Omalizumab: indications for allergic disease other than asthma

John Mason Rohrs
The University of Toledo
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Dedication

I dedicate this project first of all to my wife, who has been there for me since I began the PA program at UT. Being a full-time student has been a trial to our new marriage because of time spent away from her. Nevertheless, she has been the one who has motivated me not to give up despite the challenges of a demanding graduate program. I also dedicate this project to my parents, who have not only given me financial support for my education, but also their loving guidance and spiritual foundation. Lastly, this project is dedicated to the many patients like myself who suffer with asthma and allergies, and to the clinicians who treat them.
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Introduction

Background and Identification of the Problem

Allergic disorders affect millions of people worldwide. Though rarely life-threatening, allergies can severely affect one’s quality of life. With modern technology and newer treatments being released, it may be possible for those suffering from allergies to achieve better symptom control, even when traditional treatments no longer work or produce marginal relief at best. Omalizumab, a recombinant DNA-derived humanized IgG1x monoclonal antibody that selectively binds to immunoglobulin E (IgE), is a newer injectable drug for the treatment of moderate-to-severe persistent asthma that is refractory to inhaled corticosteroids. Because IgE is a common factor in other types of allergic reactions, treatment focusing on IgE may play a vital role not only in allergic asthma, but also in other allergic manifestations. It makes sense that omalizumab could be useful in treating other allergic disorders, especially those that are concomitant with asthma and poorly controlled with other forms of treatment.

Problem statement

According to the manufacturer, omalizumab (Xolair) is only indicated for patients with moderate-to-severe persistent asthma due to perennial air-borne allergens, determined either by exposure in vitro or from skin testing, and whose symptoms are poorly controlled with inhaled corticosteroids. What are its applications, if any, in other types of allergic conditions, since IgE mediates allergic responses besides asthma? If this drug is in fact effective in treating other allergic conditions that are difficult to manage with traditional therapies, clinicians and patients should be made more aware of this drug and its potential applications.
Purpose

The purpose of this study is to examine the drug omalizumab, how it works, and current indications for its use. This study will also examine research regarding other allergic conditions that may benefit from omalizumab’s ability to block IgE. Other issues, such as potential side effects of the medication, cost considerations, and barriers to usage will also be discussed.

Research Question and Hypothesis

This study asks the question of whether or not there is current, accepted use of omalizumab in the treatment of other allergic conditions besides asthma. What off-label indications, if any, are there for omalizumab? Since IgE plays a key role in mediating different allergic disease states other than asthma, one could assume omalizumab would be an effective treatment for those conditions and should therefore be utilized.

Scope

This study shall focus on literature from reviewed scholarly and clinical journals published in 2001 through July 2007. The literature cited will include epidemiological statistics of asthma and allergic disorders, traditional treatments of asthma and other allergic disorders, studies of omalizumab’s efficacy in treating asthma, and whether or not omalizumab has demonstrated efficacy in alleviating symptoms of allergic conditions besides asthma.

Summary

Utilizing data and literature from 2001 through July 2007, this study shall examine the drug omalizumab and its mechanism of action. To understand omalizumab’s role in inhibiting
the IgE-mediated allergic response, the pathogenesis of that response shall be examined. Since 
IgE does play a role in other allergic manifestations such as allergic rhinitis, ocular allergy, 
atopic dermatitis, and food allergy, omalizumab may be a treatment for these conditions in 
addition to allergic asthma. Traditional treatments are briefly described for each allergic 
manifestation, and research of the use of omalizumab in these manifestations will also be 
described.
Literature Review

*Impact of Allergic Diseases*

Allergic disorders such as asthma, allergic rhinitis, and atopic dermatitis affect millions of people worldwide, especially as the prevalence of these disorders has increased over the last thirty years (Fendrick & Baldwin, 2001). Specifically, between 1% and 20% of children and young adults have asthma; 20% of all individuals suffer from allergic rhinitis, and about 7% have atopic dermatitis (Fendrick & Baldwin). Asthma has not only become more prevalent; it has also become more severe (Fendrick & Baldwin). In both wealthy and third-world countries, there has been an increase of the prevalence of asthma and allergy in children (Milgrom, 2002). Allergic disorders are among the most chronic diseases in developed countries, and particularly within the U.S., they are a leading contributor of outpatient, inpatient, and emergency department utilization (Fendrick & Baldwin). With atopic dermatitis, 10% to 15% of children are affected and the incidence is increasing; it is the most common allergic condition first seen in children (Fendrick & Baldwin). Allergies and asthma are a significant cause of morbidity in patients, and they significantly impact the quality of life in these individuals in the areas of physical, psychological, and social well-being (Fendrick & Baldwin). Traditional treatments often help patients with allergies, but in some instances, the relief is not sufficient. The patient’s productivity is impacted while other acute problems may arise as the result of poorly controlled symptoms (Fendrick & Baldwin). As of 1999, direct health care costs due to allergic rhinitis alone exceed $6 billion annually in the United States (Mankad & Burks, 2005). In 1998, asthma was estimated to cost $12.7 billion (Weiss & Sullivan, 2001). An understanding of allergic diseases and their common components is not only important for reducing costs of healthcare utilization, but also for treating these patients, thus improving the quality of their lives.
In asthma and other allergic diseases, Immunoglobulin E (IgE) plays an important role in mediating the allergic response (Owen, 2007). Many of these diseases are often concomitant, run in families, and may frequently be seen in the same individual because of elevated serum levels of IgE (Gern & Busse, 2003). There appears to be some sort of genetic predisposition to form IgE to airborne allergenic proteins (Storms, 2002). IgE levels seem to also correlate with allergy severity. At any age, those with asthma tend to have increased total IgE levels regardless of their level of allergen sensitization (Storms). Children whose serum levels of IgE are elevated before one year of age will continue to have elevated IgE levels at six and eleven years of age (Milgrom, 2002).

In the allergic mechanism of sensitization, an allergen enters the body, most commonly by inhalation, ingestion, or through skin contact. Common allergens include dust mites, pollens, molds, spores, and insect and animal dander (Fendrick & Baldwin, 2001). The onset of asthmatic symptoms is related to the sensitization of these few allergens (Milgrom, 2002). The concentration and degree of exposure to these allergens determines how quickly and how severe a reaction will be. For example, the concentration of dust mites in a given area affects the onset of wheezing (Milgrom). Studies have shown that exposure to dust mites at concentrations between 2 mcg/g and 10 mcg/g increases one’s risk of sensitization and development of asthma symptoms (Storms, 2002). These allergens are recognized as “foreign” by the immune system and bind to antigen-presenting cells as well as to Immunoglobulin M (IgM) receptors on the surface of resting B-lymphocytes. The antigen-presenting cell then activates a helper-T-lymphocyte (Gern & Busse, 2003). The T-cell releases mediators to activate the B-cells, which in turn become immunoglobulin-secreting plasma cells. The IgM receptors undergo an isotypic
shift and become Immunoglobulin E (IgE), which will now recognize and bind the specific allergen first introduced (Gern & Busse). The IgE antibodies bind to FcεRI receptors, which are receptors with high affinity for IgE. FcεRI receptors are found on many different cells but specifically on the mast cell, which plays a key role in the allergic response. When exposed to the allergen, IgE cross-links the mast cell and the antigen. If the allergen cross-links two adjacent IgE molecules, the mast cell releases mediators of inflammation, which include histamine, cytokines, leukotrienes, and prostaglandins. These mediators are responsible for the common symptoms of allergic reactions in whatever body tissue the allergen contacts (Chiang, Clark, & Casale, 2005). For instance, the rhinorrhea and itchy eyes of allergic rhinoconjunctivitis result from allergen contact within the nasal and ocular mucosa. IgE is responsible in the early phase allergic response, or Type 1 hypersensitivity reaction, which takes only minutes to occur. In asthma, IgE may even play a role in the late phase reaction, which occurs two or more hours after inhalation of an allergen in which the airways become more inflamed and reactive to stimuli other than the original allergen. This may be due to continued allergen inhalation causing the release of additional inflammatory mediators (Fendrick & Baldwin).

*Traditional Treatment of Allergic Asthma*

The most effective method to treat allergies is to eliminate the causative allergens and prevent future exposure to them. However, to completely remove all the allergens to which one may be exposed on a daily basis is difficult and nearly impossible; patients may continue to be exposed to minute amounts of allergens or have occasional or accidental contact (Gern & Busse, 2003). Therefore, other means of treatment must be implemented to symptomatically treat the patient as well as prevent future exacerbations. In the case of asthma, the goal is to restore
normal activity and lung function, to prevent acute and chronic symptoms, and to prevent side effects from asthma medication (Gern & Busse). All asthma patients receive a $\beta_2$ agonist bronchodilator, such as albuterol, for quick relief of asthma exacerbations. For patients characterized as having mild intermittent symptoms, a bronchodilator is often all that is necessary for treatment (Gern & Busse). If the patient has mild persistent asthma with the patient reporting symptoms more than two times a week but less than once daily, and the symptoms occasionally interfere with normal activities or disturb sleep, there is often some lower airway inflammation, even though PEF or FEV$_1$ may be normal. The treatment in this case may involve low-dose inhaled corticosteroids, leukotriene receptor antagonists (zafrirlukast [Accolate] or montelukast [Singulair]), oral theophylline, cromolyn sodium, or nedocromil sodium (Gern & Busse). If a patient has daily symptoms or they occur more than one night a week with the PEF and FEV$_1$ showing signs of obstruction (>60% to <80%), this is moderate persistent asthma. The preferred treatment is to combine low to medium dose inhaled corticosteroids with a long acting $\beta_2$-agonist, as found in the inhalation device Advair (fluticasone/salmeterol). Leukotriene modifiers or oral theophylline can also be used (Gern & Busse). Patients with severe persistent asthma require more aggressive therapy. These patients will often have exacerbations along with daily wheezing, histories of frequent hospitalizations, limited physical activity, and frequent awakening at night. To treat these patients, a high-dose corticosteroid inhaler is used along with intermittent or daily doses of oral corticosteroids. Multiple concomitant therapies are frequently used with the inhaled steroids, such as long acting bronchodilators, theophylline, or leukotriene antagonists (Gern & Busse). Allergen immunotherapy, whereby an individual is exposed to minute amounts of allergen in order to become desensitized to that allergen, is also an effective treatment for allergic asthma and allergic rhinitis (Milgrom, 2002). Clinical trials have shown
how immunotherapy improves the quality of life in patients with asthma while decreasing medication use, especially in children. Of those children who received immunotherapy for dust mites, 75.4% had no new sensitizations in six years, whereby only 33.3% of children who were only taking medication had no new sensitizations in the same period (Panjo, Barberio, De Luca, Morabito, & Parmiani, 2001). Immunotherapy may even prevent the progression of allergic disease, including allergic asthma, as well as the sensitization to other allergens. Immunotherapy does, however, require a long course of treatment and may even produce an allergic reaction by itself (Milgrom).

**Omalizumab in the Treatment of Allergic Diseases**

**Omalizumab in the Treatment of Asthma**

One of the most recent treatments for asthma is omalizumab (Xolair). According to the manufacturer and the FDA, omalizumab is indicated for adults and adolescents (12 years and older) with moderate-to-severe persistent asthma who react positively to airborne allergens either by skin test or *in vitro* and whose symptoms are inadequately controlled with inhaled corticosteroids (Genetech, 2006). Omalizumab (Xolair) works differently from other forms of treatment in that it directly binds free IgE in the serum and interstitium (Soresi & Togias, 2006), thus inhibiting the binding of IgE to the high-affinity IgE receptor (FCεRI) on the surface of mast cells and basophils (Busse et al., 2001). This reduces the amount of free serum IgE by more than 95% in patients with allergic asthma, leading to reduction in the amount of allergic response mediators released (Busse et al.). The usual route of administration is via subcutaneous injection. However, when given intravenously at two to four times the usual dose (0.016mg/kg per IU/mL), omalizumab reduced the level of free serum IgE by an average of 99%; thus, the
benefit of a low IgE level is reduced asthmatic symptoms (Soresi & Togias). Omalizumab also reduces the number of FCεRI receptors on basophils (Genetech). While inhaled corticosteroids are effective at reducing inflammation, they have predictable side effects that are of concern, especially at higher doses. Omalizumab offers an advantage over inhaled corticosteroids because it does not have any steroid-associated side effects. Since omalizumab directly blocks IgE-mediated effects and prevents mediator release in the allergic cascade, inflammation is not only suppressed, but also prevented (Busse et al.).

In clinical trials of omalizumab, its safety and efficacy were tested in three randomized, placebo-controlled, double blind studies. Patients ages 12 to 76 participated in the study. They each had a history of moderate to severe persistent asthma for at least one year and had a positive skin test to a seasonal allergen. Patients in Studies 1 and 2 had an FEV₁ between 40% and 80%, while in the third study the FEV₁ was not utilized in the screening. All patients were using inhaled corticosteroids (beclomethasone in Studies 1 and 2) and β₂-agonists. In Study 3, patients were receiving doses of 1000 mcg/day fluticasone propionate (Flovent) and long acting beta-agonists, while a smaller number in that group were also on oral corticosteroids. The amount of omalizumab or placebo received was based on baseline serum IgE concentrations and body weight. Patients’ IgE levels needed to be between 30 and 700 IU/mL, with body weight not over 150 kg. The patients were to receive at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo. In all groups, the subjects received either placebo or omalizumab every two weeks or every four weeks for 16 weeks with no change in inhaled corticosteroids unless needed for exacerbations. Next, the patients began to reduce their levels of inhaled and oral corticosteroids in a stepwise manner over the subsequent 12 weeks in Studies 1 and 2, and over 16 weeks, in Study 3. The number of exacerbations was then analyzed for each group. An exacerbation was
defined as a worsening of asthma symptoms that required treatment with oral corticosteroids or a
doubling of the inhaled corticosteroid. In Studies 1 and 2, there were fewer exacerbations among
those taking omalizumab versus those taking placebo in both phases (stable steroid phase and
reduction steroid phase), while there was not a significant difference between groups receiving
placebo or omalizumab in Study 3. This may have been due to a smaller sample size, differences
in patient population, or other unidentified factors (Genetech, 2006).

Multiple studies have also demonstrated omalizumab’s ability to reduce exacerbations in
patients with moderate to severe asthma. Busse et al. (2001) studied 525 patients age 12 to 75 on
inhaled corticosteroids but still symptomatic. Inclusion requirements for the participants were a
diagnosis of asthma for more than a year, a positive skin test to an aeroallergen, total serum IgE
between 30 IU/mL and 700 IU/mL, and taking 420 to 840 mcg/day of beclamethasone.
Participants received injections of either placebo or omalizumab every two or every four weeks,
based on weight and serum IgE concentrations. The participants received the injections over 16
weeks while maintaining steady doses of inhaled corticosteroid. Then after the initial 16 weeks,
the dosages of inhaled corticosteroid were reduced over a subsequent 12-week period. Patients
receiving omalizumab experienced fewer exacerbations of asthma than those receiving placebo
(0.28 vs. 0.54 exacerbations per subject), and furthermore, a lower number of patients
experienced exacerbations versus the placebo group (Busse et al.). In addition to exacerbation
reduction and allowing patients to decrease their doses of inhaled corticosteroids, omalizumab
has also been reported to reduce the need for unscheduled outpatient visits, emergency
department visits, and hospitalizations (Spector, 2004).
Omalizumab in the Treatment of Allergic Rhinitis

Allergic rhinitis is a condition that has also benefited from omalizumab, although this is considered an off-label indication. Allergic rhinitis and asthma are often concomitant in a patient, as patients with asthma often report symptoms of allergic rhino-conjunctivitis. Current treatments for allergic rhinitis include allergen avoidance, topical and systemic corticosteroids, antihistamines, chromones (cromolyn sodium and nedocromil sodium), and immunotherapy (Casale et al., 2001). Some of the medications that are helpful in allergic rhinitis are also helpful in reducing asthma exacerbations, further proving their interrelated nature (Spector, 2004). One study by Casale et al. selected 536 patients for a randomized, double-blind, dose-ranging, placebo-controlled study. Participants each had at least a two-year history of moderate-to-severe ragweed-induced seasonal allergic rhinitis and a baseline IgE level between 30 and 700 IU/mL. Patients randomly received either 50 mg, 150 mg, or 300 mg of omalizumab or placebo subcutaneously. Subjects began the treatments just before the start of ragweed season and continued receiving injections throughout the pollen season for twelve weeks. Those participants with an IgE level of 30 to 150 IU/mL received injections every four weeks, while subjects with an IgE level of 151 to 700 IU/mL received treatments every three weeks. Participants receiving 300 mg of omalizumab reported less daily use of rescue antihistamines, less daily severity and duration of nasal and ocular symptoms, and higher quality-of-life scores, compared to those who received placebo. Adverse effects were similar between those of the placebo group and those receiving omalizumab (Casale et al.).

In a similar study, it was reported that omalizumab was effective in seasonal allergic rhinitis caused by Japanese cedar pollen. One-hundred patients in the study were ages 20 to 64, shared at least a two-year history of seasonal allergic rhinitis caused by Japanese cedar pollen
and reported four out of eight symptoms of moderate-to-severe quality (sneezing, itchy nose, runny nose, stuffy nose, watery eyes, red eyes, itchy eyes, and itchy throat). The duration of these symptoms was one or more weeks in the previous pollen season. They each had the presence of IgE specific to Japanese cedar pollen as determined by skin test, baseline serum levels of IgE of 30 to 700 IU/ml, and baseline body weights of 30 to 150 kg. Following the initial four-week screening period, patients were given either placebo or omalizumab (150, 225, 300, or 375 mg) at a 1:1 ratio every two or four weeks for 12 weeks. This study demonstrated that the daily nasal severity score and daily medication usage for ocular symptoms were less in patients who received omalizumab versus patients who received placebo. Although patients who received omalizumab reported higher levels of injection site reactions, other adverse reactions were similar between the two groups (Okubo, Ogino, Nagakura, & Ishikawa, 2006).

Additional studies have demonstrated similar outcomes with omalizumab in treating allergic rhinitis. Chervinsky et al. (2003) found omalizumab to be well-tolerated and effective in a study involving two hundred eighty-nine patients whose ages were between 12 and 70 years. They all had moderate-to-severe symptomatic perennial allergic rhinitis. They received either omalizumab or placebo over a period of 16 weeks. The average daily nasal severity scores improved significantly for 69% of the subjects who had been on omalizumab, and they also reported less daily use of antihistamines (Chervinsky et al.). Overall, the patients in these studies report a decrease in usage of traditional medicines for allergic rhinitis symptoms while on omalizumab as well as improved quality of life, therefore showing that omalizumab is effective treatment for both seasonal and perennial allergic rhinitis (Berger, 2006).
Omalizumab in the Treatment of Ocular Allergy

Typical treatments of ocular allergy start with avoidance of allergens, cool compresses and lubrication, but also topical decongestants, topical and oral antihistamines, nedocromil, mast-cell stabilizing agents, topical corticosteroids and immunotherapy (Bielory, 2002). The occurrence of ocular symptoms with allergic rhinitis often allows health care providers to use the same treatments for both conditions because of the IgE-mediated response (Bielory). According to Williams & Sheppard (2005), there was a small study in which six patients with ocular allergy were treated with omalizumab. Their symptoms and IgE levels were severe enough to warrant oral or topical steroid usage. According to FDA dosing standards for asthmatic patients, these patients were given appropriate amounts of omalizumab at intervals of two or four weeks based on their IgE levels and weight. Baseline and interval symptoms were evaluated, with the patients rating severity of asthma symptoms, eczema, itchy or watery eyes, hives, sneezing, or cough. All six patients showed improvements in ocular symptoms, five reported lower levels of topical steroid use, four had improved asthma symptoms, four reported less complaints of allergic rhinitis, and three had improved eczema symptoms (Williams & Sheppard).

Omalizumab in the Treatment of Atopic Dermatitis

Atopic dermatitis is another condition that may benefit from omalizumab. Like other allergic disorders, atopic dermatitis does not often respond to just one form of treatment but is often much more difficult to treat (Lane, Cheyney, Lane, Kent, & Cohen, 2006). Also for many, it is one of the more frustrating conditions to live with due to the severe pruritis with continual scratching, leading to sleep disturbances (Lane et al.). Traditional therapies include topical
steroids, bland emollients, topical tacrolimus (Protopic), systemic corticosteroids, sedating and non-sedating antihistamines, leukotriene inhibitors, antibiotics, and cyclosporine (Lane et al.).

Studies regarding treatment of atopic dermatitis with omalizumab are few and with mixed results. In one study, three pediatric patients with unremitting atopic dermatitis were treated with omalizumab. Their IgE levels were greater than 700 IU/ml, as are many patients with atopic dermatitis. One patient started out with 300 mg of omalizumab, while the other two began with 150 mg. They received their injections every two weeks for 24 weeks, varying the amount of omalizumab, depending on severity of symptoms. The participants reported marked improvement in their symptoms (Lane et al., 2006). A more recent case study also demonstrates success with omalizumab in treatment of atopic dermatitis. Although the report only involved one patient, omalizumab proved effective in relieving his symptoms. The patient’s IgE level was 7340 IU/mL, and he had tried topical corticosteroids, pimecrolimus (Elidel), oral prednisone, antihistamines, azathioprine (an immunosuppressant), and narrowband UV light therapy. The patient only reported relief of symptoms with use of the oral corticosteroids. Despite his high level of IgE, he was placed on a 12-week course of omalizumab, to which he responded favorably. Not only did his symptoms improve with omalizumab, he did not report any adverse reactions during the course of treatment (Forman & Garrett, 2007). However, another study reported that omalizumab failed to improve atopic lichenified dermatitis in three adult patients. They received 450 mg of omalizumab every two weeks for four months. Unfortunately, none of the patients in this study reported an improvement in conditions (Krathen & Hsu, 2005). This may be due to the fact that patients with atopic dermatitis have extremely high levels of IgE, (above 1990 IU/ml) (Graves, Nunley, & Heffernan, 2007). Given these conflicting results and
not to mention extremely small sample sizes, further research with omalizumab is therefore warranted in the treatment of atopic dermatitis.

**Omalizumab in the Treatment of Food Allergy**

One of the more severe allergic disorders is that of food allergy. In outpatient settings, the most common cause of anaphylaxis can be attributed to food allergy (Nowak-Wegrzyn & Sampson, 2006). There has been a tremendous increase in the incidence of food allergy in recent years, with the number among children having doubled (Nowak-Wegrzyn & Sampson). Fifty to one-hundred people die annually from peanut allergy, while 1.5 million are affected by this single allergy (Leung et al., 2003). The most common food allergens include cow’s milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish. In adults, the most common are peanuts, tree nuts, fish and shellfish. Allergic reactions can be IgE-mediated, non-IgE-mediated, cell-mediated, or mixed: IgE- and cell-mediated (Nowak-Wegrzyn & Sampson). The IgE reaction starts within minutes and can affect many systems, such as the skin with urticaria and angioedema, the respiratory tract with sneezing, congestion, rhinorrhea, dyspnea, and the gastrointestinal tract with nausea, vomiting or diarrhea. Particularly with peanut allergy, serum IgE concentrations are higher in susceptible patients compared to those who do not have allergies (Keller & Amsden, 2005). Medical management of food allergy includes avoidance, nutritional counseling, and prompt recognition and treatment of allergic reaction (Keller & Amsden). Treatment usually involves the administration of diphenhydramine and an epinephrine injection immediately followed by going to the emergency room (Keller & Amsden; Nowak-Wegrzyn & Sampson).

One study involving peanut allergy was examined with an anti-IgE antibody called
TNX-901, which works similarly to omalizumab in that it inhibits binding of IgE to both mast cells and basophils, while down-regulating the FcεRI receptors on basophils. Eighty-four subjects with a history of severe allergic reactions to peanuts were involved in a randomized, double-blind, dose-ranging trial. The participants underwent an oral food challenge test with peanut flour to first determine their threshold of reactivity. Then over the course of four months, they randomly received in 3:1 ratio either TNX-901 in 150, 300, or 450 mg or placebo every four weeks. Following this, an oral food challenge test was administered within two to four weeks. The group who received 450 mg of TNX-901 increased their sensitivity to peanut on oral food challenge from a level equivalent to half a peanut to a level equivalent to almost nine peanuts. Although the subjects of the test groups who had received the 150 mg or the 300 mg doses also increased their levels of sensitivity to peanut flour, these levels were not statistically significant compared to the placebo group. However, the trend of the increase in sensitivity for all groups was statistically significant (Leung et al., 2003).
Discussion

Further Research of Omalizumab

While omalizumab is currently approved for use in treatment of moderate-to-severe allergic asthma and its efficacy in treating asthma has been demonstrated, further research regarding its efficacy is warranted. One reason for obtaining further research is simply because omalizumab is a relatively new drug. Research is needed to see what the long-term effects are on individuals. Efficacy of omalizumab has also been demonstrated in the treatment of allergic rhinitis and food allergies. However, since these diseases are not the main conditions for which omalizumab was approved, further research in this area may allow them to be formally added as secondary indications for omalizumab therapy. Regarding ocular allergy, though there has only been one study demonstrating omalizumab’s effectiveness in treating allergic conjunctivitis, subjects in studies who were treated for allergic rhinitis also reported fewer complaints of ocular allergies. So, although it seems to work on ocular allergies because these symptoms are related to allergic rhinitis, more research involving only ocular allergies should be performed. Regarding atopic dermatitis, omalizumab should be tested in clinical trials with larger sample sizes because it has only been tested on a small number of subjects.

Other Considerations in the Use of Omalizumab

Before omalizumab can be indicated in other allergic manifestations, there are questions regarding its use in patients who have IgE levels above the indicated therapeutic window (Avila, 2006). Originally, dosing for omalizumab was based on weight and free levels of IgE, with the formula for dosing being 0.016 mg/kg per IU of baseline serum IgE concentration. However, to minimize dosing errors and to make calculation easier, the dosing regimen was converted into a
dosing table of serum IgE from 30 IU/mL to 700 IU/mL (see Appendix B) (Lanier, 2006). Since this became the standard dosing regimen on the package insert of omalizumab, those who fall outside this range face problems, mostly regarding legal and insurance issues, and are not able to potentially benefit from omalizumab (Lanier). This begs the question of whether or not there is an associated level of danger in giving omalizumab to patients with IgE levels higher than 700 IU/mL. Moreover, why can’t the original 0.016 mg/kg formula be used from which the dosing table was derived? To treat this level, patients would have to receive higher levels of the drug, which might lead to accumulation of minute amounts of endotoxin (Lanier). Even though there are no published reports of endotoxin accumulation or reactions with a more frequent dosage or larger doses at the usual frequency, treating patients with high IgE levels can be problematic. Most of the IgE in these patients is nonspecific, so larger doses may not be as efficient as it would be in patients with lower levels. Although a patient with atopic dermatitis with an IgE level of 7340 IU/mL was successfully treated with omalizumab in one case study there is no research that demonstrates positive effects of omalizumab on asthmatic and allergic patients with higher IgE levels, so this is an area that should be further explored (Forman & Garrett, 2007; Lanier).

There are issues of omalizumab’s efficacy and pharmacodynamics that have yet to be answered. For example, omalizumab’s onset of action is not exactly known, as it takes at least twelve weeks to assess efficacy in a patient, and studies need to be done to evaluate its effects after discontinuation (Strunk & Bloomberg, 2006). Even though it is more efficacious than placebo, its benefit with newer inhaled corticosteroids, such as fluticasone (Flovent), are less than with beclomethasone, an older corticosteroid (Avila, 2006). A clearer picture of
omalizumab’s mechanism of action should also be evaluated, since IgE does not produce disease, nor does reduction in IgE levels result in relief by itself (Lanier, 2006).

There is also the issue of cost-effectiveness. What does it cost the patient out-of-pocket? Omalizumab comes with a high price, which limits its cost-effectiveness to patients who are hospitalized five or more times per year or for more than 20 inpatient days (Avila, 2006). Depending on the dose, its price can range from $4,000 to $20,000 per year, with an average cost of around $12,000 per year (Strunk & Bloomberg, 2006). Before omalizumab is considered, current management of asthma recommends a long acting beta-agonist be used in addition to high-dose inhaled corticosteroids, certainly a less expensive alternative. Omalizumab is cost effective only for a few asthmatic patients who are on high dose inhaled steroids, long-acting bronchodilators, leukotriene antagonists, and who have frequent flare-ups requiring hospitalization (Avila).

In terms of safety, there may be unwanted effects from the drug’s mechanism of action including anaphylaxis, parasitic infections, teratogenicity, and malignancy. In regards to anaphylaxis, two patients who had been on omalizumab for more than a year were reported to have experienced anaphylaxis following administration of omalizumab. To assess the nature of these reactions, the two patients were tested using skin tests and unique IgE and IgG anti-omalizumab serological assays. Although the skin tests and the serological assays for IgE or IgG antibodies against omalizumab were negative, in vitro and in vivo immunologic data reveal that the reactions experienced by these two patients were in fact anaphylactoid in nature. One subject had a positive skin reaction to polysorbate, an excipient in omalizumab, which has also caused similar reactions with other medicines. This may be the potential source of the anaphylaxis (Price & Hamilton, 2007). In developing countries, anti-IgE therapy may aggravate parasitic
infections because parasites lead to eosinophilic inflammation and increased IgE levels (Avila, 2006). While research shows it may be helpful in mice with parasitic infections, a study in Brazil showed that among patients at a higher than average risk for geohelminthic infections, 53% of those treated with omalizumab became infected compared to 42% of those receiving placebo (Avila; Genetech, 2006). Those who became infected were 0.88 to 4.36 times more likely to have received omalizumab compared to those who did not have an infection (Genetech). However, Genetech does not specify in the prescribing information whether or not the subjects at higher risk for geohelminthic infection were tested for the presence of parasites before treatment. Regarding pregnancy, although omalizumab is a category B drug and there have been no reports on the spontaneous abortion rates for pregnant women taking it, there is no research to indicate whether these rates are greater than expected. Birth defects as a result of therapy also have yet to be determined (Lanier, 2006). Regarding issues of malignancy, the rate of malignancy in clinical trials was 0.5% in omalizumab-treated patients compared to 0.2% of control patients in studies involving patients with asthma and other allergic disorders (Genetech). Malignancy risk for those more susceptible (elderly, smokers) has not been studied (Avila).

Another issue related to use of omalizumab is how long the duration of treatment should last in a patient. There is no research at the present time to suggest a specific length of treatment for asthmatic patients on omalizumab, which is another reason why receiving approval from insurance companies is often difficult (Lanier, 2006). Stopping omalizumab in a patient will likely result in a recurrence of symptoms as IgE levels return to pre-treatment levels. However, follow-up studies of asthmatic patients treated with omalizumab in longer clinical trials have not been performed, so it is difficult to determine whether or not IgE levels rise following discontinuation of therapy (Lanier). Lanier mentions however there is “evidence” of the “central
effects” of anti-IgE treatment which may lead to the establishment of an end point of omalizumab therapy, but he offers no research in support of this.
Conclusion

Omalizumab is a newer drug approved for the treatment of moderate to severe allergic asthma that is refractory to conventional treatments such as inhaled corticosteroids and albuterol. Although these other treatments are often effective in treating asthma, adding omalizumab to the treatment regimen for patients with difficult-to-control asthma will lead to improved symptoms and outlook, allowing decreased usage and dosage of current medications. Omalizumab works by binding free IgE in the serum to reduce available IgE, thus mediating asthmatic symptoms caused by allergens. Because of this unique ability to bind to IgE, other allergic manifestations that are mediated by IgE may benefit from omalizumab. Efficacy in treating other allergic disorders such as allergic rhinitis, ocular allergy, and food allergy has been demonstrated by omalizumab. However, treatment of atopic dermatitis with omalizumab has not fully been demonstrated as clinical trials have only involved smaller populations and with mixed results.

Other issues that have yet to be addressed and researched include proper dosing regimens and length of treatment. Patients must have a specific IgE level before they can begin therapy with omalizumab, but there may be those with IgE levels above or below that recommended by the manufacturer who may also benefit from omalizumab. Cost-effectiveness is an issue for many patients because the price of omalizumab can be up to $20,000 per year. Because of this, some patients may not be able to afford omalizumab. Insurance companies create more barriers to coverage because of this high cost. Issues of safety regarding omalizumab’s side effects must also be considered. Studies have demonstrated increased rates of parasitic infections while on omalizumab. Regarding usage during pregnancy, studies have yet to determine whether omalizumab causes greater-than-expected rates of spontaneous abortion and birth defects. Furthermore, clinical trials have demonstrated greater rates of malignancy among participants on
omalizumab versus placebo. However, regardless of these issues, the benefit of omalizumab may be favorable for those patients who have poorly controlled asthma and other allergic disorders. Further research may find the benefits outweigh the cost and risk of potential side effects from administration of omalizumab. Should these benefits be observed, insurance companies might increase access to omalizumab. Clinicians may be more inclined to prescribe it, and most importantly, patients that suffer from allergies and asthma possibly will report significant improvement of symptoms and quality of life.
References


Appendix A: Definitions

**Allergen**: an environmental substance that can produce a hypersensitive allergic reaction in the body but may not be intrinsically harmful. Common allergens include pollen, animal dander, house dust, feathers, and various foods. Methods to identify specific allergens affecting individuals include the patch test, the scratch test, the radioallergosorbent test (RAST), and the Prausnitz-Küstner (PK test).

**Allergy**: a hypersensitive reaction to common, often intrinsically harmless substances, most of which are environmental.

**Allergic Rhinitis**: inflammation of the nasal passages, usually associated with watery nasal discharge and itching of the nose and eyes, caused by a localized sensitivity of an allergen.

**Anaphylaxis**: an exaggerated life-threatening hypersensitivity reaction to a previously encountered antigen. It is mediated by antibodies of the E or G class of the immunoglobulins and results in the release of chemical mediators from mast cells. The reaction may consist of a localized wheel and flare of generalized itching, hyperemia, angioedema, and in severe cases vascular collapse, bronchospasm, and shock.

**Antibody**: an immunoglobulin produced by lymphocytes in response to bacteria, viruses, or other antigenic substances. An antibody is specific to an antigen. Each class of antibody is named for its action.

**Asthma**: a respiratory disorder characterized by recurring episodes of paroxysmal dyspnea, wheezing on expiration and/or inspiration caused by constriction of the bronchi, coughing, and viscous mucoid bronchial secretion. The episodes may be precipitated by inhalation of allergens or pollutants, infection, cold air, vigorous exercise, or emotional stress.

**Basophil**: a granulocytic white blood cell characterized by cytoplasmic granules that stain blue when exposed to a basic dye. Basophils represent 1% or less of the total white blood cell count.

**FEV₁**: Forced Expiratory Volume in the first second. The volume of air that can be forced out in one second after taking a deep breath, an important measure of pulmonary function.

**FCεRI**: Cellular receptors on mast cells and basophils which have a high affinity for IgE antibodies.

**Immunoglobulin (Ig)**: any of five structurally distinct classes of proteins that function as antibodies in the serum and external secretions of the body.

**Immunoglobulin E (IgE)**: one of the five classes of antibodies produced by the body. It is concentrated in the lungs, skin, and mucous membranes. It provides the primary defense against environmental antigens and is believed to be responsive to immunoglobulin A. IgE reacts with certain antigens to trigger the release of chemical mediators that cause anaphylactic hypersensitivity reactions characterized by wheal and flare.
**Immunoglobulin M (IgM):** a class of immunoglobulins of high molecular weight that include the primary antibodies released into the blood early in the immune response to be replaced later by IgG, IgA, or IgE of lower molecular weight and that are highly efficient in binding complement

**International Unit (IU):** a unit of measure in the International System of Units

**Mast Cells:** a constituent of connective tissues containing large basophilic granules that contain heparin, serotonin, bradykinin, and histamine

**Ocular allergy:** a collection of hypersensitivity disorders that affect the lid, conjunctiva and/or cornea. Various clinical forms are included in the classification of ocular allergy: seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis, and contact or drug-induced dermoconjunctivitis

**PEF: Peak Expiratory Flow:** the greatest rate of airflow that can be achieved during forced expiration beginning with the lungs fully inflated
Appendix B: Dosage and Administration of Xolair (Omalizumab)

150 to 375 mg of Omalizumab is administered subcutaneously every 2 or 4 weeks. Dosage and frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.

Table 1: Administration every 4 weeks for adults and adolescents 12 years of age and older

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Table 2: Administration every 2 weeks for adults and adolescents 12 years of age and older

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From Xolair (Omalizumab) Prescribing Guide (Genetech, 2006)
Abstract

Omalizumab is a newer drug administered subcutaneously for the treatment of moderate-to-severe allergic asthma. Because it binds free Immunoglobulin E in the serum to reduce asthmatic symptoms, it may also prevent symptoms of other IgE-mediated allergic conditions.

OBJECTIVE: This project examines omalizumab’s efficacy in treating allergic asthma and its efficacy in preventing symptoms of allergic rhinitis, ocular allergies, atopic dermatitis, and food allergies. METHODS: Data and literature from 2001 through 2007 were obtained using online databases Medline, PubMed, and CINAHL. Search terms included omalizumab, Xolair, anti-IgE, asthma, allergic rhinitis, hypersensitivity, atopic dermatitis, food allergy, peanut allergy, and ocular allergy. CONCLUSIONS: Omalizumab improved symptoms and quality of life scores in patients with asthma, allergic rhinitis, ocular allergy, and food allergy. Studies involving patients with atopic dermatitis reveal mixed results. More research is needed in the areas of atopic dermatitis and food allergy, dosing and treatment regimens, cost-effectiveness, and side-effects.