

NEW TO THE CLINIC

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Omalizumab (Xolair) for the Treatment of Chronic Idiopathic Urticaria

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Omalizumab (Xolair, Novartis Pharmaceuticals, East Hanover, NJ; Genentech Inc, South San Francisco, CA) is a recombinant humanized monoclonal antibody that blocks the immunoglobulin E (IgE) high-affinity Fc receptor.¹ Omalizumab stops free-serum IgE from attaching to mast cells and other immune cells by preventing IgE-mediated inflammatory changes.

Omalizumab was originally approved in 2003 for patients 12 years and older with moderate to severe persistent allergic asthma caused by year-round allergens in the air not controlled by asthma medicines such as inhaled steroids. More recently, studies have been directed toward patients with chronic idiopathic urticaria (CIU), where upwards of 50% of CIU patients have inadequate response to H₁-antihistamines, previously the only approved therapy for CIU.² Women are twice as likely as men to experience CIU, and most develop symptoms between the ages of 20 and 40 years.² The agent has now been approved since March 2014 for the treatment of CIU in patients 12 years and older who remain symptomatic despite H₁-antihistamine treatment.

Omalizumab 150 mg or 300 mg is administered by the physician as a subcutaneous injection every 4 weeks. Dosing appears to be a decision that the physician makes, with the 300-mg dose being more effective for CIU than the 150-mg dose. Most patients will likely receive the 300-mg dose, as side effects do not appear to be dose related. In addition, dosing of omalizumab for CIU patients is not dependent on serum IgE (free or total) level or body weight.

MECHANISM OF ACTION

A variety of studies have found that omalizumab decreases inflammatory mediators. The result of blocking the IgE high-

affinity Fc receptor is manifold. Omalizumab treatment down-regulates dendritic cell FcεRI expression.³ The combined effect of specific immunotherapy and omalizumab is associated with prevention of nasal eosinophilic cationic protein increase and decreased tryptase levels in nasal secretions.⁴ Anti-IgE therapy reduces leukotriene release of peripheral leukocytes stimulated with allergen in children with allergic rhinitis undergoing allergen immunotherapy independent of the type of specific immunotherapy allergen used.⁵

In a study assessing the immunologic effects of omalizumab on airway inflammation in allergic asthma, the mean percentage sputum eosinophil count decreased significantly from 6% to 1.7% in the omalizumab group, a reduction significantly greater than that with placebo (8.5% to 7.0%). This was associated with a significant reduction in tissue eosinophils, FcεRI+ cells, CD3+, CD4+ and CD8+ T lymphocytes, B lymphocytes, and cells staining for IL-4+, but not with improvement in airway hyper-responsiveness to methacholine.⁶ Treatment with omalizumab normalized the number of myeloid dendritic cells during the grass-pollen season.⁷

Omalizumab induces complex changes in interleukin (IL) levels and does not decrease all Th-2-related ILs. In a study of patients with asthma, circulating levels of IL-5, IL-6, IL-8, IL-10, IL-13, and soluble intercellular adhesion molecule-1 (s-ICAM) were measured before and after 16 weeks of treatment.⁸ In addition, IL-13 and s-ICAM were measured before and after 16 weeks of treatment. The results of the aforementioned study were interesting: IL-13 decreased significantly, IL-5 and IL-8 decreased in the omalizumab group compared with baseline, and other circulating mediators did not change.⁸⁻¹⁰ The mechanism with which omalizumab induces long-term remission is also unclear. Most patients may require ongoing maintenance dosing.⁴ The drug did not seem to alter the natural history of the disease.⁸

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As in patients with asthma, some authors correlated the clinical improvement induced by omalizumab in patients with CIU with the reduction in free IgE levels; however, numerous patients with CIU successfully treated with omalizumab in published case reports or studies exhibited neither increased total IgE levels nor IgE specific to allergens. Omalizumab may also serve as a mast cell stabilizer by downregulating the high-affinity IgE receptors on mast cells and basophils.

OMALIZUMAB AND CIU

In this phase 3, multicenter, randomized, double-blind study,⁹ researchers evaluated omalizumab's efficacy and safety in patients with CIU despite H-antihistamine therapy (ie, fexofenadine 180 mg or cetirizine 10 mg once a day). The investigators randomized 323 patients to receive three subcutaneous injections, spaced 4 weeks apart, of omalizumab dosed at 75 mg, 150 mg, or 300 mg or placebo. They monitored the patients for 16 weeks, with the primary efficacy metric as the change from baseline in weekly validated itch-severity score of the urticaria (score 0–21).

Patients' 7-day itch-severity score was approximately 14 in each of the four CIU groups. At 3 months, the mean ($\pm$ standard deviation) change from baseline in the weekly itch-severity score was 5.1 ± 5.6 in the placebo group, -5.9 ± 6.5 in the 75-mg group, -8.1 ± 6.4 in the 150-mg group ($P=.001$), and -9.8 ± 6.0 in the 300-mg group. The 300-mg group had the lowest P value.

A number of case reports and series have also reported that omalizumab is highly effective at a dose of 300 mg/kg for CIU. Improvement in quality-of-life impairment was followed by relapse with 6-month periodic administration of omalizumab for severe treatment-refractory CIU and urticarial vasculitis.¹⁰ With long-term and continued use, 300 mg of omalizumab controlled CIU in 7 patients.¹¹

HOW TO USE OMALIZUMAB

Dermatologists should be prepared for possible anaphylaxis after administration of omalizumab and have an epinephrine autoinjector on hand. The patient should remain in the office for observation for 30 minutes following each injection. After the first injection, the time the patient must wait in the office should be extended to 2 hours after each of the first 3 injections; however, it could be modified based on a physician's clinical judgment after discussing the risks with the patient. It should not be used in patients who are infected with helminthes, ie, strongylosis, and if used in patient with a high risk of infection with helminthes, must be monitored closely. Omalizumab is not indicated for the treatment of other allergic conditions or other forms of

urticaria. In addition, it is not indicated for the relief of acute bronchospasm or status asthmaticus or for use in pediatric patients younger than 12 years.

HOW TO RECONSTITUTE OMALIZUMAB

Omalizumab comes as a powder that must be reconstituted with Sterile Water for Injection (SWFI), USP, only, that the physician must prepare for subcutaneous injection. Each vial of omalizumab is for single use only and contains no preservatives.¹²

The lyophilized product takes 15 to 20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent, and it is acceptable if there are a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous. In order to obtain the full 1.2-mL dose, all of the omalizumab combined with saline must be withdrawn from the vial before expelling any air or excess solution from the syringe.¹²

The solution must be used within 8 hours following reconstitution when stored in a vial at 2°C to 8°C (36°F–46°F) or within 4 hours of reconstitution when stored at room temperature. Reconstituted Xolair vials should be protected from sunlight. Following are the steps for reconstituting omalizumab.¹²

Step 1: Draw 1.4 mL of SWFI, USP, into a 3-mL syringe equipped with a 1-inch, 18-gauge needle.

Step 2: Place the vial upright on a flat surface using the standard aseptic technique, insert the needle, and inject the SWFI, USP, directly onto the product.

Step 3: Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

Step 4: After completing Step 3, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present.

Note: If it takes longer than 20 minutes to dissolve completely, repeat Step 4 until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely by 40 minutes.

Step 5: Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 3-mL syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the

plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

Step 6: Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

Step 7: Expel air, large bubbles, and any excess solution in order to obtain the required 1.2-mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe.

Three steps need to be taken for each 150-mg dose of omalizumab. Because 300 mg is given, these steps must be performed for each vial. Omalizumab is then administered by subcutaneous injection. The injection may take 5 to 10 seconds to administer because the solution is slightly viscous. Each vial delivers 1.2 mL (150 mg) of omalizumab. Do not administer more than 150 mg per injection site. Divide the 2 doses of 150 mg between 2 injection sites.

SIDE-EFFECT PROFILE

Omalizumab has a favorable side-effect profile and is classified as pregnancy category B.¹² Its specific side effects are listed below. A U.S. Food and Drug Administration (FDA) review in September of 2014 of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the asthma drug omalizumab than in those who were not treated with omalizumab. As a result, the FDA added information about these potential risks to the drug label.

ANAPHYLAXIS

Anaphylaxis^{13,14} occurred in approximately 0.09% of patients receiving omalizumab injections for asthma, with 61% of these reactions occurring within the first 2 hours after the first 3 injections and 14% occurring within 0.5 hours after the fourth or later injection. Food and Drug Administration (FDA) and World Health Organization experts expect that the rate of anaphylaxis will be the same for CIU patients. The Omalizumab Joint Task Force report published in 2007, which focused on asthma, recommended 5 steps for physicians prescribing omalizumab (Xolair) injections to ensure the safety of patients receiving omalizumab injections. When Xolair is given (1) informed consent should be obtained; (2) patients should be made aware that Xolair can induce anaphylaxis, the symptoms of which should be explained to the patients; (3) patients who take Xolair should have an epinephrine autoinjector in case anaphylaxis occurs; and (4) before injection, the state of health of patients should be assessed by the administering doctor, with vital signs taken and lung function (eg, peak expiratory flow or forced ex-

piratory volume in 1 second) established. After taking Xolair, patients should wait in the doctor's office for 2 hours after the first 3 injections and then change to 30 minutes after each injection; however, this can be modified based on the physician's judgment after discussing the risks of anaphylaxis with the patient.¹⁵ The anaphylaxis warning is a black box warning for asthma and CIU.

OTHER SIDE EFFECTS

EOSINOPHILIC CONDITIONS, FEVER, ARTHRALGIA, AND DERMATITIS

A constellation of signs and symptoms including arthritis/arthralgia, dermatitis (urticaria or other forms), fever, and lymphadenopathy similar to serum sickness have been reported in post-approval use of omalizumab.²¹ Severe thrombocytopenia and hair loss have been linked to omalizumab. Malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents (12 years and older) with asthma and other allergic disorders.²¹ A variety of malignancies were seen in patients treated with omalizumab including several cases of breast cancer, nonmelanoma skin cancer, prostate cancer, melanoma, and parotid cancer occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year.²¹ It is unclear whether these cancers were related to omalizumab. The impact of longer exposure to omalizumab or use in patients at higher risk for malignancy (eg, elderly and current smokers) is not known.

WORM INFECTIONS AND OMALIZUMAB

Patients at risk for infections with helminths, eg, geohelminth strongylosis, should be monitored for such infection while on omalizumab therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment. In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminth infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Xolair-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups. Insufficient data are available to determine the length of monitoring required for helminth infections after stopping omalizumab treatment.

The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88–4.36), indicating that a patient who had an infection in this study was anywhere from 0.88 to 4.36 times as likely to have received omalizumab than a patient

who did not have an infection. Response to appropriate anti-helminth treatment of infection as measured by stool egg counts was not different between treatment groups.¹²

OMALIZUMAB COMPARED WITH OTHER AGENTS FOR CIU

Omalizumab, an agent that has been on the market for asthma related to elevated IgE levels since 2003, is a promising treatment for CIU. Its rate of side effects is low, and since it is pregnancy category B, for women considering pregnancy, omalizumab can succeed when other treatments have failed (eg, cyclosporine). In a series of 30 patients treated with omalizumab for CIU,²² all patients had moderate to severe symptoms at least 4 times per week despite the use of immunosuppressive medications including cyclosporine, prednisone, and methotrexate. It should be noted that after treatment with omalizumab, 10 patients had complete resolution of their symptoms, 8 had a significant response, 4 had a partial response, and 8 had no response. These findings provide evidence on the use of omalizumab in cases other than chronic idiopathic urticaria and in cases that are refractory to standard immunosuppressive medications.¹⁹ Mycophenolate mofetil was not a treatment used in this study. It should be mentioned that mycophenolate mofetil has been used to successfully treat CIU but is pregnancy category D and is part of the FDA Risk Evaluation and Mitigation Strategy program.¹⁶

CONCLUSIONS

Medically minded dermatology should view omalizumab as a new and useful treatment for CIU but should follow the guidelines in the package insert when using omalizumab. The risk profile of omalizumab is favorable when compared with other immunosuppressive agents. Omalizumab injections must be monitored in the office and might be suited for dermatologists who have experience in infusing infliximab or intravenous immunoglobulin in their office with equipment such as epinephrine autoinjectors, heart rate monitors, and a crash cart. This is not necessary but could be helpful if a patient has anaphylaxis caused by omalizumab. Omalizumab is expensive (\$20,000+ a year) and is not without rare but serious side effects. When used within the guidelines, it can be used safely and effectively and is a useful agent for the treatment of CIU.

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