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Omalizumab—A Review

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Abstract

Omalizumab is a recombinant, humanized, monoclonal antibody against human immunoglobulin E (IgE). The US FDA has approved this molecule for chronic urticaria.

Keywords: Anaphylaxis, atopic dermatitis, chronic urticaria, FDA approval, monoclonal antibody

What was known?

- Omalizumab is a humanized monoclonal anti-IgE antibody.
- Used in asthma.

Introduction

Omalizumab is a recombinant, humanized, monoclonal antibody against human immunoglobulin E (IgE). It is derived from a murine monoclonal antibody, which was humanized to produce Omalizumab in its present form. It contains 5% non-human (murine) amino acid residues, which make up the complementarity determining regions (CDRs) of the protein.[1]

Role of IgE in pathogenesis of allergic conditions including urticaria

An environmental allergen, when it first enters the body, is taken up by antigen-presenting cells (APCs), processed, and presented to T and B lymphocytes. This is followed by B-lymphocyte activation and production of allergen-specific IgE. This IgE is then secreted by plasma cells (converted B lymphocytes) and is available to bind to IgE receptors on various other cells.

IgE binds to high-affinity (FcεRI) and low-affinity (FcεRII) receptors on various cells of the immune system. On subsequent antigenic exposure, cross-linking of the antigen occurs by multiple FcεRI-bound IgE molecules on the surface of basophils and mast cells. This causes activation of mast cells and histamine release, producing wheals and other symptoms of urticaria.

Mechanism of action of Omalizumab

Omalizumab exerts its clinical effects by means of various pharmacologic interactions. Omalizumab binds to free IgE with a greater affinity than IgE itself binds to the high-affinity FcεRI receptors present on basophils. Thus, it reduces availability of free IgE for binding. Omalizumab itself does not bind to the FcεRI receptors, nor does it bind to receptor-bound IgE. It only binds to free IgE. These binding

characteristics allow Omalizumab to neutralize IgE-mediated responses without causing basophil degranulation or cross-linking with basophil-bound IgE.[1]

Omalizumab also promotes FcεRI downregulation on basophils because of the direct correlation between free serum IgE and the number of FcεRI receptors expressed on basophils. The reduced free IgE levels ultimately cause dissociation of IgE from basophils with subsequent receptor downregulation.[1]

Some authors have also postulated that in patients with chronic autoimmune urticaria (CAU), Omalizumab would effect a sufficient reduction in FcεRI expression to prevent IgG antibody-mediated cross-linking of adjacent α-subunits, thereby preventing basophil activation.[2]

Indications and usage

Urticaria

A recently published, phase III, randomized, double-blind study by Maurer *et al.*, evaluating the safety and efficacy of Omalizumab in 323 patients with antihistamine-unresponsive, moderate-to-severe chronic urticaria (CU), demonstrated significant efficacy in a dose-dependent manner. Omalizumab was given subcutaneously in doses of 150 mg or 300 mg, repeated every 4 weeks for a period of 12 weeks.[3]

A study published from Denmark in December 2013 by Uysal *et al.* described an algorithm for use of Omalizumab in the treatment of CU. The authors suggested that unlike the usage of Omalizumab in asthma, dose adjustment based on serum IgE and body weight were unnecessary for successful treatment in urticaria. A total of 27 patients (6 children and 21 adults) with recalcitrant urticaria and an Urticaria Activity Score (UAS) of 6 and above at baseline were included in the study. The study observed no correlation between the type of urticaria, presence of concomitant disease, serum level of IgE, body weight, or age of the patients and the response to Omalizumab treatment. Subcutaneous Omalizumab (150 mg every second week) was administered to all patients irrespective of serum IgE levels and body weight, while simultaneously continuing high-dose antihistamine therapy. UAS was evaluated at each visit. Each time the UAS fell below 2, the dose interval was prolonged by 1 week, up to a maximum interval of 8 weeks. However, if the remission in UAS was not sustained, or if there was no fall in UAS, the dosing interval was maintained at 2 weeks, or the interval reduced by 1 week on each visit until the minimum interval of 2 weeks was reached. In patients with treatment failure (UAS > 3) after two to three doses of 150 mg of Omalizumab, the dose was increased to 300 mg. Patients who had full remission of symptoms after three doses of Omalizumab injections with 8-week intervals had their treatment paused but were monitored closely.[4]

15 out of 27 patients (55.5%) reached an UAS of less than 2 after 150 mg of Omalizumab; 12 of these patients (44.4%) ended up with a maintenance dose interval ranging from 5 to 8 weeks while 3 patients (11.1%) could completely pause treatment with Omalizumab; these were maintained solely on a high dose of antihistamine without any relapse. Of the remaining 12 patients, 4 (14.8%) had treatment failure, whereas 8 (29.6%) patients ended on a dose interval of 4 to 8 weeks on 300 mg. This algorithm proved to be cost-effective, efficient, and convenient for the patient, with no safety issues being revealed during the course of the study.[4]

In a study to investigate the efficacy of Omalizumab in patients with chronic autoimmune urticaria (CAU), 12 patients with CAU for greater than 6 weeks duration, with either a positive autologous serum skin test or a positive histamine release assay, who were symptomatic despite therapy with antihistamines, were recruited to the study. These patients were treated with placebo for 4 weeks, followed by Omalizumab every 2 or 4 weeks for the next 16 weeks. Changes in mean UAS, rescue medication use, and quality of life were assessed. Mean UAS declined significantly from baseline values, with 7 patients achieving complete symptom resolution. Rescue medication use was reduced significantly and quality of life improved. No adverse effects were reported.[2]

In a retrospective analysis from Korea of patients treated with Omalizumab for refractory CU, 26 patients were recruited in the study and Omalizumab was administered subcutaneously every 2 or 4 weeks for 24 weeks. In total, 19 (73.1%) of the patients were responsive to Omalizumab. Only mild and tolerable

adverse effects such as rash, dyspepsia, edema, weight loss were reported during the study. All patients could complete the duration of treatment. There was a significantly higher prevalence of personal or family history of allergic diseases in the group which was in remission at 24 weeks as compared with the other patients.[5]

A case series was reported from India, with 5 patients with treatment resistant CSU who were treated with Omalizumab. They were evaluated with a weekly UAS, and there was a significant improvement in all the patients, with reduction in UAS and the need for antihistamines. At end of 4 months, two patients were symptom free and other three reported symptom control on use of only antihistamines. Two patients had side effects in the form of headache and fatigue.[6]

In an analysis by Metz *et al.*, published in March 2014, they report that retreatment with Omalizumab can be effective and safe in patients with CU who have previously benefited from this treatment. All of the patients recruited had shown a complete response on first treatment with Omalizumab, but most of them had relapsed within 2 to 8 weeks of stopping treatment. On retreatment, these patients showed a 100% response rate and a 0% relevant adverse event rate. Thus, this study adds to the evidence suggesting that treatment with Omalizumab does not lead to measurable anti-Omalizumab antibodies.[7]

In a study correlating CU phenotype and patient demographic characteristics with Omalizumab response, Viswanathan *et al.* reported no statistically significant differences among autoimmune positive and negative patients. The study showed that Omalizumab has robust efficacy in refractory CU patients regardless of their autoimmune status, age, gender, IgE levels, or dosing protocol.[8]

Omalizumab was approved by the US FDA on 21 March 2014 for use in chronic spontaneous urticaria (CIU). It is to be administered in subcutaneous injections of 150 mg or 300 mg every 4 weeks. This dosage is not based on body weight or serum IgE level. The appropriate duration of Omalizumab therapy for CIU has not been evaluated. Periodic reassessment of the need for continued medication is recommended.[9]

Atopic dermatitis

Due to the frequent finding of elevated IgE levels in patients with atopic dermatitis (AD), it was postulated that reducing IgE levels in peripheral blood and skin by use of agents such as Omalizumab, may have beneficial effects in AD.[10] There have been mixed reports about the efficacy of Omalizumab in treatment of AD, with Lane *et al.*[11] reporting significant improvement in three patients, Vigo *et al.*[12] showed improvements in five out of seven patients, while Krathen and Hsu[13] described three cases of severe AD in adults who did not respond well to Omalizumab. Based on these reports it is currently difficult to make recommendations about use of Omalizumab in cases of AD, and more studies are needed.

Adverse events

In the phase III study by Maurer *et al.*, the percentage of patients who reported at least one adverse event was similar in all the groups (placebo, 75 mg, 150 mg, and 300 mg). During the 28 weeks study period, there were reports of nine serious adverse events, with five from the 300 mg group and two from the placebo group, and one each in the remaining groups. The reported serious adverse events were as follows: 75-mg group: Influenza viral infection (1); headache (1); angioedema (1); urticaria (4). 150-mg group: Neck pain and discomfort (1); upper respiratory tract infection (1); angioedema (2); urticaria (3). 300-mg group: Asthenic conditions (1); musculoskeletal and connective tissue pain and discomfort (1); tendon disorders (1); mononeuropathies (1); urticaria (2). No deaths or episodes of anaphylactic shock occurred during the period of the study, although there were two cases of adverse events fulfilling the Sampson criteria for anaphylaxis.[3]

In another multicenter randomized, placebo-controlled phase III trial by Kaplan *et al.*, the incidence and severity of adverse events was reported to be similar between both the drug and placebo groups. Headache and upper respiratory tract infections were more common in the Omalizumab group, whereas sinus congestion, migraine, and spontaneous urticaria were more common in the placebo group. During the 16-week follow-up period, upper respiratory tract infections, urinary tract infections and spontaneous urticaria were reported more frequently in the Omalizumab group. The trial included 252 patients in the Omalizumab group and 84 patients in the placebo group.[14]

As per the Omalizumab Joint Task Force (OJTF) report published in 2007 for Omalizumab-associated anaphylaxis, an anaphylaxis-reporting rate of 0.09% has been noted. A total of 41 episodes of anaphylaxis occurring in 35 patients were reported. 61% of these reactions occurred in the first 2 hours after one of the first three doses. 14% of the events after the fourth or later doses occurred within 30 minutes. Considering the timing of these 36 events, an observation period of 2 hours for the first three injections and 30 minutes for subsequent injections has been recommended.^[15] In post marketing spontaneous reports, the frequency of anaphylaxis attributed to Omalizumab use was estimated to be at least 0.2% of patients.^[9]

Omalizumab should only be administered by a physician or health care professional, who is trained in the recognition and treatment of anaphylaxis, and should only be administered in a setting where the appropriate medications and equipment are available to respond to an episode of anaphylaxis.^[16]

In the second OJTF report published online on May 20, 2011, there was no significant change in the pattern of Omalizumab-associated anaphylaxis. The authors stressed the importance of several safety-related interventions, such as taking an informed consent prior to beginning Omalizumab therapy, patient education about the signs and symptoms of anaphylaxis, and prescription of epinephrine auto-injectors with appropriate training for usage.^[17]

What is new?

- Omalizumab approved by US FDA for use in chronic spontaneous urticaria.
- Dosage in urticaria is independent of body weight, serum IgE levels, and type of urticaria.
- Precautions for Omalizumab-associated anaphylaxis.

Footnotes

Source of support: Nil

Conflict of Interest: Nil.

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