



REVIEW ARTICLE

Omalizumab: Pharmacological Properties, Primary Therapeutic Effect Mechanisms and Adverse Effects

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Abstract

Since it was approved in 2003 by the FDA for the therapy of adult and adolescent moderate-severe persistent uncontrolled allergic asthma, the studies on asthma patients have demonstrated that omalizumab has an encouraging safety report, regardless of the allergic sensitization type. Omalizumab was later tried in the therapy of other Th2-type allergic disorders e.g. allergic asthma. Omalizumab hinders IgE effector functions by preventing IgE joining to high-affinity IgE receptors (FcεRI) on effector cells of allergy and does not give rise to mast cell or basophil degranulation. Clinical levels are reached an average of seven-eight days after a single dose of subcutaneous application; steady-state serum levels happen in 14-28 days, after multiple dose of administration. The terminal half-life is variable, ranging from 1 to 4 weeks. Adverse effects are generally mild, such as injection location reaction and headache (especially in children), and also include pharyngitis.

Keywords

Omalizumab, Allergy, Sinusitis, Rhinitis, Polyp

Introduction

Discovered in 1966 by Ishizaka, immunoglobulin (Ig) E antibody was shown to have a central role in the pathophysiology of allergic disorders. Anti-IgE antibody, omalizumab, in June 2002, was firstly approved by the Therapeutic Goods Administration in Australia and then it was approved in 2003 by the FDA for the therapy of adolescent and adult moderate-severe persistent uncontrolled allergic asthma [1]. Since the studies on asthma patients have demonstrated that omalizumab has an encouraging safety report, regardless of the

allergic sensitization type, omalizumab was later tried in the therapy of other Th2-type allergic disorders e.g. rhino-conjunctivitis, eczema and food allergy [2]. Also, because it is applied from time to time, omalizumab can be helpful in patients having difficulty in putting up with a daily basis treatment of allergic diseases [3,4].

What is Omalizumab?

A murine (95% humanized) anti-human IgE, IgG1 κ monoclonal antibody, was produced to target the region (CE3) on the Fc fragment of IgE. Omalizumab hinders IgE effector functions by preventing IgE joining to high-affinity IgE receptors (FcεRI) on effector cells of allergy and does not give rise to mast cell or basophil degranulation. It cannot attach to IgE on cell surfaces where the FcεR1 receptor earlier blocked the anti-IgE epitope [5].

What are the Reasons for Omalizumab Utilized in Studies of Allergic Diseases?

Treatment targeting at IgE impedes with its connecting to the high-affinity receptors (FcεRI) and, in the long-standing, not directly to the low-affinity receptors (FcεRII), hampering the augmentation of a Th2-type response. By means of prevention of mast cell and basophil degranulation, it also diminishes upper and lower airway inflammatory reactions at several phases of the allergic reaction (early and late phase reactions) and has been demonstrated to lessen asthma and allergic rhinitis (AR) symptoms effectively [2,5].

The omalizumab effect on the reaction of nasal

provocation test was detectable within two weeks. Therefore, to protect patients from allergic symptoms during the pollen season, administration of omalizumab ought to begin at least 1 week earlier and maintain during the pollen season. Because serum free IgE quickly may decrease after omalizumab application, by the way of continuous therapy, there is consequent down-regulation of the FcεR1 expression on the inflammatory immune and allergy cells happening over the next 4 to 6 months [6]. For instance, the expression of basophil IgE receptors was shown to decrease *in vivo* and *in vitro* after bi-weekly omalizumab application for 3 months [7]. Omalizumab considerably suppresses skin test reactivity to inhalant allergens, and this effect was found to depend on the extent of suppression of serum free IgE levels.

Pharmacological Properties of Omalizumab

IgE binds to high-affinity (FcεRI) as well as low-affinity (FcεRII: CD23) receptors on several immune system cells. The location whereby IgE attaches to FcεRI is positioned on the Fc fragment in the area where the Cε3 domain being next to the Cε2 domain. Even different from the FcεRI binding spot, the FcεRII binding location of IgE is also positioned on the Cε3 domain [8]. Omalizumab creates significant and rapid reductions ($\leq 99\%$) in serum free IgE concentration [7]. One trial showed a 96% decrease in mean serum total IgE level 3 days following omalizumab administration [9]. Inhibition of serum free IgE to the lowest levels of determined necessitates a proportion of around 10-15: 1 omalizumab/total IgE concentration in the serum [10]. While area under the serum concentration level varies between intravenous and subcutaneous application, identical doses generate comparable omalizumab trough levels. The doses and dosing schedule must depend on the serum basal total IgE level and patient's body weight.

Climax levels are reached an average of seven-eight days after a single dose of subcutaneous application; steady-state serum levels happen in 14-28 days, after multiple dose of omalizumab administration. The terminal half-life of omalizumab is variable, ranging from 1 to 4 weeks. Immune complexes are removed by urinary excretion. Although both the subcutaneous and the intravenous administration were effective, aerosolized omalizumab application did not decrease serum IgE levels and change asthmatic reaction to allergen. Consequently, aerosolized omalizumab application was not considered to be helpful. Also, one individual given aerosolized form of omalizumab developed antibodies against it [11].

Primary Therapeutic Effect Mechanisms of Omalizumab on Basophil and Mast Cells

Irrespective of antigen kind, omalizumab primarily combines circulating IgE preventing it to bind the α -chain of the trimeric high affinity IgE receptor (FcεRI)

on mast cell and basophil, consequently inhibits IgE binding to FcεRI without crosslinking IgE. Nonetheless, omalizumab does not attach to cell-bound IgE (non-anaphylactogenic). In these IgE molecules, the epitope against which omalizumab is directed is covered since already combined to the receptors [8].

In vitro, omalizumab and human IgE form several immunocomplexes differing in dimension as the 2 components' molar ratios are altered. The principal complex, a stable cyclic hexameric structure consisting of 3 IgE and 3 omalizumab molecules, is found at a 1:1 molar ratio. With surpluses of either IgE or omalizumab, the most of the complexes is consisted of a trimer including 1 IgE and 2 omalizumab molecules or vice versa. Combination of IgE and may not prevent IgE attaching to allergens. IgE: Omalizumab complexes may compete with basophil/mast cell-bound IgE for allergens, so decreasing the possibility of degranulation with allergen re-exposure [10,12].

Briefly; effect mechanisms of omalizumab in allergy are as following:

- Attaches to serum free IgE and reduce its serum level
- Shows a high degree of IgE isotype specificity and blocks IgE without affecting other isotypes
- Prevents mast cell/basophil degranulation following provocation with sensitizing allergens
- Decreases the early- and late-phase reactions to allergens
- Does not cause anti-antibodies development [13].

Secondary Therapeutic Effect Mechanisms of Omalizumab on Other Immune System Cells

Low-affinity receptors (FcεRII or CD23) of IgE are expressed on monocytes, macrophages, lymphocytes, epithelial and dendritic cells. Besides stimulating basophils/mast cells via FcεRI binding, IgE interacts with other immune cells in less clear ways. For instance, IgE binds to FcεRI on antigen-presenting cells and eosinophils. This interaction seems to mediate antigen presentation by antigen-presenting cells and their immunologic response [8]. Although the effect on eosinophils is less clear, it is hypothesized that such interactions may adjust local tissue IgE levels. The other low-affinity IgE receptor, FcεRII, is detected on B lymphocytes; IgE attachment to the FcεRII increases antigen presentation through these cells [8]. *In vitro* and animal studies imply that omalizumab attachment to membrane IgE (mIgE) inhibits or lyses mIgE-expressing B cells and lessens IgE synthesis. Although omalizumab does not attach basophil-bound IgE, omalizumab can attach mIgE on mIgE-expressing B lymphocytes because mIgE expression of these cells happens in such a way that IgE-FcεRI attachment regions stay unmasked. Even though serum free IgE are quickly reduced after omalizumab given,

and the expression of high-affinity IgE receptors on the inflammatory immune cells is significantly diminished after long-term therapy. Omalizumab does not attach to high- or low-affinity IgE receptors on inflammatory cells, but prevents IgE attaching to these receptors. Moreover, there is data that FcεRI and FcεRII expression density on other immune cells varies based on serum total IgE concentrations [14].

Reported Adverse Effects of Omalizumab

Adverse effects are generally mild, such as injection location reaction and headache (especially in children), and also include pharyngitis. While these side effects of omalizumab therapy have generally been insignificant, concerns have been raised about three key areas: Malignancy, cardiovascular disease, and hypersensitivity reaction (anaphylaxis). A new report utilizing collective data from 67 clinical trials showed no discrepancy in the rate of malignancy in omalizumab vs. placebo-treated patients. Malignant solid tumors were described in twenty-five (0.5%) omalizumab-treated patients, when compared to 5 (0.2%) control patients thru all finished trials (all but one were solid tumors) [15]. The beginning of most of the solid tumors led to omalizumab therapy, and 60% of malignancy occurred within ≤ 6 months of therapy. A team of blinded, independent oncologists decided that none of the cases was associated with omalizumab therapy. In general, the data do not indicate an underlying association between omalizumab and solid tumors [16].

Interestingly, recent EXCELS (Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma) study demonstrated that unequal increase in ischemic heart disease, arrhythmias, cardiomyopathy, cardiac failure, pulmonary hypertension, cerebrovascular disorders, embolic, thrombotic and thrombophlebotic episodes [17]. It may also be related to an elevated risk of geohelminth infection in patients at high risk for parasitic infections but omalizumab therapy does not seem to influence the response to therapy or the parasitic infection severity [18].

There was no reported increase in the incidence of type I hypersensitivity adverse reactions. The most common drug-related type I hypersensitivity reaction was mild-moderate urticaria. Anaphylactoid reactions were unusual and were not along with systemic manifestations e.g. hypotension. The anaphylaxis frequency is roughly 0.2%, requiring omalizumab application in a health care facility. The OJTF (Omalizumab Joint Task Force) report suggests a two hour observation time for the first 3 injections and 30 minutes for following injections because 75% of the anaphylactic reactions happened within these time intervals [19,20].

There are still unsolved issues of omalizumab therapeutic use nowadays. The serum total IgE levels were not reduced in all patients after omalizumab therapy,

although this does not affect therapeutic efficiency. However, relapse/recurrence of the disease with same symptoms frequently happens immediately after discontinuation of the omalizumab therapy. The treatment dose of omalizumab for different diseases such as chronic rhinosinusitis with nasal polyposis is still not well-known [21]. The cost of omalizumab therapy is currently very expensive.

Conclusion

The danger of anaphylaxis and other treatment-associated adverse reactions of omalizumab were found to be quite little. Nevertheless, most of the clinical trials were performed in comparatively small cohort of patients and in a relatively short period. Even though the risk-benefit of omalizumab has been established in allergic asthma, long-term trials will help elucidate the risk-benefit profile of omalizumab in the therapy of other allergic disorders by larger patient groups [22].

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