
Omalizumab-associated anaphylactic reactions reported between January 2007 and June 2008

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Background: Anaphylaxis associated with omalizumab treatment is a growing concern. The broader context in which omalizumab-associated allergic reactions occur has not been well described.

Objective: To identify and characterize recently reported anaphylactic reactions associated with omalizumab administration.

Methods: The US Food and Drug Administration Adverse Event Reporting System reports between January 1, 2007, and June 30, 2008, were queried for new reactions primarily suspected to be due to omalizumab. Reaction characteristics were analyzed for a reaction descriptor of anaphylactic or anaphylactoid shock or reaction and for dermal, respiratory, cardiovascular, and gastrointestinal reaction descriptor terms that in combination could be interpreted as constituting anaphylaxis. Associated narratives for these reports were obtained and were examined further.

Results: There were 85 cases with an anaphylaxis descriptor and 33 cases without a descriptor of anaphylaxis but with multisystem allergic reactions (mostly respiratory and skin or mucosal) that were consistent with anaphylaxis. Of these 118 cases, 32 were after the first dose and 14 were after the second dose of omalizumab. Seventy-seven of the 118 cases were categorized as requiring hospital admission or prolongation, had life-threatening reactions, underwent treatment with epinephrine or corticosteroids, or had omalizumab treatment withheld or discontinued. Nineteen of the 118 reactions were described as occurring within 1 hour of omalizumab injection.

Conclusions: Allergic reactions to omalizumab continue to be reported. Some patients not labeled as having anaphylaxis have multisystem allergic reactions consistent with anaphylaxis, raising questions about the adequacy of the Food and Drug Administration categorizations. The characteristics of these patient reports point toward a spectrum of systemic allergic reactions associated with omalizumab use.

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INTRODUCTION

Omalizumab is a unique biosynthetic molecule with antiallergic characteristics. It is currently used as an add-on treatment for moderate to severe allergic asthma.¹ Recent reports of anaphylaxis as an adverse effect of omalizumab therapy^{2,3} have prompted reconsideration of the overall risk-benefit ratio of using this treatment.⁴ Unlike self-administered subcutaneous biological treatments in other disease states, such as rheumatoid arthritis,⁵ the current recommendations regarding the use of omalizumab call for injection in the physician's office.⁶ This recommendation has implications in terms of patient convenience and medical resource allocation. Investigators at the US Food and Drug Administration (FDA) recently profiled omalizumab-associated anaphylaxis from 2003 through 2006.² The calculated prevalence of these reactions of approximately 0.2% was higher than expected on the basis of clinical trial data,⁷ where a 0.1% prevalence was noted. Furthermore, they showed that omalizumab-associated anaphylaxis may have delayed onset in some cases, which can obscure identification of the cause of the anaphylaxis.⁸

There also may be underreporting of allergic reactions to omalizumab due to the fear of not being able to continue treatment deemed effective by the patient. We hypothesized that reports of omalizumab-associated anaphylaxis could be increasing on the basis of continuing publicity regarding its anaphylaxis potential. We, thus, sought to characterize new reports of omalizumab-associated reactions involving anaphylaxis descriptors and related allergic signs using the FDA Adverse Event Reporting System (AERS) databases for 2007 and the first 2 quarters of 2008.⁹

METHODS

Case Selection

The 6 AERS quarterly databases from January 2007 through June 2008 were extracted from ASCII files using SPSS for Windows version 13 (SPSS Inc, Chicago, Illinois). The drug files were queried for drug names containing the text *omalizumab* or *Xolair* to identify all generic and brand names that constitute omalizumab. These rows were then selected for those with drug roles that indicated that omalizumab was a primary suspect and not a concomitant medication. These rows were then matched with the demographic files based on matching AERS unique numbers to identify the specific case numbers (each case may have more than 1 unique number) to determine whether the report was a follow-up or an initial report, to obtain the drug reaction event date, and to obtain demographic information about the patient. Only cases ini-

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tially reported after 2006 were examined. Matching was performed for outcome files, therapy files (which provide dates of starting and stopping drug administration), drug files (to identify concomitant medications), reaction files, and indication files (which report the disease omalizumab was treating). Reaction files had 1 to 24 listings of individual reaction terms. Outcomes chosen by the reporter included hospitalization, disability, life-threatening events, death, rapid intervention to prevent permanent impairment, and other serious medical events. Other reaction consequences reported included discontinuation of omalizumab therapy and administration of medications in response to the reactions. Although some drug treatment durations were reported, in many cases this information had to be extracted from the narrative or calculated by subtracting the drug start date (when available) from the reaction event date.

Categorization of Reactions

Reaction descriptor terms from the Medical Dictionary for Regulatory Activities (MedDRA)¹⁰ are used by the FDA to abstract reactions. To characterize key organ system components that can occur in anaphylaxis based on the 2005 expert panel on anaphylaxis,¹¹ various system reaction terms were queried. Skin and mucosal MedDRA terms considered to possibly relate to anaphylaxis included *throat swelling*, *lip edema*, *larygoedema*, *angioedema*, *lip swelling*, *swelling face*, *eye swelling*, *eyelid swelling*, *tongue edema*, *pharyngeal edema*, *swollen tongue*, *flushing*, and *urticaria* (excluding the chronic type). Respiratory MedDRA terms considered to indicate possible respiratory compromise included *dyspnoea*, *wheezing*, *bronchospasm*, *bronchoconstriction*, *stridor*, *asthma*, and *status asthmaticus*. The MedDRA terms considered to indicate possible cardiac involvement include *hypotension*, *syncope*, and *blood pressure decreased* (diastolic or systolic). The MedDRA terms considered to indicate possible gastrointestinal involvement included *abdominal pain*, *diarrhea*, and *vomiting*. We characterized omalizumab-associated reaction reports consisting of 2 or more systems as having multisystem reactions consistent with anaphylaxis because omalizumab can be regarded as a possible allergen based on the 2005 expert symposium criteria.¹¹ Deidentified image files with narratives by the reporter(s) were obtained from the FDA if they were consistent with anaphylaxis (as described previously) or involved the MedDRA terms *anaphylactic reaction*, *anaphylactic shock*, or *anaphylactoid*. Cases were then reviewed for descriptions relating to omalizumab administration details, anaphylaxis manifestations, treatments, and other outcomes. To simplify the terms, cases involving 2 or more systems without MedDRA anaphylaxis descriptor terms are henceforth termed *multisystem allergy*, and cases with MedDRA anaphylactic descriptor terms are termed *MedDRA anaphylaxis*.

RESULTS

There were 86 new cases with MedDRA descriptors of anaphylaxis (MedDRA anaphylaxis) and 35 additional cases that

had multisystem allergy-related MedDRA descriptors (mostly respiratory and skin or mucosal) that were consistent with anaphylaxis (multisystem allergy). One MedDRA anaphylactic case occurred in a nurse administering omalizumab and not in the patient who received it. This case was not considered in the analysis, leaving 85 new MedDRA anaphylactic cases. Of the 35 multisystem allergy cases, 2 had predominantly nonallergy features, including intestinal obstruction, herpes zoster, arthritis, fever, and cholestasis. The remaining 33 cases were believed to be consistent with anaphylaxis and were characterized further. Two MedDRA anaphylactic cases were reports requested by the FDA based on publications. Two cases (1 in each category) were reported by omalizumab trial investigators. The most common reporter countries were the United States followed by Switzerland. There were no reports of death. Some of the clinical and demographic characteristics of the MedDRA anaphylactic cases and the multisystem allergy cases are given in Table 1. Allergen immunotherapy was a concomitant treatment in only 2 patients (both of which were MedDRA anaphylactic cases) and was not believed to have contributed to the reactions. Omalizumab doses ranged from 150 mg every 2 weeks to 600 mg every 4 weeks. There were no cases in which anaphylaxis, urticaria, mastocytosis, or angioedema was the indication for omalizumab therapy.

Multisystem Allergy Cases

Of the multisystem allergy cases, MedDRA descriptions consistent with angioedema (throat swelling, lip edema, larygoedema, angioedema, lip swelling, swelling face, eye swelling, eyelid swelling, tongue edema, pharyngeal edema, or swollen tongue) were observed in 18 cases, whereas 14 had non-chronic urticaria MedDRA descriptors. After examining the narratives and the MedDRA descriptors, skin or mucosal reaction manifestations consistent with anaphylaxis criteria were found in 27 cases. Fourteen of the multisystem allergy cases underwent emergency medical treatment with corticosteroids, epinephrine, or a combination of both with or without antihistamine use. Overall, 24 patients required hospitalization, had life-threatening reactions, required emergency medical treatment, or had omalizumab therapy discontinued or held. Twelve and 5 reactions occurred after the first and second injections, respectively. Three patients had been taking omalizumab for 1 year or longer. The time between injection and reaction onset was 1 hour or less in 6 patients, 90 to 120 minutes in 2 patients, and 6 to 7 hours in 2 patients. Nine other case-reported reactions, which did not specify hours or minutes, occurred either on the same day or the day after the injection. One patient had urticaria with the first dose and then anaphylaxis 3 months later 6 to 7 hours after injection. Another patient had recurrent flushing with each of 3 omalizumab injections.

MedDRA Anaphylactic Cases

The narratives were searched for descriptions consistent with skin or mucosal, respiratory, cardiovascular, and gastrointes-

Table 1. Clinical and Demographic Features of Patients With MedDRA Anaphylaxis and Patients With Multisystem Allergy^a

Variable	MedDRA anaphylaxis (n = 85) ^b	Multisystem allergy (n = 33) ^c
Demographic characteristics		
Female sex	65 (76)	22 (67)
Age, median, y	34	38
Reporter characteristics		
Non-health professional or consumer reporter involved in case report	23 (27)	8 (24)
Reporter country: United States	57 (67)	15 (45)
Reporter country: Switzerland	19 (22)	16 (48)
Organ system involvement		
Skin mucosal narrative descriptions or MedDRA descriptors	30 (35)	27 (82)
Respiratory or asthmatic narrative descriptions or MedDRA descriptors	30 (35)	31 (94)
Cardiovascular narrative descriptions or MedDRA descriptors	7 (8)	4 (12)
Gastrointestinal narrative descriptions or MedDRA descriptors	5 (6)	4 (12)
Onset of reaction		
After first dose	18 (21)	14 (42)
After second dose	4 (5)	5 (15)
Clinical severity or intervention		
Hospitalization or life-threatening reaction	19 (22)	16 (48)
Received corticosteroids or epinephrine	32 (38)	14 (42)
Drug discontinuation or dose held	13 (15)	3 (9)
Combined intervention: hospitalization, life-threatening reaction, received corticosteroids or epinephrine, or had dose held or drug discontinuation	53 (62)	24 (73)

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

^a Data are given as number (percentage) except where indicated otherwise.

^b Cases with MedDRA descriptors of anaphylaxis.

^c Cases involving 2 or more systems without MedDRA anaphylaxis descriptors.

tinal manifestations. Examination of the narrative and MedDRA descriptors of the MedDRA anaphylactic cases revealed multisystem allergic reaction features in 23. Thus, whereas 85 cases were MedDRA anaphylactic cases, only 23 had documented features of anaphylactic reactions on further analysis. Further analysis revealed that 32 of the MedDRA anaphylactic cases underwent emergency medical treatment with corticosteroids, epinephrine, or a combination of both with or without antihistamine use. Overall, 53 patients required hospitalization, had life-threatening reactions, required emergency medical treatment, or had omalizumab therapy discontinued or held. Eighteen and 4 reactions occurred after the first and second injections, respectively. In 2 other reports, a reaction after the first injection was suggested but could not be confirmed because of report alteration (to achieve de-identification). The interval between starting omalizumab therapy and the reaction could not be determined or was not stated in 22 patients. Eight patients had been taking omalizumab for 1 year or longer. Two of these patients had reactions either after a dose increase or after a long interval since the preceding injection. The time between injection and reaction onset was 1 hour or less in 13 patients, 90 to 120 minutes in 3 patients, and 3 to 4 hours in 3 patients. Twelve case reports of reactions did not specify minutes or hours but occurred either on the same day or the day after the injection. One patient report described repeated allergic reactions after omalizumab treatment, and another report included a Med-

DRA anaphylaxis description after a serum sickness reaction to omalizumab.

DISCUSSION

Continuing reports of MedDRA-described anaphylaxis and multisystem allergic reactions due to omalizumab underscore a clinical dilemma involving this medication. Treatments that have the potential to initiate or worsen anaphylaxis are often avoided in poorly controlled asthma because it may be difficult to distinguish exacerbations of asthma from adverse effects of the medicine, including allergen immunotherapy injections and nonselective β -blockers.¹² Omalizumab, which is indicated for the treatment of severe asthmatic patients, seems to offer a way to avoid the occasional anaphylactic reactions observed in allergen immunotherapy by globally blocking IgE. Omalizumab has been anecdotally described as being potentially useful in preventing reactions during venom immunotherapy.¹³ The fact that omalizumab seems to provoke anaphylaxis in certain patients is a counterargument for the use of omalizumab to protect against immunotherapy-associated reactions in severe or poorly controlled asthmatic patients. If an asthmatic patient experiences cutaneous, mucosal, gastrointestinal, or cardiovascular signs or symptoms with omalizumab treatment in addition to an exacerbation of asthma, systemic anaphylaxis is likely to be diagnosed. This scenario would be more likely to occur with a patient with severe or poorly controlled asthma. In addition, this is pre-

cisely the type of patient for whom omalizumab would be prescribed.

The 118 cases of MedDRA anaphylaxis and multisystem allergy in this study were reported in an 18-month period. Examination of the narratives and the nonanaphylaxis MedDRA descriptor terms showed documented features consistent with anaphylaxis in 56 patients (23 MedDRA anaphylactic cases plus 33 multisystem allergy cases), which calculates to a case rate of 3.1 new case reports per month. This compares with the 124 cases of anaphylaxis reported during a 4-year period (2.6 new case reports per month) by the FDA investigators.² The FDA investigators estimated that at least 2 of 1,000 omalizumab-treated patients develop anaphylaxis.² This prevalence is similar to the systemic reaction rate associated with allergen immunotherapy injections of 2.5 per 1,000.¹⁴ We believe that with a comparable new case report rate as that reported by the FDA investigators, this supports the notion that omalizumab-associated anaphylaxis is a continuing phenomenon.

It may be argued that some patients were improperly described as having anaphylaxis because the components of anaphylaxis were not listed in addition to the umbrella descriptor *anaphylaxis*. However, the use of anaphylaxis as a single descriptor does not necessarily indicate improper reporting. Instruction on the selection of reaction descriptors dictate that it is appropriate to choose a term for the diagnosis and not for the signs and symptoms¹⁵ based on the Primary System Organ Class Allocation principle. Thus, a case with anaphylaxis calls for a single descriptor, as described in a given example¹⁴: if “anaphylactic reaction” is reported with rash, dyspnea, hypotension, and laryngospasm, selecting “anaphylactic reaction” alone is considered appropriate. It would be much more informative if abstractors for this example used 4 MedDRA terms (*rash*, *dyspnea*, *hypotension*, and *laryngospasm*) in addition to the umbrella term *anaphylaxis*. Thus, although some cases were described as anaphylactic reactions, the narrative demonstrated a lack of detail to support the diagnosis of anaphylaxis. This may be the result of a combination of questionable MedDRA categorization and lack of narrative detail.

Although a higher proportion of multisystem allergy reaction cases had reported outcomes of hospitalization or life-threatening reactions compared with MedDRA anaphylactic cases, further examining the narratives revealed a smaller difference in serious outcomes (Table 1) as defined by a composite of antiallergic emergency medical treatment, omalizumab therapy discontinuation, or reporting of defined outcomes of hospital admission or prolonged stay and life-threatening reactions. The data, nevertheless, raised questions about the adequacy of the categorizations used in the FDA adverse reporting forms in terms of capturing bona fide anaphylaxis cases and characterizing outcomes.

Adverse outcomes, which are sometimes used to evaluate the efficacy of new antiasthma medications, include hospital visits and admissions and unplanned medical encounters. If

serious reactions occur often, these adverse outcomes may result, and the net benefits of medications on these variables may be diminished for the population at risk. Thus, it may be reasonable to recalculate the risks to benefits and the economic consequences after taking into account the continuing reactions observed with omalizumab therapy.⁴

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