Review

Questions and Answers
About the use of omalizumab in clinical practice

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1. What is the lower value of total IgE that omalizumab will be effective and what is the maximum dose?

According to the summary of product characteristics (SPC) and the revised dosing table, the range of values of IgE for drug administration ranges from 30 to 1500 IU/ml. However, initial clinical studies have shown higher probability for clinical response in patients with IgE >76 IU/ml. The maximum dose is 1200mg per month divided into two doses every 15 days.[1,2]

2. When retesting of total IgE after starting treatment is required?

Binding of omalizumab to free serum IgE leads to the formation of immune complexes. These immune complexes (i.e. "binded IgE") increase the levels of total IgE by 5 to 6 times because their clearance by the reticuloendothelial system of the liver, is much slower than that of free IgE. Commercially available laboratory assays cannot separate and measure the free IgE. Thus, the measurement of IgE after administration of omalizumab reflects not only the free but also the binded IgE with omalizumab. For this reason, **retesting of total IgE after initiation of treatment with omalizumab is not required**.[1,3]

3. How common are allergic reactions after administration of omalizumab?

According to various reviews, the rate of allergic reactions associated with omalizumab administration was very low, ranging between 0.09 and 0.1%. These low rates may be attributed to the following:

a) omalizumab is a humanized monoclonal antibody to a large extent (approximately 94-95%)
b) omalizumab binds to the C3ε receptor of the heavy chain of IgE. This place is the same with which the IgE binds to the high and low affinity receptors on the mast cells, basophils and other inflammatory cells, thereby forming complexes. Omalizumab connected to free IgE prevents its binding to these receptors.
c) omalizumab cannot bind to IgE receptors on the cell surface or to IgE that is already binded to FceRI receptor. Consequently, omalizumab cannot activate mast cells, basophils or other inflammatory cells by interacting directly with their FceRI receptor.

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In patients treated with omalizumab no measurable anti-omalizumab antibodies have been found.[4-7]

4. For how long should the patient be monitored after administration of omalizumab for possible allergic reaction?

As mentioned in various reviews and in the American Academy of Allergy, Asthma and Immunology guidelines, it is recommended that the patient must be monitored for about 2 hours for the first 3 administrations in the waiting room of the private clinic or the outpatient clinic of a hospital. For the next administrations, the incidence of allergic reaction is practically minimal and therefore only half an hour stay of the patient is recommended after injection of omalizumab.[4,8]

5. Are there biomarkers to serve as predictors of treatment effects to omalizumab?

Analysis of biomarkers in the EXTRA study after 48 weeks of omalizumab administration, revealed that reductions of exacerbations were greater in those patients with fractional exhaled nitric oxide (FeNO) ≥19,5 ppb, peripheral blood eosinophils ≥260/μL and serum periostin ≥50ng/ml. Recently, it was reported that using ROC curve analysis the best predictors of response to omalizumab were FEV1 (≤60% pred) and IL-13 (≥65 ng/ml) in sputum supernatant. Furthermore, late responders had higher serum IgE levels, shorter disease duration and greater number of blood eosinophils compared to early responders.[9,10]

6. For how long should the drug be administered before deciding that it is effective or not in a patient?

To achieve clinical benefit, free IgE should be reduced to extremely low levels because there are 10.000-1.000.000 FceRI receptors on mast cells and basophils that are almost all occupied by IgE. Only 2000 IgE molecules are sufficient to achieve 50% of maximum (half-maximal) histamine release from basophils. Accordingly, because great reduction of IgE is necessary to prevent the activation of mast cells and basophils, at least four months of drug administration are necessary to provide clinical response.

However, in a more recent study it was shown that approximately 25% of patients were responders after eight months of administration, which means that some patients may respond later than others.[11-13]

7. What is the effect of omalizumab when rhinitis and/or nasal polyps coexist?

Several studies in patients with asthma treated with omalizumab and good response showed a reduction of symptoms of concomitant allergic rhinitis. A decrease of the size of nasal polyps as assessed both endoscopically and with computed tomography was also observed.[14-16]

8. Can omalizumab be combined with classical sublingual or subcutaneous immunotherapy?

There is no contraindication for co administration of omalizumab with sublingual or subcutaneous immunotherapy. In fact, there are studies showing that co-administration of the two treatments or administration of omalizumab before starting immunotherapy, improves the results of immunotherapy, prevents any anaphylactic reactions and allows the maximum target dose of immunotherapy to be administered.[17,18]

9. Can omalizumab be co-administered in patients with immunological diseases?

The case of co-administration of omalizumab with treatment for immunological diseases (ankylosing spondylitis, rheumatoid arthritis, etc.) refers mainly to the tumor necrosis factor (TNF)-alpha inhibitors, as so far our knowledge of the literature is limited in that co-administration.

Clearance of omalizumab follows the process of immunoglobulins G (IgG) and involves its degradation of the reticuloendothelial system (DES). TNF-alpha inhibitors, with etanercept as the most common representative (a water soluble dimer molecule of p75-TNF receptor), is speculated that are also metabolized primarily by the DES.

Bearing this in mind, the medical literature database Stockley's Drug Interactions argues that "the co-administration of monoclonal antibody (omalizumab) with TNF-alpha inhibitors may potentially increase the frequency of neutropenia and severe infections".[1,19,20]

10. What will happen in case of administration of omalizumab in patients with Churg-Strauss vasculitis?

It is known that Churg-Strauss Vasculitis may be diagnosed in patients with asthma and underlying eosinophilic inflammation during tapering of systemically administered corticosteroids. A similar mechanism has been reported in cases of patients under treatment with omalizumab, in which either the dose of oral corticosteroids was reduced

due to improved asthma control or their administration was delayed for the same reason.

Administration of omalizumab in patients with Churg-Strauss vasculitis **is not contraindicated**. On the contrary there are studies showing that the use of omalizumab in such patients has anti-inflammatory properties, such as reducing the number of eosinophils in the circulation and tissues. However, greater attention is required in these patients during the tapering of systemically administered steroids in order to identify a possible relapse of the basic disease.[21-23]

11. Is omalizumab administration contraindicated in patients with hematological diseases?

After the administration of omalizumab in animal models incidents of thrombocytopenia with bleeding diathesis were reported. However, such incidents have not been observed during clinical studies in humans for drug approval.

A retrospective analysis of published clinical studies reported rare cases of a progressive decrease in the number of platelets. This reduction was not accompanied by a simultaneous reduction of the level of hemoglobin, or the incidence of bleeding.

The recommendation today is that omalizumab should be administered cautiously in patients suffering from idiopathic thrombocytopenia or other forms of platelets dyscrasias.[1,24]

12. How is the dose modified in patients with renal or hepatic impairment?

There are no pharmacokinetic studies regarding renal or hepatic impairment. However, the clearance of omalizumab takes place in the reticuloendothelial system and therefore it seems that no dose adjustment is required in patients with renal or hepatic impairment.[1]

13. Is the administration of omalizumab safe in pregnancy and breastfeeding?

In individual cases in which omalizumab was administered to pregnant women with severe uncontrolled asthma, good clinical results were reported without adverse effects on the mother or the fetus. A recent observational study of 191 pregnant women confirmed the safety of omalizumab in pregnancy, showing that cases of congenital abnormalities, prematurity or low birth weight did not differ from other studies in pregnant women with asthma.

It is not known whether omalizumab is excreted in human milk, but as data in animals have shown to be excreted in milk, it should not be used during breastfeeding.[1,25,26]

14. For how long should omalizumab be administered?

There is no definite answer to this question so far.

There are several studies in which the drug was administered for a period of 2 to 7 years, showing that the longer the period the better the results.

Of interest is the study of Nopp et al in which the drug was administered for 6 years in patients with severe allergic asthma.

Three years after the discontinuation, most patients had mild, stable asthma, and reduced sensitivity of basophils to specific allergens was found. Based on the available clinical studies and expert opinion, it appears that six years is a reasonable time for administration of the omalizumab before thinking discontinuation. This is supported by the fact that it takes a long time for free IgE to be reduced to very low levels and maintain the clinical outcome.[27-30]

15. How safe is omalizumab in long-term use?

The long-standing experience of over 10 years from the use of omalizumab in clinical practice shows that it's long-term use is safe. The rate of anaphylactic reactions is very low. The approval for administration in children > 6 years of age further supports its safety. Of interest is a recent prospective observational study which focused on the safety of the drug after 5 years of observation in relation to the incidence of malignancies, which found that treatment with omalizumab is not associated with an increased risk of malignancy.[4,31,32]

16. Is omalizumab as effective if re-administered after discontinuation?

In most cases, re-administration had the same good results as the primary administration. A recent study, however, showed that about 20% of patients in whom the drug had been administered for a period of 2 years and then discontinued for 1 year, had no response after re-administration.[27,33]

17. Are there indications that omalizumab prevents or improves airway remodeling?

There is evidence that in airway smooth muscle cells of asthma patients, IgE increased the deposition of collagen type- I,- III, -VII and fibronectin. Serum IgE from patients

with allergic asthma promotes airway remodeling independently of the presence of allergens

Recent studies have shown that incubation of airway smooth muscles with omalizumab prevented proliferation and deposition of collagen type I, III and fibronectin after exposure in serum from patients with allergic asthma.

In bronchial biopsies from patients with severe asthma, smooth muscle proteins, mainly myosins and actins, decreased after treatment with omalizumab.[34-36]

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