Clinical Commentary Review

The Use of Anti-IgE Therapy Beyond Allergic Asthma

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Omalizumab is a monoclonal anti-IgE antibody that has been used to treat allergic asthma for over a decade. The use of omalizumab to treat other diseases has largely been limited to case reports until the recently reported large multicenter studies that have established omalizumab as an effective treatment option for chronic spontaneous urticaria. The utility of omalizumab to treat nonallergic asthma and allergic rhinitis and the added safety and therapeutic benefits in combination with allergen immunotherapy have been demonstrated in placebo-controlled trials. Data supporting the clinical efficacy of omalizumab in treating atopic dermatitis, physical urticarias, mast cell disorders, food allergy, and various other allergic disorders have shown promise in small clinical trials and case studies. More carefully designed, large clinical trials of high quality are needed to fully appreciate the potential of omalizumab in treating various allergic and nonallergic diseases. © 2015 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

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Omalizumab is a recombinant humanized monoclonal IgG antibody that binds to the Fcε3 portion of the IgE antibody. Omalizumab forms complexes with the free IgE and reduces total IgE, thereby reducing IgE expression on mast cells, basophils, and antigen-presenting cells. This results in decreased expression of the high-affinity IgE receptor (FcεRI) on these cells. Omalizumab was initially approved by the US Food and Drug Administration for the treatment of moderate to severe perennial allergic asthma. However, omalizumab has been reported to benefit many different patient populations other than those with allergic asthma. This review focuses on the potential therapeutic utility of omalizumab for diseases other than allergic asthma.

URTICARIA

Urticaria and/or angioedema that occurs daily or near daily for more than 6 weeks with no identifiable cause has been termed chronic idiopathic urticaria or chronic spontaneous urticaria (CSU). H1 antihistamines are effective for 50% to 60% of these patients.[1,2] Several small studies have demonstrated the effectiveness of omalizumab in chronic autoimmune urticaria, nonimmune chronic urticaria, and CSU.[3-5]

A randomized, placebo-controlled study involving 90 patients with antihistamine refractory CSU evaluated a single administration of 3 different doses of omalizumab, 75, 300, or 600 mg, versus placebo. Only the 300- and 600-mg doses demonstrated an improvement in urticaria scores 4 weeks after treatment and there was no significant difference in efficacy between the higher doses.[6] This led to 3 large, phase III, randomized, double-blind, placebo-controlled studies: Asteria I, Asteria II, and Glacial. All the 3 studies evaluated 12- to 75- year-old patients with CSU that was refractory to standard of care with oral H1 antihistamines.[7-9]

Results of the Asteria I trial were published in 2014.[7] In this study, 318 patients were randomized to 1 of 3 different doses of omalizumab (300, 150, 75 mg) or placebo every 4 weeks for 24 weeks after failing licensed doses of H1-antihistamine therapy. The 300-mg dose improved urticaria by the first week of treatment compared with placebo. All 3 omalizumb doses significantly reduced patients' weekly itch score at 12 weeks compared with placebo. By week 12, 52% of the patients on high-dose omalizumab had their urticaria symptoms well controlled and 36% had their symptoms completely controlled. Angioedema symptoms also improved with the 300-mg dose.

The Asteria II trial was similar in design with the same 3 doses of omalizumab or placebo and enrolled 323 patients with CSU who remained symptomatic despite licensed doses of H1-antihistamine therapy.[8] In this study, patients were treated for only 12 weeks. By week 12, the patients on 150- and 300-mg doses of omalizumab demonstrated significant improvements in symptom scores and number of hives compared with those on placebo. By week 12, 53% of the group members receiving 300 mg of omalizumab were hive free, with 44% free from both hives and itching.

The Glacial trial had a significant difference compared with Asteria trials. These patients all failed H1 antihistamines up to 4 times the licensed doses plus patients were allowed to have been on an H2-blocker and/or leukotriene antagonist. In this study, 335 patients were randomized to either 300 mg of omalizumab or placebo every 4 weeks for 24 weeks of treatment and 16 weeks follow-up with continuation of their baseline medications.[9] This study reaffirmed the effectiveness of 300 mg of omalizumab every 4 weeks in reducing urticarial lesions and symptoms at 12 weeks of therapy, which was sustained for the 24 weeks of therapy. The overall incidence of adverse events and serious adverse events was similar between omalizumab and placebo recipients in all the 3 trials, and no new omalizumab safety issues were identified.

In a review of more than 900 patients with CSU, the response rate to omalizumab in patients symptomatic despite conventional

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Abbreviations used
ABPA- Allergic bronchopulmonary aspergillosis
CSU- chronic spontaneous urticaria
FcεRI- High-affinity IgE receptor
SCIT- Subcutaneous immunotherapy

therapy was 65%, with complete resolution in 40%, and improvement was noted in just a few days in a subset of patients.[10] When omalizumab is discontinued in successfully treated patients with CSU or physical uriticarias, relapse may occur within a few weeks. In these patients, retreatment with omalizumab was effective in again treating their symptoms.[11]

Current urticaria guidelines of the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization give a strong recommendation for the use of omalizumab after failing a second-generation antihistamine at 4 times the standard dose.[12] The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology have recommended the use of omalizumab after failure with antihistamines and leukotriene receptor antagonists.[13] In March 2014, the US Food and Drug Administration approved the use of omalizumab 150 or 300 mg every 4 weeks in chronic idiopathic urticaria for patients 12 years and older who remain symptomatic despite H1 antihistamines.[14]

The exact mechanisms of how omalizumab works in chronic idiopathic urticaria are unclear. In a subset of patients, IgG autoantibodies against FcεRI, IgE, or both may exist.[15] Because omalizumab decreases the free IgE available with subsequent downregulation of FcεRI, it was natural to postulate that omalizumab's effects might be due to decreasing the targets for these autoantibodies. However, no differences in effectiveness have been found in patients with or without the autoantibodies. Furthermore, analysis of previous data suggests that it takes time to significantly decrease the expression of high-affinity IgE receptors on either basophils (2 weeks) or mast cells (10 weeks), whereas a therapeutic effect within 1 week is noted in some patients.[16,17] An alternative postulate is that IgE antibodies against autoallergens are present and omalizumab reduces the level of these autoantibodies.[15] Another possibility is that the binding of free IgE to FcεRI, which promotes the proliferation of mast cells and potentiates their ability to store and synthesize cytokines, would be inhibited by omalizumab. This may result in a nonspecific desenstitization. It is likely that omalizumab works in different ways in subsets of patients and the exact mechanisms remain to be elucidated because its effectiveness in urticaria is not dependent on IgE level or weight.

PHYSICAL URTICARIAS

Omalizumab has also improved symptoms in patients with different types of physical urticarias, including solar, cold, localized heat, cholinergic, dermatographic, and pressure.[18]

NONALLERGIC ASTHMA

Omalizumab has clearly shown benefit in patients with allergic asthma, but recent data demonstrate that patients with nonallergic asthma may benefit from omalizumab as well. This may be in part due to local IgE production in the absence of systemic measurable allergen-specific IgE either by skin tests or by *in vitro* testing. The presence of respiratory IgE produced in response to Staphylococcal enterotoxins has also been proposed as a possible stimulus for IgE-mediated inflammation. An initial case study reported a steroid-dependent asthmatic patient with elevated total IgE level but negative aeroallergen skin and *in vitro* test results who was treated with omalizumab. The patient noted improvement in his symptoms after 16 weeks of omalizumab therapy that continued for 4 years.[19] A similar case study of a patient with severe asthma with elevated IgE level but negative food and aeroallergen skin prick and *in vitro* test results was reported. Treatment with omalizumab dramatically improved symptoms and pulmonary functions, allowing the discontinuation of oral corticosteroids.[20] A study comparing 29 patients with severe, nonatopic asthma and 266 patients with severe, atopic asthma all treated with omalizumab showed similar improvements in symptoms in both groups.[21]

A randomized, placebo-controlled, phase 3B, double-blind study evaluated omalizumab treatment in 41 patients with severe refractory nonatopic asthma. All patients were on high-dose inhaled corticosteroid/long-acting β_2-agonist medications, with 33% of the patients requiring oral corticosteroids.[22] Omalizumab significantly decreased the expression of FcεRI on basophils and plasmacytoid dendritic cells. All patients treated with placebo (20) had a decrease of less than 50% in basophil FcεRI expression, whereas 90% of omalizumab-treated patients had a decrease of more than 50%. Omalizumab-treated patients had an improvement in lung functions despite no significant changes in exacerbations or asthma control symptoms after 16 weeks of therapy.

Occupational asthma can have either allergic or nonallergic causes. Ten patients with uncontrollable occupational asthma were treated with omalizumab. After 4 months, 9 of the 10 patients had improvements in their symptoms and 7 patients were able to continue to work in the same environment.[23]

ALLERGIC RHINITIS

Several early studies demonstrated the effectiveness of omalizumab in reducing symptoms and rescue medication use in patients with allergic rhinitis to ragweed, birch, cedar, and perennial allergens.[24-31] A recent meta-analysis published in 2014 screened 352 citations, with 78 articles eligible for review.[32] Of these studies, 11 qualified for evaluation, with 2870 patients randomized. In the 9 studies that measured daily nasal symptom scores, omalizumab significantly reduced symptoms. Rescue medication use was also decreased in the 9 studies that evaluated that end point. No significant differences in adverse events in 2005 in these patients were reported on comparing omalizumab with placebo.

ATOPIC DERMATITIS

The use of omalizumb in atopic dermatitis has been limited to case studies and small trials. Conflicting data on the effectiveness may be due to the exceptionally high level of IgE in these patients making it difficult to reduce the levels to below 10 ng/mL.[33] A recent trial in 7 pediatric patients with severe atopic dermatitis found that omalizumab was effective in reducing atopic dermatitis symptoms in a patient with a baseline IgE level as high as 17,190 IU/L.[34] The use of omalizumab in atopic dermatitis has been reported to reduce cytokines involved in T_H2 polarization.[35] Patients with atopic dermatitis without filaggrin