Anti-IgE: beyond asthma
Yehia El-Gamal, MD, PhD, FAAAAI
Professor of Pediatrics
Pediatric Allergy and Immunology Unit
Children’s Hospital, Ain Shams University
Member, WAO Board of Directors

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Objectives

- Recognize the effects of anti-IgE therapy in allergic diseases.
- Identify candidates for treatment with anti-IgE.
- Be aware of the side effects and cost-benefit of such therapy.

Introduction

Omalizumab (anti-IgE ab) is a recombinant humanized monoclonal antibody (rhuMAb-E25) developed by immunizing mice with human IgE. Then, a monoclonal antibody was selected that recognizes IgE at the same site as the high-affinity receptor for IgE (FcεRI). Omalizumab is the only Mab to date that has been found to be effective and approved by both the FDA and European Medicines Agency (EMA) for the treatment of difficult allergic asthma.

Mechanisms of Action of Omalizumab

- Reduces serum levels of free IgE.
- Down-regulates expression of IgE receptors (FcεRI) on mast cells and basophils.
- In the airways of patients with allergic asthma, it reduces FcεRI+ and IgE+ cells and causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers.
- The reductions in circulating levels of IgE resulting from omalizumab treatment leads to reductions in FcεRI expression on mast cells, basophils and dendritic cells. This combined effect results in attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia, levels of GM-CSF, IL-2, IL-4, IL-5 and IL-13.
- It may also reduce allergen presentation to T-cells and the production of Th2 cytokines.
Potential Uses of anti-IgE in Allergic Diseases Other than Asthma

Data from double-blind, placebo-controlled clinical trials are only available for allergic rhinitis and moderate to severe bronchial asthma. The effectiveness of omalizumab in other atopic diseases has been demonstrated by some smaller studies and case reports.

Examples include:

- Allergic rhinitis
- Nasal polyposis/sinusitis
- Specific immunotherapy
- Food allergy
- Eosinophil-associated gastrointestinal diseases
- Atopic eczema
- Urticaria/angioedema*
- Allergic bronchopulmonary aspergillosis
- Mastocytosis
- Aspirin-exacerbated respiratory disease
- Hyper-IgE syndrome
- Latex allergy
- Drug allergy
- Insect allergy
- Idiopathic anaphylaxis

Omalizumab in allergic rhinitis

The Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations suggest that ideally, a combined strategy should be used to treat the upper and lower airway diseases.

A randomized, double-blind, placebo-controlled, multi-centre trial revealed that during the grass pollen season, a combination of omalizumab with SIT was safe and reduced the symptom load in a statistically significant and clinically meaningful manner. In a recent study on safety of anti-IgE treatment in seasonal allergic rhinitis children undergoing specific immunotherapy simultaneously, children receiving omalizumab showed a better tolerance to SIT. Daily nasal and ocular symptom score was lower in patients of Japanese cedar pollinosis on Omalizumab compared to the placebo group.
Omalizumab in chronic rhinosinusitis

From a randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis (CRS), it seemed that IgE plays, at most, a small role in the mucosal inflammation. In patients with nasal polyps, a local monoclonal IgE response has recently been described, initiated by Staphylococcus aureus-derived enterotoxins. Evidence accumulates that these enterotoxins act as superantigens resulting in a monoclonal T- and B-cell activation with massive IgE formation within the airways. There is a proof-of-concept treatment trial with omalizumab in nasal polyposis.

Omalizumab in combination with allergen-specific immunotherapy (SIT)

Allergen-specific immunotherapy (SIT) is the only causal treatment of allergic disorders. The most relevant limitation in the daily routine use of SIT is in patients with moderate-to-severe allergic asthma. A strategy to overcome this limitation is to combine SIT with omalizumab as an immune-modulator. The combination of omalizumab and SIT was found to be safe and clinically more effective than SIT alone. Moreover, administration of Omalizumab prior to SIT reduces the risk of SIT-related systemic reactions and might be a useful approach to broaden the indication of specific immunotherapy in allergic patients.

Omalizumab in food allergy

While treating asthma with omalizumab, patients subjectively observed a reduction in their concomitant IgE-mediated food allergy symptoms. Clinical improvement was noted by the 6th dose of omalizumab (150-300 mg /2-4 weeks).

A recent phase II, randomized, double-blind, parallel-group, placebo-controlled trial of omalizumab in peanut allergy was conducted by Sampson et al (2011). While no firm conclusions could be drawn from the limited data and although the study was stopped early, omalizumab seemed to increase the tolerability to peanut in a subset of patients with peanut allergy and this may deserve further investigation.

Omalizumab in eosinophil-associated gastrointestinal diseases

The potential efficacy of omalizumab was tested in a 16 week open label study of 9 subjects with allergic eosinophilic gastroenteritis. Omalizumab was associated with a 35–45% drop in peripheral blood eosinophil count as well as 60–70% decrease in duodenal and antral eosinophils. In contrast, esophageal eosinophils were modestly increased during the study, providing further support that eosinophilic esophagitis and eosinophilic gastroenteritis are distinct clinical entities with different pathophysiologic features.
Food allergen specific T cell responses were examined during a 16-week clinical trial of omalizumab in nine subjects with eosinophilic gastroenteritis and food sensitization. This study failed to demonstrate that anti-IgE therapy broadly or potently inhibits allergen specific T cell responses.

Omalizumab improved the quality of life of two patients with multiple food allergies and eosinophilic esophagitis on a very restrictive diet by improving symptoms of food allergy, but it did not appear to change endoscopic and histological features of eosinophilic esophagitis in a short follow-up.

**Omalizumab in atopic eczema**

A study of Low-dose anti-IgE therapy was conducted on atopic eczema patients with high serum IgE levels. Out of 11 patients, two responded very good (SCORAD reduction of more than 50%), four showed satisfying results (SCORAD reduction between 25% and 50%), three showed insignificant changes (reduction or increase in SCORAD of less than 25%), and two showed deterioration of their eczema (SCORAD increase of more than 25%). From a cohort of 22 patients, omalizumab was found to be effective in improving atopic dermatitis-related quality of life scores and modulated oral corticosteroid use in patients with concomitant asthma and atopic dermatitis. Another small study (11 patients) on severe atopic dermatitis (SCORAD more than 50) revealed that omalizumab treatment progressively decreased the severity of AD with a gradual decrease in symptom intensity, which was reflected by improved quality-of-life scores.

**Omalizumab in allergic bronchopulmonary aspergillosis (ABPA)**

A dramatic and rapid improvement of respiratory symptoms and lung function after a single dose of anti-IgE antibody (omalizumab) in a 12-year-old girl with cystic fibrosis and ABPA was described. Anti-IgE therapy was tried in two teenagers with cystic fibrosis with ABPA exacerbation. Treatment consisting of subcutaneous injections of 375 mg of omalizumab twice monthly was successful in rapidly improving respiratory symptoms and lung function.

**Omalizumab in systemic mastocytosis**

Omalizumab may have efficacy in the prevention of spontaneous episodes of systemic hypotension (anaphylaxis) in patients with systemic mastocytosis. This effect did not appear to rely on the ability of omalizumab to decrease mast cell numbers, because the serum tryptase levels in these patients did not change during the period of response.
Omalizumab in aspirin-exacerbated respiratory disease (AERD)

Omalizumab (225 mg every 2 weeks) was effective in the treatment of AERD in an 18-year-old female by not only controlling the disease and significantly improving the quality of life but also made her capable of tolerating aspirin and other COX-1 inhibitors. Further studies are required in to confirm this finding.

Omalizumab in hyper-IgE syndrome (HIES)

High dose omalizumab therapy was used to treat severe recalcitrant eczematous dermatitis in the setting of HIES with some success. Similar results were reported in a 32 year old woman with HIES (serum total IgE 17,300 IU/ml) using omalizumab (300 mg SC every 2 wk). Long term follow-up is required to confirm the efficacy of this treatment.

Omalizumab in drug allergy

An interesting case of insulin allergy that was treated successfully with omalizumab pretreatment for 2 months was reported. He was a 27-year-old man with type I diabetes mellitus who was assessed because of itching, hives, and some episodes of anaphylaxis coinciding with insulin bolus. A diagnosis of insulin allergy was made after positive skin prick test responses to all kind of insulin, in vitro testing with positive IgE levels, and a positive challenge result with 2 U of regular insulin. Omalizumab (300 mg) was administered subcutaneously every second week. After 20 weeks, the patient was taking only 5 mg of levocetirizine every 24 hours, with no allergic symptoms.

Insect Allergy

Omalizumab's immunomodulatory effects may play a role in difficult-to-treat insect allergy but this needs further studies to approve.

Omalizumab Safety

Omalizumab is considered generally safe. The most common adverse reaction from omalizumab is injection- site pain and bruising but the package insert contains warnings regarding malignancies, geohelminth infections and a "black box" warning about anaphylaxis.

There is some evidence for a potential increased risk of geohelminth infection in subjects receiving omalizumab. A RDBPC trial from Brazil, conducted in 137 subjects (12–30 years), revealed that 50% of the omalizumab group experienced at least one intestinal geohelminth infection compared with 41% of the placebo subjects. Omalizumab therapy did not appear to be associated with increased morbidity attributable to intestinal helminthes or to affect response to
anithelmintics. The usefulness of screening for helminth infections before considering omalizumab therapy varies widely between different exposure risk groups, and is generally not necessary except in individuals with continuing exposure, a past history of filarial or schistosomotic infection, and individuals with a history or high risk of infection with Strongyloides.

A review of post-marketing adverse events suggested that at least 0.2% of patients who received omalizumab experienced anaphylaxis between June 2003 and December 2006. An Omalizumab Joint Task Force of the AAAAI and the ACAAI concluded that the anaphylaxis-reporting rate was 0.09%. It recommended an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections as well as patient education regarding anaphylaxis. Another reported incidence of anaphylaxis was 0.14% in omalizumab-treated patients and 0.07% in control patients.

Current clinical trial data do not support an increased risk of malignant neoplasia or thrombocytopenia with omalizumab. No cases were considered drug-related by a panel of blinded independent oncologists. The majority of cases (60%) were diagnosed within 6 months of treatment. A multicenter, prospective, observational cohort study designed to evaluate the long term safety of omalizumab is currently in progress.

Omalizumab treatment may unmask Churg-Strauss syndrome (CSS) in patients who have an underlying eosinophilic disorder due to withdrawal of corticosteroids in favor of omalizumab, or may delay corticosteroid treatment allowing for CSS to manifest.

**Limitations of Use of Anti-IgE Therapy:**

- Expense
- Parenteral administration
- Adverse effects
- Host anti-drug responses limiting ongoing therapy
- Limitations in current concepts of molecular pathogenesis of disease

**Take Home Message:**

The cost-effectiveness and adverse events associated with the use of anti-IgE therapy should be considered. This could be achieved by carefully revising the existing clinical trials in light of solid evidence-based criteria. Pediatric data on cytokine-specific monoclonal antibody therapies are still needed.