Omalizumab   | 0/3                       | 0/3     | 7/0                      | 10/10 (+) | ND                       | ND   |
| Subject 2    |                           |         |                          |           |                          |      |
| Histamine    | 5/5 (+)                   | 3/3 (+) | 15/40 (+)                | 15/35 (+) | ND                       | ND   |
| Saline       | 0/0                       | 0/0     | 0/0                      | 0/0       | 0/0                      | 0/0  |
| Omalizumab   | 0/0                       | 0/0     | 0/0                      | 0/0       | 0/0                      | 0/0  |
| Polysorbate# | 0/0                       | 0/0     | 0/6                      | 10/55     | ND                       | ND   |

\*Omalizumab used for skin testing was reconstituted according to the manufacturer's instructions in the package insert to 150 mg/mL except saline was used instead of water for injection.

#Polysorbate testing performed 8.5 mon after the omalizumab testing in subject 2, subject 1 declined testing because of prior adverse reaction to omalizumab testing. Skin test reactivity in subject 2 was performed to full strength polysorbate at the epicutaneous and to a 1:100 dilution in saline at the intradermal level.

ND = not done, the same nonatopic individual was used as the control for the skin testing of both subjects who experience anaphylaxis.

are identified as an optical density <2 times the mean + 2 SD of the negative control serum.

A similar assay format was used to detect IgG anti-omalizumab antibodies with the use of different detection antibodies that were selected to not bind directly to omalizumab (a humanized IgG<sub>1</sub>-κ). Biotinylated HP6030 binds a common determinant on the Fc region of human IgG2, IgG3, and IgG4, but not human IgG1. Because HP6030-biotin would not detect human IgG1 antibodies reacting with omalizumab, biotinylated monoclonal anti-human λ-light chain (clone HP6054) was used to detect λ-containing antibodies, regardless of their isotype. A second area of the plate was coated with omalizumab and received no serum and only borate-buffered saline–5% bovine serum albumin to control for any direct binding of the anti-human IgG2, IgG3, and IgG4 Fc and anti-lambda conjugates to the insolubilized omalizumab.

## RESULTS

### Clinical Management and *In Vivo* Studies

Figure 1 displays the longitudinal changes in subject 1's percent forced expiratory volume at 1 second (%FEV<sub>1</sub>) and steroid use before and during omalizumab therapy. Low-dose steroid in the case of subject 1 refers to the use of fluticasone in combination with salmeterol based on the subject's peak flow plan and ranged between 100 and 500 µg/day. High-dose steroid refers to the use of fluticasone, 1000 µg/day, or systemic use consisting of either oral prednisone, 20–60

mg/day, or intramuscular methylprednisolone, 40–80 mg/day. Subject 1 experienced urticaria and hemodynamic compromise at the 27th omalizumab dose. Figure 2 displays the longitudinal changes in subject 2's %FEV<sub>1</sub> and steroid use before and during omalizumab therapy. In the case of subject 2, low-dose steroid use refers to the use of beclomethasone HFA, 40–480 µg daily, and high-dose steroid refers to beclomethasone, 640 µg/day, or systemic use consisting of either oral prednisone, 20–60 mg/day, or intramuscular methylprednisolone, 40–80 mg/day. In subject 2, multiple episodes of urticaria/angioedema and respiratory compromise occurred temporally after the 13th dose of omalizumab.

Table 1 presents results of epicutaneous and intradermal skin testing of both subjects with undiluted (150 mg/mL) or dilutions of omalizumab, respectively. Subject 1 displayed a negative epicutaneous skin test and a positive intradermal skin test at the 0.15 mg/mL of omalizumab. The marked wheal and flare reactivity (>3 mm over the saline) in subject 1 was absent in the non-omalizumab exposed control at the same dilution. The intradermal skin test with the 1.5 mg/mL of omalizumab was not performed because subject 1 experienced severe itching and generalized urticaria 30 minutes after the intradermal administration of the 0.15-mg/mL concentration. The reaction subsided with the use of chewable cetirizine, 10 mg, and did not produce a late-phase reaction.

In contrast, subject 2 had negative epicutaneous and intradermal skin tests at all dilutions and had no immediate reaction to testing. During the week after her

Table 2 Serological evaluation of study subjects

| Subject No. | Specimen Date     | Total Serum IgE (kIU/L)* | Phadiatop (kIU/L) (pos/neg) | Free IgE (kIU/L) | % Free IgE# | IgE Anti-Omalizumab (pos/neg) | IgG Anti-Omalizumab (pos/neg) |
|-------------|-------------------|--------------------------|-----------------------------|------------------|-------------|-------------------------------|-------------------------------|
| 1           | February 27, 2006 | 199 ± 6                  | 4.5<br>Positive             | 204              | 100%        | Negative                      | Negative                      |
| 2           | April 7, 2006     | 200 ± 8                  | 29.6<br>Positive            | 41               | 80%         | Negative                      | Negative                      |

IgE and IgG anti-omalizumab data are derived from results presented in Figs. 3 and 4, respectively.

\*Total serum IgE is presented as the mean ± 1 SD in kIU/L.

#Free IgE is computed as a percentage of the total serum IgE in the same serum specimen.

negative skin testing, subject 2 reported intermittent mild facial itching, redness, and swelling. No respiratory distress was reported but because of a >20% drop in her peak flows, she increased her beclomethasone use as per her asthma action plan. Ten months after her last omalizumab treatment intradermal testing to polysorbate was positive.

### Serological Studies for Anti-Omalizumab Antibodies

The total serum IgE (free and bound) at the time of analysis for both subjects was ~200 kIU/L (Table 2). Both subjects were atopic with a positive multiallergen screen that detects IgE antibodies to the 15 principal aeroallergen specificities that trigger the majority of aeroallergen-related allergic disease.<sup>7</sup> At the time of serum collection, subject 1 had not received additional omalizumab for 8 months. Consequently, all of the IgE in her serum was free (non-omalizumab bound). In contrast, only 20% of the total IgE in subject 2's serum was free as a consequence of collecting blood only 3 months after her last omalizumab injection. The difference in the percentage of free IgE in the serum of these two subjects despite a comparable total serum IgE (free and bound) explains why less IgE was bound by insolubilized omalizumab from subject 2's serum than from subject 1's serum and detected by monoclonal anti-IgE (clone HP6061) in the IgE antibody analysis (Fig. 3, right panel).

As presented in Fig. 3, omalizumab-specific human IgE containing antibodies were not detected in the sera from the two subjects who experienced apparent anaphylaxis after omalizumab treatment (subject 1 and subject 2) or a non-omalizumab exposed negative control subject. In contrast, the mouse monoclonal anti-human IgE (HP6061) detected IgE bound by omalizumab in a dose-dependent manner in relation to the dilution of serum from both subjects (1:2 to 1:64). As presented in Fig. 4, omalizumab-specific human IgG2, IgG3, IgG4, or human  $\lambda$ -light chain containing antibodies were not detected in the serum from the two sub-

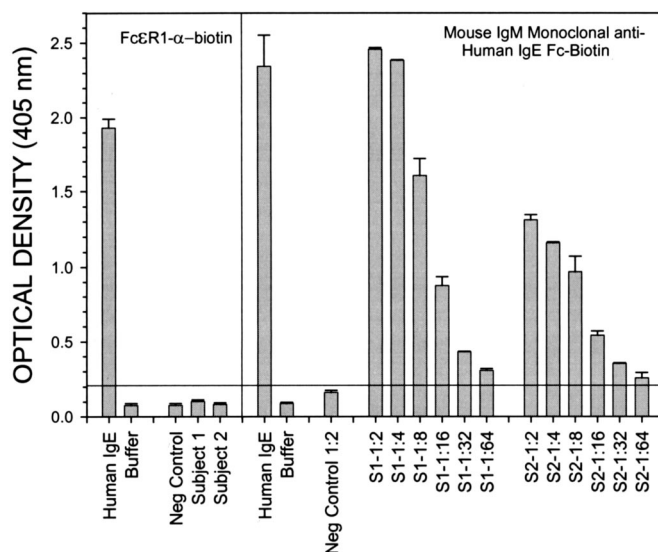


**Figure 3.** Serological evaluation of two subjects for the presence of IgE anti-omalizumab antibodies (S1, subject 1; S2, subject 2). S1-1:2 refers to the serum from subject 1 that was analyzed at a 1:2 dilution.

jects who presented with anaphylaxis after omalizumab treatment (subject 1 and subject 2) or a non-omalizumab-treated negative control subject.

### DISCUSSION

Systemic reactions to omalizumab have been described in three cases during clinical studies. These reactions occurred within 2 hours of either the first or the second administration but to our knowledge no cases have been reported after successful long-term omalizumab therapy.<sup>3,8,9</sup> Reactions occurring on initiation of therapy potentially may be a result of prior sensitization to one of the excipients of omalizumab such as polysorbate or to the murine component of the recombinant DNA-derived humanized IgG1 itself. Omalizumab binds to the constant region of free IgE only and therefore does not cause mast cell degranulation leading to anaphylaxis.<sup>10</sup> In fact, omalizumab

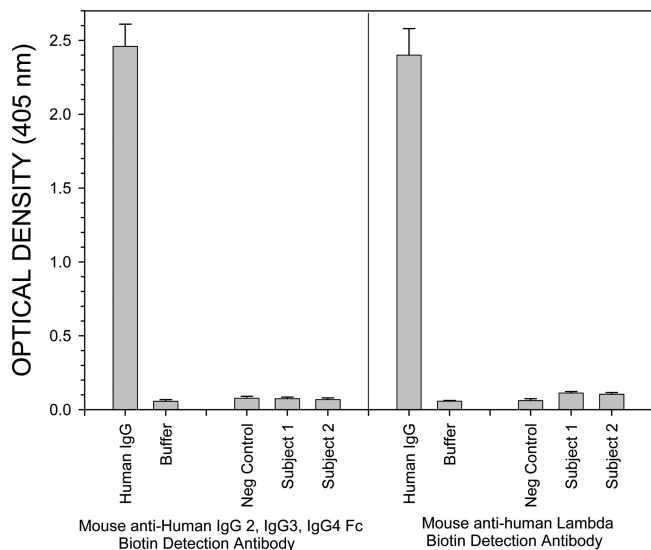


**Figure 4.** Serological evaluation of two subjects for the presence of IgG anti-omalizumab antibodies.

therapy has been shown to rapidly reduce both free (non-omalizumab bound) IgE as well as IgE receptor expression (FcεR1) on various immune cells, potentially preventing both sensitization and effector phases of IgE-mediated allergic responses.<sup>10</sup> Therefore, once a patient has been treated successfully with omalizumab, they should, in theory, be resistant to the development of new IgE-mediated anaphylaxis.

In our study, subject 1 experienced a systemic reaction immediate to omalizumab administration, with urticaria, hemodynamic compromise, and reactivity at the injection sites after more than a year of successful omalizumab therapy. An IgE-mediated reaction was indicated 4 weeks later with a positive intradermal omalizumab skin test. However, serological investigations suggested a nonantibody-mediated (anaphylactoid) mechanism because of an absence of detectable IgG and IgE anti-omalizumab. Importantly, 6 months after the termination of omalizumab treatment, this patient developed ocular and generalized itching and swelling after the use of eye drops containing polysorbate. Unfortunately, subject 1 was fearful of further reactions and declined polysorbate skin testing. These investigations suggest that her reactions to omalizumab were the result of reactivity to the polysorbate excipient (Tween) and not to the humanized IgG1 component. There have been reports of anaphylactoid reactions to polysorbate, which is a mixture of oleic esters of sorbitol and sorbitanes containing chains of polyethylene glycol.<sup>11,12</sup> In studies of polysorbate as an ingredient in anticancer drugs, the reported incidence of hypersensitivity has ranged from 5 to 40%.<sup>12</sup> Patients who experienced reactions to i.v. administered polysorbate-containing drugs could tolerate the oral formulation, which was free of polysorbate. Subject 2

in our study experienced a month-long recurrent respiratory compromise and urticarial reactions after omalizumab administration. There was a lack of any observable reaction at the injection sites. All skin test results to omalizumab 6 weeks after the anaphylaxis and once her asthma had stabilized off of systemic steroids were negative. Omalizumab treatment has been shown to significantly reduce skin test responses to allergen; therefore, negative testing in subject 2 may not have precluded an IgE-mediated anaphylaxis.<sup>2</sup> However, the negative IgE anti-omalizumab serology, in combination with the positive wheal/flare reaction to polysorbate 10 months after her last omalizumab treatment, clarified this further and suggested an anaphylactoid or anaphylactic reaction to polysorbate. A recent case report of an apparent anaphylactoid reaction to omalizumab described a serum sickness-like reaction after attempted desensitization. This study raises further mechanistic questions, such as a possible IgG-mediated reaction.<sup>13</sup>

The absence of detectable serum tryptase in this protracted case of anaphylaxis could have pointed to an IgG macrophage-mediated event. In theory, the large antigen load afforded by the 300-mg injection may have been sufficient to cross-link omalizumab-specific IgG bound to macrophages through low-affinity FcγRIII, causing release of PAF and thus inducing the airway smooth muscle contraction. The negative IgG anti-omalizumab serology, however, minimized the possibility of this reaction mechanism.

In summary, successful long-term omalizumab therapy does not preclude the possible development of adverse reactions to this humanized monoclonal antibody or its excipients. Recent reports of two cases of anaphylaxis to specific immunotherapy in omalizumab-treated patients illustrates the need for caution.<sup>14</sup> Decline in asthma control requiring escalating steroid treatment in a previously omalizumab responsive patient may alert one to potential allergic sensitization and require careful monitoring of further omalizumab treatments. Skin testing to omalizumab should use saline as a diluent to avoid irritant reactions from sterile water and testing to the polysorbate excipient should be considered. When questionable skin test results occur, serology may help clarify the presence of IgE and IgG anti-omalizumab antibodies in serum. The possibility that skin tests may be falsely negative because of the omalizumab therapy should be remembered when interpreting results and deciding on additional treatment. At the time of preparation of this article subject 1 and subject 2 have been off of omalizumab for 15 and 11 months, respectively; both are doing well off of preventative steroids (using leukotriene receptor blockers), have not required controlling high-dose inhaled or systemic steroids and have re-

quired only short courses of 1–2 weeks of controlling low-dose inhaled steroids.

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