# An Update On: The Observed Incidence of Anaphylaxis and Serum Sickness in Patients Receiving Omalizumab in a Tertiary Allergy and Asthma Clinic in Canada

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## Abstract

Background

In a post-marketing analysis last updated in July 2007, the FDA reported that an estimated 0.2% of patients suffered treatment related anaphylaxis and rare incidence of serum sickness. To substantiate this rate, we assessed the occurrence of treatment related anaphylaxis and serum sickness in our large Canadian allergy and asthma tertiary clinic.

Methods

We performed a retrospective chart review of our entire database of omalizumab administration in patients between 2005 and 2017.

Results

The FDA defined treatment related anaphylaxis as the development of bronchospasm, hypotension, syncope, urticaria, chest tightness, generalized pruritus, and/or angioedema post injection. They reported 51% of anaphylactic incidents occurred between 0-60 minutes of injection, 8% occurred between 60-120 minutes of injection, and 41% occurred more than 120 minutes of injection.

During our post market experience, between 2005-2017, our clinic administered 49,776 injections of omalizumab to 434 patients (147 males & 287 females) over the course of 1498 patient-years and no cases of anaphylaxis or serum sickness like symptoms were observed.

Conclusions

Meticulous care is taken by our omalizumab administration clinic to ensure optimal safety based on the emphasized warnings of anaphylaxis and indicated warnings and precautions for serum sickness. Data collected in this analysis observed no cases of anaphylaxis or serum sickness like symptoms in the treatment of 434 patients who received a combined total of 49,776 injections of Omalizumab. Thus healthcare professionals should have more confidence in treating patients with omalizumab based on the rare occurrence of anaphylaxis and serum sickness.

## Introduction

Omalizumab is currently indicated for patient's diagnosed with moderate to severe persistent Allergic Asthma and Chronic Idiopathic Urticaria.

-For a diagnosis of allergic asthma to be deduced, patients must test positive for perennial or seasonal allergen sensitivities and have an elevated serum Immunoglobulin E (IgE). Allergic asthmatics have respiratory inflammation, mucus production, and bronchial constriction associated with exposure to allergens . Patients will often suffer from allergic rhinitis, conjunctivitis and sinusitis in addition to wheezing, coughing, shortness of breath, and chest tightness.

-For a diagnosis of Chronic Idiopathic Urticaria to be deduced, patient's must experience persistent or episodic itching, swelling, and /or hives for at least 6 weeks and remain symptomatic despite high doses of H1 antihistamine treatment.

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptors on the surface of mast cells and basophils thus causing a reduction in surface bound IgE. This results in a decreased level of released mediators that cause the allergic response. Considered an anti-IgE therapy, omalizumab therefore decreases the patient's symptoms and thus their required controller medications; it also improves their quality of life.

## Rationale

Omalizumab has been given a boxed warning by the FDA due to a risk of anaphylaxis, it reads as follows:

> **WARNING**
>
> Anaphylaxis, presenting as angioedema of the throat or tongue, bronchospasm, hypotension, syncope, urticaria, and/or urticaria has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair administration, and health case providers administering Xolair should be prepared to manage anaphylaxis that can be life threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur.

The FDA (2011) reports the criteria for Boxed Warnings as follows:

- A boxed warning ordinarily used to highlight for prescribers one of the following situations:

There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug.

OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in specific manner, avoiding use in a specific clinical situation)

OR

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).

**Omalizumab has been approved for use in more than 90 countries. The US and Canada are the only countries with an emphasized warning (the boxed warning) for omalizumab associated anaphylaxis.**

The Omalizumab Joint Task Force in 2007 recommended that patients wait 2 hours post injection after their first three omalizumab dosings, and for 30 minutes of all subsequent doses. Also recommended was that patients be prescribed, carry, and be educated on proper use of an epinephrine auto-injector for the first 24 hours after each injection.

### Varying Definitions for Interpretation

**Genentech relies on spontaneous reporting of anaphylaxis cases – these reports can come from any source and as stated in the 2010 omalizumab prescriber information "these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."**

**Genentech, Inc. Prescribing Information Definition (2010):**

**"Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms of anaphylaxis include:**

**- wheezing, short of breath, cough, chest tightness or trouble breathing**
**- Low blood pressure, dizziness, fainting, rapid or weak heart beat, anxiety, or feeling of "impending doom"**
**- Flushing, itching, hives, or feeling warm**
**- Swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing**
**Get emergency medical treatment right away if you have signs or symptoms of anaphylaxis after receiving Xolair."**

**Simons et al. (2011):**

"Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following : A) Respiratory compromise (e.g., dyspnea, wheeze -bronchospasm, stridor, reduced peak expiratory function (PEF), hypoxemia) B) reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) **OR**
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): A) involvement of the skin -mucosal tissue (e.g., generalized hives, itch-flush, swollen lips/tongue/uvula) B) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) C) Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) D) Persistent gastrointestinal symptoms (e.g., cramping abdominal pain, vomiting) **OR**
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): A) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic blood pressure B) Adults: systolic BP of less than 90mm HG or greater than 30% decrease from that person's baseline"

### The Omalizumab Joint Task Force

A Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology formed the Omalizumab Joint Task Force (OJTF) with the purpose of reviewing omalizumab related data up until it's founding in 2007.

The OJTF's first report focused on post marketing data from June 2003 to December 2006. After careful review it was found that anaphylaxis likely only occurred in approximately 0.09% of patients receiving omalizumab injections, which was less than half the original number reported (0.2%) by the FDA for that time period.

A second review was conducted reviewing cases from January 1, 2006 to December 31, 2008. Reviewed were 127 post marketing cases of possible omalizumab-associated anaphylaxis filed with the FDA. Reviewers found only 77 of the 127 cases to be probably or likely Omalizumab-associated anaphylaxis. This indicates that only 60% of anaphylaxis cases could be "probably" linked to omalizumab. The OJTF went on to describe that there were many difficulties in being certain that an adverse event was truly anaphylaxis even though a widely accepted consensus definition for anaphylaxis was used to interpret the adverse event reports. The OJTF also indicates there was a wide variation in interpretation of some events with a trend toward being conservative. This makes it highly likely that there was over-reporting of anaphylactic episodes.

Many events reported wheezing several hours after the injection and a sensation of warmth or mild flushing (without pruritus). The reality is that some of these events might have been due to other problems, such as the patients' underlying poorly controlled asthma, which is , in fact, the indication of omalizumab treatment. It is difficult to ascertain how many of the remaining 60% of cases had an acute asthma exacerbation or an anaphylactic episode.

### Serum Sickness

Genentech describes serum sickness like syndrome to be the constellation of the following sign and symptoms as similar to those seen in patients with serum sickness. The symptoms include: arthritis/arthralgia, rash, fever and lymphadenopathy. These symptoms can have an onset within 1 to 5 days after the first or subsequent injections of omalizumab.

In 2003, using the definition for serum sickness like syndrome, Genentech reported 3 study subjects and one control subject who developed the symptoms. In all 3 study subjects, the symptoms resolved despite continuation of treatment with omalizumab. Genentech commented that, due to the continuation of treatment and the resolution of symptoms, this suggests the serum sickness like events may have little clinical meaning.

There have been no recent cases reported and the last reported case of serum sickness like symptoms associated with treatment with omalizumab was in 2007.

## Methods

The FDA defined treatment related anaphylaxis as the development of bronchospasm, hypotension, syncope, urticaria, chest tightness, generalized pruritus, and/or angioedema post injection. In the FDA report 51% of anaphylactic incidents occurred between 0 – 60 minutes of injection, 8% occurred between 60 – 120 minutes of injection and 41% occurred more than 120 minutes of injection.

Meticulous care is taken by our omalizumab administration clinic by incorporating the OJTF recommendations as well as, the product monographs indicated warnings and precautions for serum sickness :

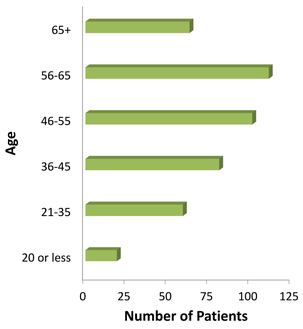
-At Yang Medicine we ensure patients are well educated about the potential benefits, mechanisms of action, dosing, expected time of effectiveness, efficacy, duration of treatment and rare adverse events such as serum sickness like symptoms associated with omalizumab, as well as stressing knowledge of signs and symptoms of anaphylaxis, emergency planning and epinephrine auto-injector use.

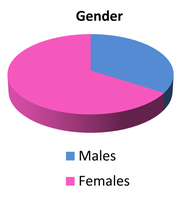
- Regular review of patient medications to ensure there are no beta-blockers (as they interfere with rescue epinephrine), and that patients are compliant with their medication regime and are on appropriate medications.

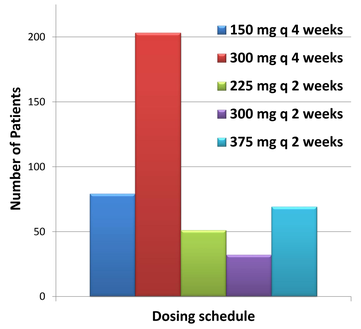
- Patient health is monitored regularly by health assessments at each injection visit depending on dosing schedule..

- Omalizumab is only administered by licensed health care professionals who are trained in the recognition and treatment of anaphylaxis. Appropriate medications and equipment to treat an episode of anaphylaxis are available and kept up-to-date.

This ensures optimal safety based on the emphasized warnings of anaphylaxis and possible serum sickness. Retrospective statistics of our 434 patients who received treatment with omalizumab between 2005- June 2017are represented in the following charts:




## Results

### Comparison of Anaphylaxis Incidence

Omalizumab Clinical Trial Experience

3 of 3854 patients who received omalizumab had reported cases of anaphylaxis (<0.1%). All occurrences were between 1 and 2 hours post injection with no other identifiable allergic triggers.

Post Marketing Cases

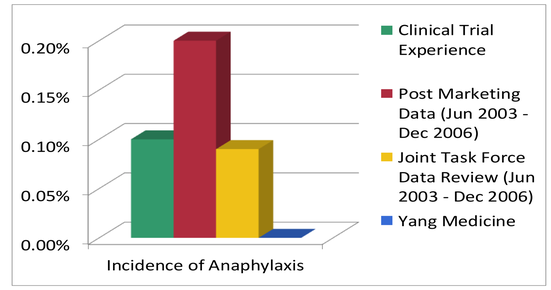
Based on a review of 124 spontaneous case reports of 57,300 patients between June 2003 and December 2006 a frequency of anaphylaxis was estimated to be 0.2% of patients.

OJTF

After reviewing the FDA data from June 2003 and December 2006, the OJFT found the probable frequency of anaphylaxis was only 0.09% of patients.

Yang Medicine

With our post marketing experience, between 2005 and June 2017, our clinic administered almost 50,000 injections of omalizumab to more than 200 patients and experienced no cases of anaphylaxis.




### Time of Onset to Anaphylaxis

Adverse reactions are reported voluntarily, the actual frequency of anaphylaxis and percent of patients with onset during specific time periods after administration of omalizumab may differ from these estimates and this case series. The FDA post marketing report from June 2003 – Dec 2006 concluded 51% of anaphylactic incidents occurred between 0-60 minutes of injection, 8% occurred between 60-120 minutes of injection and 41% occurred more than 120 minutes of injection.

| | 0-60 minutes | 60-120 minutes | > 120 minutes |
|---|---|---|---|
| Clinical Trial Experience | 0% | 100% | 0% |
| Post Marketing Data | 51% | 8% | 41% |
| Yang Medicine | 0% | 0% | 0% |

### Serum Sickness

There have been no cases of serum sickness like symptoms at Yang medicine from 2005 to June 2017.

## Conclusion

Data collected in the analysis of Yang Medicine observed NO cases of anaphylaxis or serum sickness like symptoms in the treatment of 434 patients during a period of 12 years, who combined received over 49,776 injections of omalizumab thus confirming the low incidence of both anaphylaxis and serum sickness.

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