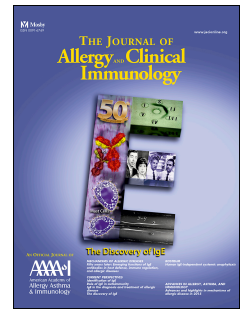


Accepted Manuscript

Anaphylaxis associated with omalizumab administration: Risk factors and patient characteristics

Phillip L. Lieberman, MD, Ilisen Jones, MD, MPH, Richa Rajwanshi, MD, Karin Rosén, MD, PhD, Dale T. Umetsu, MD, PhD



PII: S0091-6749(17)31269-1

DOI: [10.1016/j.jaci.2017.07.013](https://doi.org/10.1016/j.jaci.2017.07.013)

Reference: YMAI 12950

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 18 April 2017

Revised Date: 16 June 2017

Accepted Date: 10 July 2017

Please cite this article as: Lieberman PL, Jones I, Rajwanshi R, Rosén K, Umetsu DT, Anaphylaxis associated with omalizumab administration: Risk factors and patient characteristics, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.07.013.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Anaphylaxis associated with omalizumab administration: Risk factors and patient characteristics

Phillip L. Lieberman, MD,^a Ilisten Jones, MD, MPH,^b Richa Rajwanshi, MD,^c Karin Rosén, MD, PhD,^c and Dale T. Umetsu, MD, PhD^c

From ^aDepartments of Internal Medicine and Pediatrics, Division of Allergy and Immunology, University of Tennessee College of Medicine, 6139 Chapelle Circle West, Memphis TN 38120 USA; ^bDepartment of Pediatrics, Division of Allergy and Immunology, University of California, 400 Parnassus Ave, San Francisco, San Francisco, CA 94913, USA; and ^cGenentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA.

Corresponding author: Phillip L. Lieberman, MD, Departments of Internal Medicine and Pediatrics Divisions of Allergy and Immunology, University of Tennessee College of Medicine, 6139 Chapelle Circle West, Memphis TN 38120. Phone: 901-758-1078; fax: 901-761-2617; e-mail: phillieberman@hotmail.com.

Role of the funding source

This study was designed and funded by Genentech, Inc., South San Francisco, CA, USA and Novartis Pharma AG, Basel, Switzerland. I. Jones participated in data analysis as part of her fellowship at Genentech, Inc. P. Lieberman participated in the case adjudication, reviewed the data, and participated in the manuscript preparation. R. Rajwanshi, K. Rosén, and D. T. Umetsu are employees of Genentech, Inc. and participated in data analysis and manuscript preparation. Third-party writing assistance was provided by Charlotte Kenreigh, PharmD, of Envision Pharma Group (Excel Scientific Solutions, Inc.), and funded by Genentech, Inc. and Novartis Pharmaceuticals Corporation.

Acknowledgments

We thank Dr. Abdelkader Rahmaoui of Genentech, Inc. for his help in analyzing data for this project.

Disclosure of potential conflict of interest

P. L. Lieberman has received consulting/speaker fees from Genentech, Inc. and has received research support from Novartis. I. Jones completed work on this project during a Genentech, Inc.–sponsored fellowship. R. Rajwanshi, K. Rosén, and D. T. Umetsu are employees of Genentech, Inc.

Word count [limit 1000 words]: Current 1069

Tables/figures [limit 2]: 1 figure

Capsule summary: 35 word limit; current 35 words

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 al¹, 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 al² and Lieberman et al¹ is provided in Fig. 1. Data from the current analysis and that from the Limb et al study² 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).⁶ Both of these new biologics have been associated with anaphylaxis^{7,8} 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.”⁹ A reexamination of these recommendations may be warranted based on collective data from adjudicated cases.¹ 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 reported²) 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,

Phillip L. Lieberman, MD, Departments of Internal Medicine and Pediatrics Divisions of Allergy and Immunology, University of Tennessee College of Medicine, 6139 Chapelle Circle West, Memphis, TN 38120, USA

Ilisten Jones, MD, MPH, Department of Pediatrics, Division of Allergy and Immunology, University of California, 400 Parnassus Ave., San Francisco, CA 94913, USA

Richa Rajwanshi, MD, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA

Karin Rosén, MD, PhD, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA

Dale T. Umetsu, MD, PhD, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA

REFERENCES

1. Lieberman PL, Umetsu DT, Carrigan GJ, Rahmaoui A. Anaphylactic reactions associated with omalizumab administration: analysis of a case-control study. *J Allergy Clin Immunol* 2016;138:913-15.e2.
2. Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007;120:1378-81.
3. González-Pérez A, Aponte Z, Vidaurre CF, Rodriguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol* 2010;125:1098-104.e1.
4. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. *Arch Intern Med* 1995;155:1749-54.
5. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy* 2003;33:1033-40.
6. Khan DA. Hypersensitivity and immunologic reactions to biologics: opportunities for the allergist. *Ann Allergy Asthma Immunol* 2016;117:115-20.
7. Cinqair [prescribing information]. Frazer, PA: Teva Respiratory, LLC; 2016.
8. Nucala [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
9. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007;120:1373-7.

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

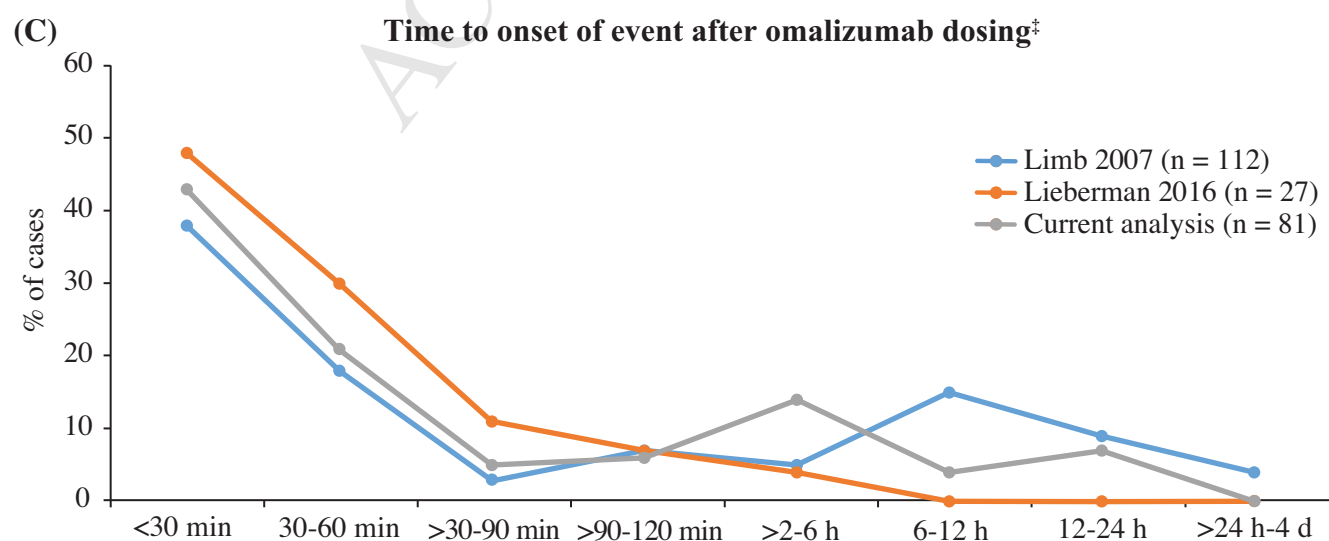
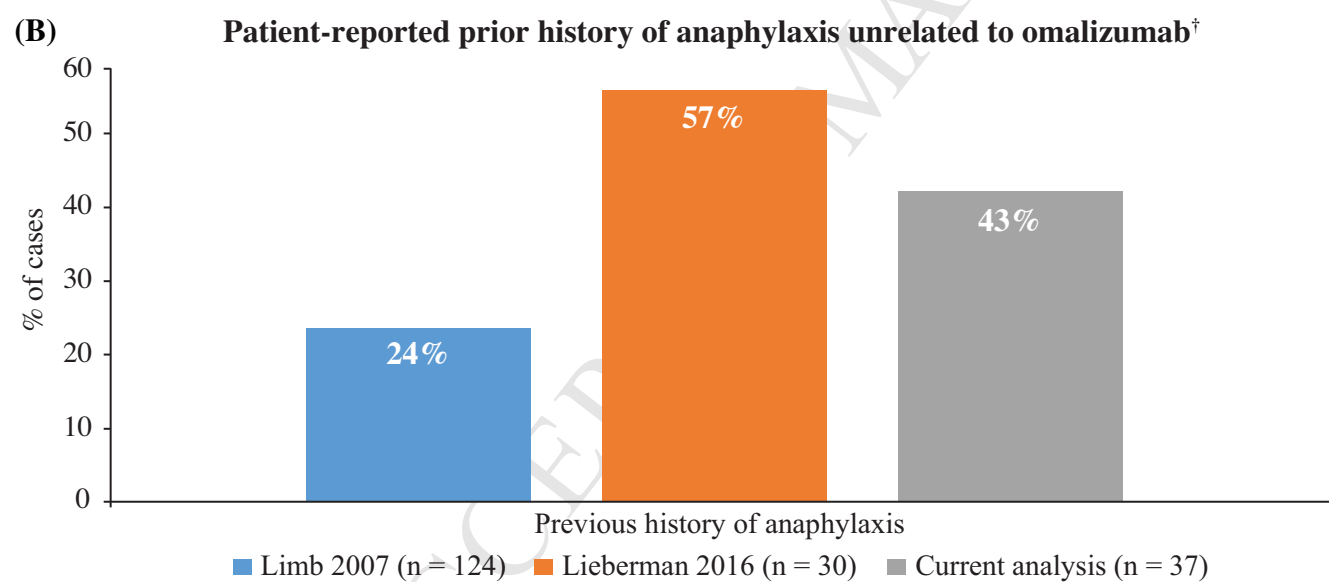
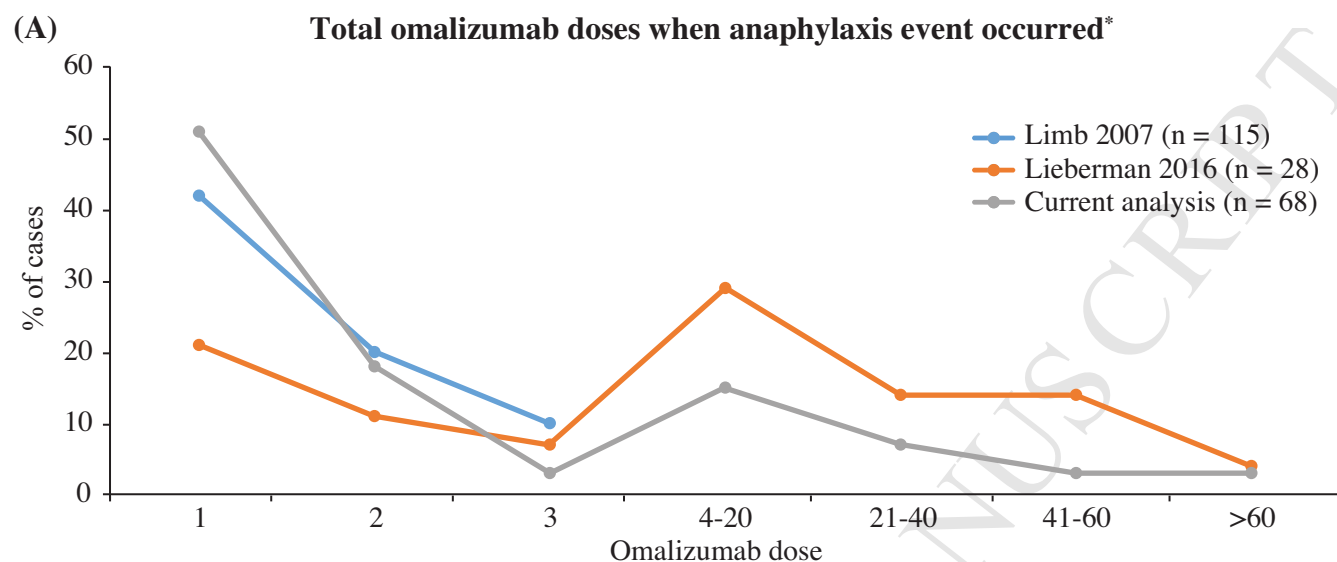
provided this history.

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.



Online repository

TABLE E1. Clinical signs and symptoms experienced during the anaphylactic event

Symptom	Anaphylaxis cases, n (%)
	n = 96
Cutaneous/angioedema, respiratory	66 (69)
Cutaneous/angioedema, respiratory, gastrointestinal	12 (13)
Cutaneous/angioedema, respiratory, cardiovascular	8 (8)
Cutaneous/angioedema, cardiovascular	3 (3)
Respiratory, cardiovascular	3 (3)
Cutaneous/angioedema, respiratory, gastrointestinal, cardiovascular	1 (1)
Respiratory, gastrointestinal, cardiovascular	1 (1)
Cutaneous/angioedema, gastrointestinal	1 (1)
Cardiovascular	1 (1)

TABLE EII. Total omalizumab doses administered at time of anaphylactic event

Anaphylaxis cases, n (%)	
No. of doses	n = 68*
1	35 (51)
2	12 (18)
3	2 (3)
4-20	10 (15)
21-40	5 (7)
41-60	2 (3)
>60	2 (3)

*Data missing for 28 patients.

Table EIII. Time to onset of event after omalizumab dosing

Time to Onset	Anaphylaxis cases, n (%)
	n = 81*
<30 min	35 (43)
30-60 min	17 (21)
>60-90 min	4 (5)
>90-120 min	5 (6)
>2-6 h	11 (14)
>6-12 h	3 (4)
>12-24 h	6 (7)
>24 h	0

*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.

