CHAPTER 30

# OMALIZUMAB TREATMENT IN DERMATOLOGY

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Immunoglobulin E (IgE) is one of the most important mediator in type 1 hypersensitivity reactions. IgE binds to high affinity receptors (FCεRI) on mast cells and basophils to induce an allergic reaction through the release of a wide range of inflammatory mediators such as histamine, leukotrienes, prostaglandins, and others. Omalizumab (Xolair, Novartis Pharmaceuticals) is a recombinant humanized monoclonal antibody that inhibits immunoglobulin E's (IgE) high-affinity Fc receptor. Omalizumab blocks free-serum IgE from attaching to mast cells and other immune cells and prevents IgE-mediated inflammatory changes. Omalizumab treatment used in various dermatologic disorders such as atopic dermatitis, urticaria, bullous pemphigoid, drug-induced hypersensitivity syndrome, vasculitis, mastocytosis, angioedema, Hyper- IgE Syndrome and anaphylaxis. In this review, the dosage, indications, effectiveness, and possible use in dermatology of omalizumab are discussed.[1-3]

## Mechanism of action

Omalizumab is a 150-kDa humanized monoclonal antibody against IgE obtained using recombinant DNA tecnology. It contains 95% of a human IgG1 antibody and 5 % murine fractions. Murine fraction has the specific antibody-binding site and represents the portion of omalizumab that binds to IgE. The murine fraction is the active fraction and is minimized to prevent anaphylactic reactions. It has two main mechanisms of action. The first is marked reduction of serum free IgE levels. Omalizumab binds to a region in the IgE molecule that overlaps with the site through which IgE binds to its receptor on the target cells (mast cells and basophils), regardless of IgE specificity. In the case of high affinity receptors present on mast cells and basophils, omalizumab blocks IgE-FCεRI binding and prevents cellular activation and the release of vasoactive molecules including histamine, leukotrienes, tryptase, prostaglandine D2, and cytokines. Thus, it limits the release of mediators of the allergic response. Several studies reported clinical improvement in patients with severe atopic eczema with high serum IgE level. The second mechanism of action is down-regulation of IgE receptors on circulating basophils. The immune mechanism of omalizumab demonstrated by an increase in eosinophil apoptosis and decrease in granulocyte macrophage colony stimulating factor, IL-2 and IL-13. IL-2 influences eosinophil activity. Omalizumab also decreased mRNA ratio for IgE/IgG and might be a promising marker to identify patients responding to its treatment.[3]

## Side effects

Omalizumab is a safe and well tolerated drug. The most common adverse effects are upper respiratory tract infections, headache, injection-side reactions and urticaria. Side effects of omalizumab is shown in table 1. The most serious adverse reactions reported in clinical studies were malignancies (0.5%) and anaphylaxis (0.1%). The difference in malignancy between patients treated with omalizumab and placebo was not statistically significant. Some authors suggested that altered thyroid function temporally related to use of omalizumab in a patient with antithyroid antibodies and chronic urticaria.[4] They concluded that monitoring of thyroid function in patients who exhibit IgE against thyroperoxidase while taking omalizumab was necessary. Frequency of adverse events, evaluated in more that 5000 patients, was comparable for any kind of event in omalizumab- and placebo-treated subjects. Some doubt was raised about a report of malignant neoplasms, but the rate of such pathology was below 1% in both omalizumab-treated and control patients, and a panel of oncologists stated the lack of relationship between neoplasms and study treatment. During the clinical studies of phase II/III on allergic asthmatics, approximately 6700 patients received omalizumab. The most commonly reported reactions have been pain, swelling, itching, and erythema in the injection site, all of these short-lived and self-limited. Anaphylaxis has been reported as a possible adverse event, with a frequency of about 0.1%. The frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of treated patients in the wild population. Omalizumab should be administered in hospital setting, where this kind of emergency can be dealt with.[2-3]

## Dosage range

Omalizumab is available in prefilled syringes for subcutaneus administration. It is available in two doses:75

or grass immunotherapy showed a higher effi cacy of the combined treatment. An apparent advantage of adding omalizumab to allergen immunotherapy is that anti-IgE treatment is not allergen specific and thus is effective also on symptoms induced by other allergens in polysensitized patients. 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. 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. The use of omalizumab before and concomitantly with ragweed rush immunotherapy improved severity scores during the ragweed season in comparison with immunotherapy alone. 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%. 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.[93,94]

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