

Task force report

American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis

Linda Cox, MD,^a Thomas A. E. Platts-Mills, MD, PhD,^b Ira Finegold, MD,^c Lawrence B. Schwartz, MD, PhD,^d F. Estelle R. Simons, MD,^e and Dana V. Wallace, MD^f *Davie, Fla, Charlottesville, Va, New York, NY, Richmond, Va, and Winnipeg, Manitoba, Canada*

The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology Executive Committees formed the Omalizumab Joint Task Force with the purpose of reviewing the Genentech Xolair (omalizumab) clinical trials and postmarketing surveillance data on anaphylaxis and anaphylactoid reactions. Using the definition of anaphylaxis proposed at a 2005 multidisciplinary symposia, the Omalizumab Joint Task Force concluded that 35 patients had 41 episodes of anaphylaxis associated with Xolair (omalizumab) administration between June 1, 2003, and December 31, 2005. With 39,510 patients receiving Xolair (omalizumab) during the same period of time, this would correspond to an anaphylaxis-reporting rate of 0.09% of patients. Of those 36 events for which the time of reaction was known, 22 (61%) reactions occurred in the first 2 hours after one of the first 3 doses. Five (14%) of the events after the fourth or later doses occurred within 30 minutes. Considering the timing of these 36 events, an observation period of 2 hours for

the first 3 injections and 30 minutes for subsequent injections would have captured 75% of the anaphylactic reactions. The OJTF report provides recommendations for physicians who prescribe Xolair (omalizumab) on (1) the suggested wait periods after administration and (2) patient education regarding anaphylaxis. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Omalizumab, Xolair, anaphylaxis, recombinant monoclonal antibodies, hypersensitivity, IgE antibody

At the 2007 American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting in San Diego, California, the AAAAI and American College of Allergy, Asthma and Immunology (ACAAI) Executive Committees formed the Omalizumab Joint Task Force (OJTF) with the purpose of reviewing the Genentech Xolair (omalizumab) clinical trials and postmarketing surveillance data on anaphylaxis and anaphylactoid reactions. The OJTF reviewed the data and prepared a report that included recommendations for physicians who prescribe Xolair (omalizumab). The OJTF gratefully acknowledges the AAAAI Board of Directors and the ACAAI Board of Regents for their review and support of this document.

SUMMARY OF AAAAI/ACAAI OJTF RECOMMENDATIONS

1. Informed consent should be obtained from the patient after discussing the risks, benefits, and alternatives to Xolair (omalizumab).
2. The patient should be educated regarding the signs, symptoms, and treatment of anaphylaxis (Table I).^{1,2}
3. Patients should be prescribed and educated on the proper use of the epinephrine autoinjector and advised to carry this before Xolair (omalizumab) administration and for the next 24 hours after Xolair (omalizumab) administration.
4. An assessment of the patient's current health status should be made before each injection to determine whether there were any recent health changes that might require withholding treatment. This

From ^athe Department of Clinical Medicine, Nova Southeastern University College of Osteopathic Medicine, Davie; ^bthe Departments of Internal Medicine and Microbiology, Division of Allergy and Clinical Immunology, University of Virginia, Charlottesville; ^cthe Department of Allergy St Luke's-Roosevelt Hospital Center, RA Cooke Institute of Allergy, New York; ^dthe Department of Medicine, Division of Rheumatology, Allergy and Immunology, Virginia Commonwealth University, Richmond; ^ethe Department of Pediatrics and Child Health, Department of Immunology, Faculty of Medicine, The University of Manitoba, Winnipeg; and ^fthe Department of Clinical Medicine, Nova Southeastern University, Osteopathic College of Medicine.

Disclosure of potential conflict of interest: I. Finegold is on the speakers' bureau for Novartis, Genentech, Alcon, Sanofi-Aventis, and Teva. L. B. Schwartz has consulting arrangements with GlaxoSmithKline, Genentech/Novartis, and Mast Cell Pharmaceuticals; has patent licensing arrangements with Phadia; has received grant support from the National Institutes of Health, the Philip Morris Foundation, GlaxoSmithKline, and Genentech/Novartis; and is on the speakers' bureau for Genentech/Novartis and Teva. T. A. E. Platts-Mills has consulting arrangements with Bristol-Meyers-Squibb. D. V. Wallace has declared that she has no conflict of interest.

Received for publication August 27, 2007; revised September 17, 2007; accepted for publication September 19, 2007.

Reprint requests: Linda Cox, MD, Department of Clinical Medicine, Nova Southeastern University Osteopathic College of Medicine, 5333 North Dixie Highway, Suite 210, Ft Lauderdale, FL 33334. E-mail: lindaswolfcox@msn.com.

0091-6749/\$32.00

© 2007 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2007.09.032

Abbreviations used

AAAAI: American Academy of Allergy,
Asthma & Immunology

ACAAI: American College of Allergy,
Asthma and Immunology

OJTF: Omalizumab Joint Task Force

assessment should include vital signs and some measure of lung function (eg, peak expiratory flow or FEV₁).

5. The OJTF recommends that patients be kept under observation for 30 minutes after each injection. This time should be extended for 2 hours for the first 3 injections based on the data reviewed by the OJTF, as well as suggested in the 2007 National Heart, Lung, and Blood Institute Expert Panel Report 3 "Guidelines for the diagnosis and management of asthma."³ However, this could be modified based on a physician's clinical judgment after discussing risks with the patient.

MONOCLONAL ANTIBODIES AND HYPERSENSITIVITY REACTIONS

Recombinant chimeric or fully humanized mAbs are increasingly part of medical treatment not only in chronic inflammatory and malignant disease but also in allergic disease. Hypersensitivity reactions to biologic agents, including anaphylaxis, have been well described.⁴⁻⁶ Anaphylaxis has been reported with several different mAbs, including omalizumab. However, the prevalence is low (ie, $\leq 0.2\%$) for Xolair (omalizumab).⁷ Such reactions, in general, are least to most common with human (100% human), humanized ($\geq 90\%$ human), chimeric (75% human), and mouse (0% human) mAbs. They reportedly occur acutely (< 4 hours) or in a delayed manner (up to 14 days) after an infusion^{6,8} and can occur with the first or subsequent infusions.⁵ In some cases IgE against an idiotypic, allotypic, or murine portion of the mAb has been identified by means of skin testing⁹ or *in vitro* immunoassays, although typically one must wait for mAb levels in the circulation to diminish before such tests are performed. In other cases IgG-mediated hypersensitivity might be involved. When IgG anti-mAb is made against the biologic agent, the potency of the mAb can be diminished. Immune complexes formed between the mAb and the target antigen or spontaneous aggregates of the mAb preparation also could be involved. In one study of 14 infliximab infusion reactions, neither an increase in serum tryptase levels nor IgE levels against infliximab were detected. However, future reactions were avoided by decreasing the infusion rate and, in some cases, pretreating with antihistamines and glucocorticosteroids.⁸ Coadministration of immunosuppressive drugs (eg, in transplant recipients or in patients with cancer) is thought to diminish production of immune responses against the biologic agent.

Xolair (omalizumab) is a humanized mAb that forms small immune complexes with target IgE. It lacks complement fixing activity but does bind to Fc γ receptors. In the case of omalizumab, the molecule is so extensively humanized that antibodies to the remaining mouse epitopes are unlikely but merit further study. Evidence has been presented that anaphylactic reactions related to another mAb, cetuximab, which is chimeric, occur in patients who have pre-existing IgE antibodies to the oligosaccharide galactose- α -1,3-galactose. This sugar is an important posttranslational modification on cetuximab. Xolair (omalizumab) is grown in a Chinese hamster ovary cell line that does not express the enzyme α -1,3-galactosyl transferase, and thus this mAb cannot contain galactose- α -1,3-galactose. However, mAbs produced in Chinese hamster ovary cell lines are glycosylated in the Golgi apparatus, and that glycosylation could theoretically be a target for pre-existing IgE antibody responses. Studies to exclude that possibility are currently being planned by Genentech. The excipients (sucrose, L-histidine hydrochloride monohydrate, L-histidine, and polysorbate20) in Xolair (omalizumab) are generally considered safe, but reactions to these are a remote possibility. Polysorbate, an additive used to promote the rapid solubilization of pharmaceuticals in aqueous solutions,¹⁰ has been reported to cause hypersensitivity reactions.^{11,12} An *in vitro* and *in vivo* immunologic evaluation of 2 patients who experienced anaphylaxis after 1 year of omalizumab treatment concluded that the likely cause was the excipient polysorbate.¹² Priorities should include the identification of the mechanism of these reactions and, if possible, the development of a screening test to identify patients at risk. This will require studies of serum samples from a series of patients who have had reactions.

Allergy-immunology specialists who administer Xolair (omalizumab) in their offices or clinics and identify patients with anaphylaxis to Xolair (omalizumab) are in a unique position to provide detailed information about these reactions and to help their colleagues learn more about these rare events. The recently revised Xolair (omalizumab) product information sheet describes anaphylaxis-like reactions that occurred in up to 0.2% of subjects who received this medication, primarily for treatment of asthma.⁷ Possible mechanisms worth considering include antiallotypic or anti-idiotypic antibodies (IgE or IgG) against this reagent that were either pre-existing before drug administration or had developed after initial exposures or a response to the aggregated preparations of Xolair (omalizumab). Another possible mechanism is that an unrelated event happened to occur near the time of Xolair (omalizumab) administration (eg, accidental food allergen ingestion). However, there are insufficient laboratory data at present to ascertain which, if any, of these explanations relate to the Xolair (omalizumab)-associated events noted below.

Risk assessment in individuals with anaphylaxis is potentially complex, even when the antigen has been identified and the specific effector mechanism through which it produces anaphylaxis is known. It is even more

TABLE I. Anaphylaxis education sheet

Treatment of anaphylaxis in the physician's office ¹	Treatment of anaphylaxis in the community ²
Immediate measures	Patient self-management after leaving the physician's office
Assess airway breathing, circulation, and orientation	Information sheet on anaphylaxis with specific information on Xolair (omalizumab)
Inject epinephrine, 0.3 mg intramuscularly, in the vastus lateralis (lateral thigh)	Epinephrine autoinjector (EpiPen duopak or Twinject)
Activate emergency medical services (call 911 or local rescue squad)	Anaphylaxis Emergency Action Plan (downloadable from www.AAAAI.org)
Place patient in recumbent position and elevate the lower extremities, as tolerated	Anaphylaxis wallet card (available from www.AAAAI.org at no charge to members and minimal charge for nonmembers)
Establish and maintain airway	Medical identification jewelry tag (eg, MedicAlert bracelet)
Administer oxygen	
Establish an intravenous line for venous access and fluid replacement; keep open with normal saline	
Consider administration of nebulized albuterol, 2.5-5 mg in 3 mL of saline; repeat as necessary	
Consider administration of ancillary medications, such as H ₁ antihistamine or a systemic corticosteroid	

complex when the specific antigen has not yet been identified and when the mechanism is unknown.¹³

OJTF REVIEW AND SUMMARY OF CLINICAL DATA

Incidence of potential Xolair (omalizumab) anaphylactic reactions

The OJTF reviewed a composite report provided by pharmaceutical firms that manufacture and market Xolair (omalizumab), Genentech and Novartis, dated May 3, 2006, that included the pivotal Xolair (omalizumab) clinical trials, as well as the postmarketing reports filed with the Food and Drug Administration between June 1, 2003, and December 31, 2005. Also reviewed was the information provided in the revised Xolair (omalizumab) package insert that included postmarketing reports from June 2003 until December of 2006. The OJTF members concentrated their review on the postmarketing data and combined the clearly anaphylactic cases with those with less severe reactions into one group, hereafter referred to as "anaphylaxis." During this period there were 46 cases of anaphylaxis reported. In addition, there were 55 potential anaphylactic events based on composite symptoms that were reported as being temporally associated with Xolair (omalizumab). There were a total of 101 patients and 106 events because a few patients had more than 1 event. The composite report included the summary of an independent expert hired by Genentech and Novartis to review the postmarketing surveillance data. Using a consensus panel's "emerging definition of anaphylaxis,"¹⁴ the reviewer concluded that 10 of the 42 cases of reported anaphylaxis and 8 of the 55 potential anaphylactic events fulfilled the stated definition of anaphylaxis, for a total of 18 cases. The revised product information sheet reported that at least 0.2% of the 57,300 patients who received Xolair (omalizumab) between June 2003 and December

TABLE II. Summary of timing of Xolair (omalizumab) adverse reactions

Timing of the reaction	First-third Xolair (omalizumab) dose (no. of events)	Fourth or later Xolair (omalizumab) dose (no. of events)	Total
<30 min	11	5	16
30-60 min	6	1	7
1-2 h	5	0	5
2-12 h	4	1	5
>12 h	3	0	3
Unknown	3	2	5
Total	32	9	41

2006 experienced anaphylaxis, but it did not specify the criteria used to define anaphylaxis.

Using the definition of anaphylaxis proposed at the 2005 multidisciplinary symposia cosponsored by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network,¹⁴ the OJTF included all cases reported that included presentation of symptoms and findings that a clinician might reasonably consider to be anaphylaxis. Of the original 42 reported patients, the OJTF concluded that 27 patients and a total of 33 events might reasonably be categorized as anaphylaxis. Combining these 27 patients with the 8 of the 55 patients with potential anaphylaxis gave a total of 35 patients with 41 episodes of anaphylaxis associated with Xolair (omalizumab) administration. With 39,510 patients receiving Xolair (omalizumab) during the same period of time, this would correspond to an anaphylaxis-reporting rate of 0.09% of patients. All patients responded to treatment, and there were no fatalities or respiratory failures requiring intubation.

A summary report was prepared with recommendations based on analysis of the timing and character of the

Record number: _____	
Patient name: _____	Date of birth: _____
Date of visit: _____	Previous Xolair® (omalizumab) Administration date: _____
Pre-Xolair® (omalizumab) administration* Interval history: _____ Examination: blood pressure _____ pulse _____ respiration rate _____ Other assessment: _____ _____ Airway function: PEF or FEV1 can be used to assess lung function. PEF best baseline (% predicted): _____ FEV ₁ best baseline (% predicted): _____ PEF _____ FEV ₁ _____ Other assessment: _____ _____ Xolair® (omalizumab) administration: _____ mg/ml Location: _____ Xolair® (omalizumab) administered by (staff name): _____ Patient observed after Xolair® (omalizumab) administration for _____ minutes Comments: _____ _____ _____ Physician signature: _____	
*Asthma control can be assessed by patient history and/or a validated asthma questionnaire. Prescribing physician should provide guidelines on the actions staff should take based on the pre-injection evaluation. Examples of validated asthma questionnaire: Asthma Control Test™ (ACT) (well-controlled ≥ 20, not well-controlled 16-19, poorly controlled ≤15) Asthma Therapy Assessment Questionnaire (ATAQ) (well-controlled 0, not well-controlled 1-2, poorly controlled 3-4) Asthma Control Questionnaire (ACQ) (Range: 0-6, well-controlled ≤ 0.75, not well-controlled ≥ 1.5, extremely poorly controlled 6)	

FIG 1. Example of a Xolair (omalizumab) administration office note. *PEF*, Peak expiratory flow.

41 cases that occurred in the time period between June 1, 2003, and December 31, 2005. After the preparation of a summary report, the OJTF was provided with additional case reports from Genentech and Novartis dating from January 1, 2006, through December 2006. These additional reported events were from various sources, including patients and individuals who were not present at the time of the event and were often reported some time after the event. Confounding variables, incomplete information, predominant subjective symptoms, and a lack of objective medical observations prevented an accurate assessment of the number of diagnosable anaphylactic events. The pattern of timing and severity was similar to the cases reviewed in the summary report.

The incidence of adverse events was about 0.2%, but because of the paucity of data, we were unable to judge which cases were truly anaphylaxis. There were no

fatalities in any of the case reports dating from the pivotal trials to December of 2006. It was thus the OJTF's decision not to include these reports in the final tabulation.

Timing of potential Xolair (omalizumab) anaphylactic reactions

The OJTF analyzed the timing of the 41 (33 + 8) anaphylactic events (Table II). The timing of 5 events was unknown. Of those 36 events for which the time of reaction was known, 22 (61%) reactions occurred in the first 2 hours after one of the first 3 doses. Five (14%) of the events after the fourth or later doses occurred within 30 minutes. Considering the timing of these 36 events, an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections would have captured 75% of the anaphylactic reactions. Advising the patient to have an epinephrine autoinjector will, hopefully,

address reactions that occur outside the recommended observation period.

When onset of reaction was noted to be longer than 2 hours, details were usually lacking, and “a few hours later” was often the only information available. The character and severity of these reactions included tongue swelling in a patient taking a β -blocker (emergency department treatment), “lingual angioedema” (no details provided), increased asthma symptoms and urticaria (resolved with outpatient treatment) and shortness of breath, watery itchy eyes, and a sensation of throat closing (emergency department treatment).

OJTF CONCLUSIONS AND RECOMMENDATIONS

Based on the data summarized above, the OJTF concluded that Xolair (omalizumab) should only be administered by a physician or other licensed health care provider who has been trained to recognize and treat anaphylaxis and who has available appropriate medications, equipment, and staff to respond to anaphylaxis.³ It would not be appropriate to administer Xolair (omalizumab) at home or in a facility that did not have appropriate staff and equipment to treat anaphylaxis. Direct observation for 2 hours after the first 3 Xolair (omalizumab) treatments, as suggested in the National Heart, Lung, and Blood Institute Expert Panel Report 3 asthma guidelines,¹ and 30 minutes thereafter would seem to provide adequate periods of observation. These observation recommendations could be modified based on a physician's clinical judgment after the risks were discussed with the patient.

All patients taking Xolair (omalizumab) should be trained in the recognition of the signs and symptoms of anaphylaxis and in the use of the epinephrine autoinjector (Table I). Patients should be advised to have this epinephrine autoinjector immediately available during and after Xolair (omalizumab) treatments. Many prescriptions for self-injectable epinephrine never get filled, and therefore it does not suffice merely to give the patient an epinephrine prescription.¹⁵ The physician should ensure that when the patient who has experienced anaphylaxis after Xolair (omalizumab) injection is ready to leave the office, this individual not only has an epinephrine autoinjector immediately available but also that he or she has been instructed in its use.¹⁵

PRE-XOLAIR (OMALIZUMAB) ADMINISTRATION PATIENT ASSESSMENT

Before each Xolair (omalizumab) administration, an assessment of the patient's current health status should be made to determine whether there were any recent health changes that might require withholding treatment. The preinjection assessment should include measurement of vital signs, an assessment of asthma control, and some

measurement of lung function (eg, peak expiratory flow rate or FEV₁) at every visit (Fig 1). Prescribing physicians should provide guidelines on the actions staff should take based on the preinjection assessment.

INFORMED CONSENT

The administration of Xolair (omalizumab) should be balanced with regard to the possibility of anaphylaxis, and the risk to a particular patient, as well as the benefit, should be discussed. Informed consent should be obtained before beginning Xolair (omalizumab), and this can be documented in the medical record or as a written consent form.

If the physician's recommendation differs from established guidelines (ie, practice parameters) or package insert information, this should be included in the consent process and also be noted in the consent documentation.

REFERENCES

1. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(suppl):S483-523.
2. Simons FE. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol* 2006;117:367-77.
3. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007.
4. Klastersky J. Adverse effects of the humanized antibodies used as cancer therapeutics. *Curr Opin Oncol* 2006;18:316-20.
5. Baudouin V, Crusiaux A, Haddad E, Schandene L, Goldman M, Loirat C, et al. Anaphylactic shock caused by immunoglobulin E sensitization after retreatment with the chimeric anti-interleukin-2 receptor monoclonal antibody basiliximab. *Transplantation* 2003;76:459-63.
6. Cheifetz A, Mayer L. Monoclonal antibodies, immunogenicity, and associated infusion reactions. *Mt Sinai J Med* 2005;72:250-6.
7. Genentech, Inc. Xolair (omalizumab) [product insert]. South San Francisco; 2007.
8. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003;98:1315-24.
9. Leonard PA, Woodside KJ, Gugliuzza KK, Sur S, Daller JA. Safe administration of a humanized murine antibody after anaphylaxis to a chimeric murine antibody. *Transplantation* 2002;74:1697-700.
10. Kozutsumi D, Tsunematsu M, Yamaji T, Murakami R, Yokoyama M, Kino K. PS80 interferes with the antiallergic effect of Cry-consensus peptide, a novel recombinant peptide for immunotherapy of Japanese cedar pollinosis, at very low concentration through modulation of Th1/Th2 balance. *Immunology* 2006;118:392-401.
11. Steele RH, Limaye S, Cleland B, Chow J, Suranyi MG. Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. *Nephrology (Carlton)* 2005;10:317-20.
12. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007;28:313-9.
13. Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 2006;6:476-81.
14. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
15. Johnson TL, Parker AL. Rates of retrieval of self-injectable epinephrine prescriptions: a descriptive report. *Ann Allergy Asthma Immunol* 2006;97:694-7.