

Anti-IgE therapy: Clinical utility beyond asthma

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Numerous studies have demonstrated the efficacy and safety of the monoclonal anti-IgE antibody omalizumab in treating patients with perennial allergic asthma. The use of omalizumab for other allergic diseases has not undergone the same level of scrutiny as for allergic asthma, but its effectiveness in the treatment of other atopic diseases has been demonstrated by a number of small studies and case reports (Table 1¹⁻¹⁷ and see also the Reference section in this article's Online Repository at www.jacionline.org).

Allergic rhinitis is an obvious target for anti-IgE therapy. The effect of omalizumab was initially evaluated in patients with ragweed-sensitive allergic rhinitis.¹⁸ Patients were randomized to receive one of 3 doses of omalizumab or placebo just before the onset of the ragweed season and every 3 to 4 weeks throughout the pollen season. Subjects treated with 300 mg of omalizumab demonstrated significantly lower nasal symptoms scores, rhinitis quality-of-life scores, and days missed from work or school when compared with those receiving placebo. This study was among the first to demonstrate a significant correlation between the dose of omalizumab, reductions in serum IgE levels, and improvements in clinical parameters. Omalizumab has been safely readministered to patients with ragweed-induced allergic rhinitis a year after discontinuation, indicating a possible role for preseasonal and coseasonal administration.¹⁸ Similar efficacy in rhinitis symptom improvement has been demonstrated for other pollens, including birch and Japanese cedar.^{1,18}

Omalizumab was also shown to be effective in the treatment of perennial allergic rhinitis when patients with moderate-to-severe disease were evaluated.¹⁸ However, the magnitude of the effect was small. When patients with both allergic rhinitis and asthma were treated with omalizumab or placebo, more patients in the omalizumab group demonstrated a clinically significant improvement in both asthma and rhinitis quality-of-life indices (57.7% vs 40.6%). This suggests omalizumab is effective in the treatment of upper and lower airway symptoms in the same patients.¹⁸

The rationale for using the combination of anti-IgE and allergen immunotherapy comes from pre-existing data about the biologic and immunologic effects of both therapies. The addition of omalizumab to standard maintenance dose immunotherapy was evaluated in 221 children and adolescents with allergic rhinitis sensitized to birch and grass allergen.¹⁷ During the birch season, both the birch immunotherapy plus omalizumab and grass immunotherapy plus omalizumab groups had decreased symptoms compared with those seen after irrelevant (grass) immunotherapy and placebo. Similar results were seen in the grass season. When these findings were further analyzed for the children with grass pollen allergy, it was noted that the omalizumab plus immunotherapy-treated groups had significantly diminished rescue medication use and numbers of symptomatic days when compared with those treated with either omalizumab or immunotherapy alone.¹⁸

The use of omalizumab before and concomitantly with ragweed rush immunotherapy improved severity scores during the ragweed season in comparison with immunotherapy alone.¹⁸ Furthermore, pretreatment with omalizumab resulted in a 5-fold decrease in anaphylactic events caused by rush immunotherapy. A recent study found that pretreatment with omalizumab in patients with moderate persistent symptomatic asthma reduced systemic allergic reactions to cluster immunotherapy by nearly 50%.² (A case report of a patient with venom allergy, unable to tolerate venom immunotherapy because of anaphylaxis, demonstrated the potential usefulness of omalizumab in combination with venom rush immunotherapy to produce successful tolerance of venom immunotherapy.³) Thus combined therapy with omalizumab and allergen immunotherapy might be an effective strategy to permit more rapid and higher doses of allergen immunotherapy to be administered more safely and with greater efficacy. However, there are no data on the risks of discontinuing omalizumab once maintenance allergen immunotherapy is achieved.

Food allergies can be life-threatening, and the only treatment currently available is strict elimination and avoidance. However, unintended ingestion still accounts for 50 to 100 deaths a year in the United States caused by peanut allergies.¹⁸ The only published study to evaluate anti-IgE therapy in patients with peanut allergy used another humanized mAb against IgE, TNX-901. A double-blind, placebo-controlled, randomized trial in 84 patients with proved peanut hypersensitivity evaluated 3 doses of TNX-901. By the end of treatment, all groups, including the placebo group, had a greater threshold of peanut tolerability, but only the high-dose TNX-901 group had a significant improvement from a threshold dose of 178 mg (½ peanut) to 2805 mg (nearly 9 peanuts).¹⁸ However, 25% of the high-dose group had no improvement. Because there are no published data on the efficacy of omalizumab for the treatment of food allergies, its use cannot currently be recommended.

In the allergic form of atopic dermatitis, serum IgE levels are typically increased. Several small-scale reports of omalizumab therapy have demonstrated conflicting results, possibly because

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TABLE I. Studies of anti-IgE in diseases other than asthma

Indication	Noted features	References
Allergic rhinitis	Both seasonal and perennial DBPC studies	1, E1-E6
Immunotherapy	More effective when combined with immunotherapy; adds safety to immunotherapy DBPC studies	2, 3, E7-E9
Food allergy	Shown with different formulation of anti-IgE than omalizumab DBPC study	E10, E11
Atopic dermatitis	Conflicting reports, likely most effective in patients with lower baseline levels of IgE	4, E12-E14
Chronic urticaria/angioedema	Idiopathic, autoimmune, cholinergic, cold induced	5-8
ABPA	Small number of case reports	9-10
Mastocytosis	Indolent and systemic	11-13
Nasal polyposis/sinusitis	Improvement of edema	14, 15
Eosinophilic gastrointestinal diseases	Decreased serum eosinophil counts and improved symptoms	16
Latex allergy	In health care workers	E15
Drug allergy	One case report of insulin allergy	17
Idiopathic anaphylaxis	One case report	E16

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DBPC, Double-blind, placebo-controlled; ABPA, allergic bronchopulmonary aspergillosis.

of the difficulty in significantly reducing extremely increased IgE levels.^{4,18} Based on the limited data available, the role for omalizumab in the treatment of atopic dermatitis requires further investigation but shows promise in those patients with lower baseline IgE levels. For example, a study of patients with asthma, allergic rhinitis, and atopic dermatitis and baseline IgE levels from 262 to 2020 IU/mL showed improvement in 5 of 5 patients completing 7 months of omalizumab therapy.¹⁸

There have been a number of small series of patient reports detailing the utility of omalizumab in patients with chronic urticaria, including physical urticaria. The rationale for the latter includes early studies showing passive transfer factors that could be IgE related in nature. In regard to the former, a subset of patients (approximately 50%) with chronic urticaria has an autoimmune component. The most common association is the presence of IgG antibody directed to the α -subunit of the IgE receptor. Less commonly, some patients have IgG against IgE. These autoantibodies cross-link the α -subunits of the high-affinity IgE receptor or IgE bound to the cell surface, leading to degranulation of basophils and cutaneous mast cells.⁵⁻⁸ Because omalizumab decreases both cell-surface IgE levels and the number of high-affinity IgE receptors, the patients having these putatively important autoantibodies would be expected to see symptom improvement.

Since the use of omalizumab has become more widespread, a number of case reports examining its efficacy in a variety of IgE-mediated diseases have been reported. Other clinical scenarios in which anti-IgE therapy showed promise include allergic bronchopulmonary aspergillosis,^{9,10} mastocytosis,¹¹⁻¹³ nasal polyposis,¹⁴ chronic sinusitis,¹⁵ eosinophil-associated gastrointestinal disorders,¹⁶ latex allergy,¹⁸ idiopathic anaphylaxis, and insulin allergy¹⁷ (Table I).

Selective anti-IgE humanized mAb represents a novel and important therapeutic option for severe asthma and other allergic diseases. In years to come, the role of omalizumab or other anti-IgE antibody strategies in allergic rhinitis, food allergy, atopic dermatitis, chronic urticaria, allergic bronchopulmonary aspergillosis, and chronic hyperplastic sinusitis and as an adjuvant to allergen immunotherapy will evolve. Currently, the strength of evidence for omalizumab in these disorders is very low to low, with the exception of allergic rhinitis, for which several large well-controlled studies have demonstrated efficacy. More carefully designed large clinical trials of high quality are needed to fully appreciate the potential of omalizumab to treat allergic diseases other than asthma. However, with the high cost of mAb

therapy, omalizumab's role might be limited to patients with more severe symptoms and diseases that have a large effect on quality of life and for which it has a favorable pharmacoeconomic effect.

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