Anaphylaxis associated with omalizumab administration: Risk factors and patient characteristics

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Disclosure of potential conflict of interest

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The majority of omalizumab-associated anaphylactic events occurred within the first 3 doses and within 60 minutes of administration. A prior history of anaphylaxis unrelated to omalizumab was reported in 43% of cases with analyzable data.

Key words: Anaphylaxis, anti-IgE, omalizumab, pharmacovigilance

Abbreviations used

FDA: US Food and Drug Administration
To the Editor

The omalizumab product label includes a black box warning for anaphylaxis. As of the end of 2016, there has been an estimated cumulative exposure of ~31,000 patient years in clinical trials and 819,000 patient-years in the postmarketing setting. Episodes of anaphylaxis have been observed in association with omalizumab use since the initial human studies and after its approval for allergic asthma in 2003. In 2016, Lieberman et al\(^1\), reported data from a postmarketing case-control study (X-PAND, N=30) that examined cases of anaphylaxis related to omalizumab use. We now report on a larger sample size of 132 patients with potential anaphylaxis associated with omalizumab that was adjudicated by the same independent clinical expert; 96 (73%) were adjudicated as cases of anaphylaxis related to omalizumab (Fig. E1 available in this article’s Online Repository). Demographic characteristics revealed a preponderance of females (84%), and mean (range) age of 40.5 (9-86) years. Omalizumab was prescribed for asthma in most (80%) patients. A prior anaphylactic event unrelated to omalizumab was documented in 43% (n=37) of patients who provided an anaphylaxis history.

The most common symptoms reported during omalizumab-associated anaphylaxis involved the respiratory tract (95%; 91/96). The majority of patients also reported experiencing cutaneous/angioedema symptoms (Table EI available in this article’s Online repository at www.jacionline.org). The number of omalizumab doses given before the index case of anaphylaxis was recorded in 68 of the anaphylactic cases; anaphylaxis occurred within the first 2 (69%; 47/68) or 3 (72%, 49/68) doses (Table EII available in this article’s Online repository at www.jacionline.org); the median number of doses administered before an anaphylactic reaction was 1. Time to onset of reaction following administration of omalizumab was documented in 81 cases of anaphylaxis (Table EIII available in this article’s Online repository at www.jacionline.org). The reaction occurred within 60 minutes of omalizumab administration in the majority of cases (64%; 52/81); median time to anaphylactic reaction was 60 minutes. Treatment of anaphylaxis included use of antihistamines (69%; 66/96), epinephrine
(60%; 58/96), systemic corticosteroids (57%; 55/96), and inhaled beta-agonists (41%; 39/96). Hospitalization was reported in 16 (17%) cases. No treatment was needed in 2 (2%) cases, and there was no information on treatment for 11 (11%) cases. No case of anaphylaxis resulted in death.

A comparison of our data with data previously reported by Limb et al\(^2\) and Lieberman et al\(^1\) is provided in Fig. 1. Data from the current analysis and that from the Limb et al study\(^2\) indicate that most (~70%) cases of anaphylaxis occurred within the first 3 doses, while in the X-PAND study,\(^1\) this number was 40% (Fig. 1A). All three studies suggest that a significant fraction of patients with omalizumab-associated anaphylaxis have a prior history of anaphylaxis unrelated to omalizumab (Fig. 1B) and that more than half of the anaphylactic events happened within 60 minutes of omalizumab administration (Fig. 1C).

This dataset represents the largest number of adjudicated cases of anaphylaxis associated with omalizumab, and is about 3 times the number of adjudicated anaphylaxis cases reported in our initial study.\(^1\) These results suggest that a specific subpopulation of patients, ie, those with a prior history of anaphylaxis unrelated to omalizumab use, may be particularly prone to developing anaphylaxis with omalizumab administration. It is critical to note that this observation was unexpected. We are not aware of any prior report identifying risk factors for anaphylaxis against a specific drug or biologic agent, except when the risk factor includes IgE sensitization to a substance that cross reacts with the drug or biologic agent. Patients who have had episodes of anaphylaxis, particularly those in whom a causative agent can be identified (eg, with food or bee venom), are known to have a higher risk of recurrent episodes of anaphylaxis,\(^3\)\(^-\)\(^5\) but the mechanism by which prior anaphylaxis unrelated to omalizumab results in omalizumab-associated anaphylaxis is perplexing, especially because most omalizumab-associated anaphylactic events do not appear to be IgE mediated (eg, no IgE anti-omalizumab antibodies have been detected in omalizumab-associated anaphylaxis in the limited number of patients analyzed).\(^1\)
An increased knowledge of omalizumab-associated anaphylaxis may add perspective to anaphylaxis associated with 2 other biologics that have recently been FDA approved for treatment of severe asthma (mepolizumab and reslizumab). Both of these new biologics have been associated with anaphylaxis and it is possible that a small subset of individuals, particularly those with a prior history of anaphylaxis, may have a higher risk of developing anaphylaxis with any biologic prescribed for asthma and/or allergy.

The Omalizumab Joint Task Force for managing the risk of anaphylaxis in omalizumab-treated patients has previously recommended in 2007 that patients be kept under observation for 2 hours after the first 3 omalizumab injections, and 30 minutes after each subsequent injection, although this could be “modified based on a physician’s clinical judgment after discussing risks with the patient.” A reexamination of these recommendations may be warranted based on collective data from adjudicated cases. Updated recommendations might focus particularly on those patients who have a prior history of anaphylaxis. While we do not suggest changing the recommendations of maintaining vigilance for late-occurring reactions, our recent data suggest that late-occurring reactions (>60 minutes after injection as previously reported) are relatively rare with none of the adjudicated cases occurring beyond 24 hours. Nevertheless, cumulative data indicate that a large fraction of reactions occur within the first 3 doses, suggesting that clinicians might focus their attention on the initial doses of omalizumab, particularly in the first 30 to 60 minutes after the dose, and in a subset of patients, eg, those with prior history of anaphylaxis. We anticipate that as more safety data are generated, and if similar patient characteristics are observed in patients with adjudicated episodes of anaphylaxis associated with all biologics used for asthma and allergy, a common set of recommendations for managing the risk of anaphylaxis might be developed for all biologics used for asthma and allergy.

As the number and amount of biologics used for the treatment of asthma grow, understanding the risks of hypersensitivity and anaphylaxis associated with biologics is critical for responsible and safe
use. Omalizumab, the most prescribed biologic for the treatment of asthma with over 14 years of worldwide postmarketing safety experience, has been shown to be safe with an appropriate risk-benefit profile and a small risk for anaphylaxis, particularly in a subset of patients with a prior history of anaphylaxis. This information is valuable to clinicians, who must inform patients the potential benefits and potential risks of treatment.

Kind regards,

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REFERENCES


**FIGURE LEGENDS**

**FIG 1A**, total omalizumab doses received at the onset of anaphylaxis. Note that the X-axis is not linear.

After the first 3 doses, each category in the X-axis includes increasingly greater number of doses.

*Values reflect frequency out of cases with dose data reported.

**FIG 1B**, patient-reported prior history of anaphylaxis unrelated to omalizumab. †Values reflect percentage based on the number of patients reporting a prior history of anaphylaxis; not all patients provided this history.

**FIG 1C**, time to event onset across reported studies. Limb et al did not provide timing breakdown after 3 doses (29% of events occurred after 3 doses). Note that the X-axis is not linear; after the first two intervals, each category in the X-axis reflects increasingly greater time intervals. ‡Numbers reflect frequency out of all cases with timing reported.
Total omalizumab doses when anaphylaxis event occurred

 Patient-reported prior history of anaphylaxis unrelated to omalizumab

Time to onset of event after omalizumab dosing

(A) Total omalizumab doses when anaphylaxis event occurred

(B) Patient-reported prior history of anaphylaxis unrelated to omalizumab

(C) Time to onset of event after omalizumab dosing
### Online repository

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Anaphylaxis cases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous/angioedema, respiratory</td>
<td>66 (69)</td>
</tr>
<tr>
<td>Cutaneous/angioedema, respiratory, gastrointestinal</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Cutaneous/angioedema, respiratory, cardiovascular</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Cutaneous/angioedema, cardiovascular</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Respiratory, cardiovascular</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Cutaneous/angioedema, respiratory, gastrointestinal, cardiovascular</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Respiratory, gastrointestinal, cardiovascular</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cutaneous/angioedema, gastrointestinal</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
### TABLE EII. Total omalizumab doses administered at time of anaphylactic event

<table>
<thead>
<tr>
<th>No. of doses</th>
<th>Anaphylaxis cases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35 (51)</td>
</tr>
<tr>
<td>2</td>
<td>12 (18)</td>
</tr>
<tr>
<td>3</td>
<td>2 (3)</td>
</tr>
<tr>
<td>4-20</td>
<td>10 (15)</td>
</tr>
<tr>
<td>21-40</td>
<td>5 (7)</td>
</tr>
<tr>
<td>41-60</td>
<td>2 (3)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*Data missing for 28 patients.*
Table EIII. Time to onset of event after omalizumab dosing

<table>
<thead>
<tr>
<th>Time to Onset</th>
<th>Anaphylaxis cases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 min</td>
<td>35 (43)</td>
</tr>
<tr>
<td>30-60 min</td>
<td>17 (21)</td>
</tr>
<tr>
<td>&gt;60-90 min</td>
<td>4 (5)</td>
</tr>
<tr>
<td>&gt;90-120 min</td>
<td>5 (6)</td>
</tr>
<tr>
<td>&gt;2-6 h</td>
<td>11 (14)</td>
</tr>
<tr>
<td>&gt;6-12 h</td>
<td>3 (4)</td>
</tr>
<tr>
<td>&gt;12-24 h</td>
<td>6 (7)</td>
</tr>
<tr>
<td>&gt;24 h</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data missing for 15 patients.
**FIG E1.** Adjudication of potential cases of anaphylactic events related to omalizumab. *Number and timing of symptom onset not provided.*
Potential cases identified from database (n = 1,199)

- Did not meet criteria (n = 122)
- Duplicates submitted in error (n = 153)

Cases adjudicated by independent source (n = 1,077)

- Adjudication outcome: no anaphylaxis (n = 611)
  - Not evaluable (n = 151)
  - Duplicate (n = 2)

- Adjudication outcome: anaphylaxis present (n = 162)
  - Not related to omalizumab (n = 13)
  - Included in X-PAND (n = 30)

Included in current analysis (n = 132)

Final analysis (n = 96)
- Not evaluable* (n = 21)
- Not related to omalizumab (n = 13)
- Duplicate (n = 2)