Lack of omalizumab efficacy in severe atopic dermatitis with extremely elevated IgE levels: two case reports and a literature review

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Abstract

The authors present two cases of severe atopic dermatitis with extremely elevated IgE levels treated with omalizumab. The effect of this treatment was completely unconvincing in both patients, most likely because of extremely elevated IgE values, which could not be eliminated by omalizumab. Our observation is consistent with earlier published literature reporting that omalizumab as a treatment for atopic dermatitis seems to work better in patients with lower levels of IgE antibodies.

Keywords: atopic dermatitis, treatment, omalizumab

Introduction

Atopic dermatitis is a very common inflammatory skin disease whose incidence is increasing worldwide and which has a significantly negative effect on the quality of life. Treatment of this condition must be complex and combined, but also differentiated and individualized. The treatment strategy is primarily based on the severity of atopic dermatitis. For the most difficult cases, in contrast to psoriasis, there are limited therapeutic options. Cyclosporine A is currently the gold standard of treatment. However, if treatment fails or it is not tolerated by the patient, there is little more to offer except "off label" or experimental therapy. One of these options is also biological treatment, including omalizumab.

Omalizumab is a chimeric humanized monoclonal antibody composed of 95% human and 5% murine sequence. It is able to bind to the high-affinity IgE receptor (FcεR I), which prevents IgE from binding the surface of mast cells and basophils (1, 2). This leads to blocking mast cell degranulation. Long-term treatment with omalizumab also results in downregulation of FcεR I on mast cells, but also on basophils and Langerhans cells (1, 2). Omalizumab has been approved for the treatment of asthma, and recently for the treatment of chronic spontaneous urticaria as well.

The most common adverse events of omalizumab include injection site reactions, infections (nasopharyngitis, sinusitis, and upper respiratory tract infections), nausea, headache, urticaria, and angioedema. The risk of anaphylaxis is very low, yet it may occur in up to 0.1% of patients treated with omalizumab (3, 4).

For the treatment of atopic dermatitis, omalizumab has mostly been used in doses ranging from 300 to 450 mg every 2 to 4 weeks (5–7). Sometimes treatment with omalizumab has been combined with intravenous immunoglobulins, or patients were pretreated with immunoadsorption before omalizumab introduction (7, 8).

SCORing Atopic Dermatitis (SCORAD) is a clinical tool for assessing the severity (i.e., extent or intensity) of atopic dermatitis as objectively as possible. It was developed by the European Task Force on Atopic Dermatitis in 1993.

This article presents our personal experience with omalizumab in the treatment of two patients with severe atopic dermatitis and extremely elevated IgE levels.

Case reports

Case 1

A 44-year-old female had a 26-year history of atopic dermatitis along with asthma and allergic rhinitis with polyvalent inhalant and food allergy. Skin symptoms first appeared on the back of her hands at 18 years of age with a progression to flexural areas and subsequent generalization by the time she was 30 years old. In 2004 she was patch tested, and nickel sensitization was detected. From 2012 onward she had nearly continuously generalized lesions. In 2014 she was treated with narrow-band UVB, which had to be terminated after 20 sessions due to exacerbation and progression to erythroderma. In June 2014, cyclosporine A was introduced with only a temporary effect, and there was a gradual increase of IgE (8,058 IU/ml in June 2015, and 41,445 and 48,526 in October and December 2015, respectively). Moreover, several incidents of herpetic changes occurred during cyclosporine A treatment. At that point a decision was made to treat her with omalizumab, which was introduced in December 2015 with a dose of 450 mg every 2 weeks. Initial SCORAD was 55 (Fig. 1). Cyclosporin A was gradually abandoned during December 2015. The patient tolerated the treatment quite well, although she had a fever lasting 2 to 4 days after every omalizumab injection. Three months after treatment initiation (February 2016), the patient's condition was slightly improved (SCORAD 50), although itching persisted. There was also a slight decrease in IgE level (47,035 IU/ml). After 6 months of treatment (June 2016), the clinical appearance had clearly deteriorated (SCORAD 78), with prominent itching causing the patient to wake up at night. On the other hand, the fever after omalizumab applications had subsided. The level of IgE was 45,929 IU/ml. At the 9th month of treatment (September 2016), there was a further progression of the condition (SCORAD 80) and elevation of IgE to 66,000 IU/ml, and omalizumab treatment was therefore terminated in October 2016 (Fig. 2). Transformation into a T-cell skin lymphoma had been even considered, but histology from skin biopsy had fortunately ruled this possibility out. The patient is presently being treated with prednisolone at doses around 20 mg daily in a combination with methotrexate 7.5 mg weekly.

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Figure 1 | Case no. 1 at the initiation of treatment (SCORAD 55).

Figure 2 | Case no. 1 at the termination of treatment (SCORAD 80).

Case 2

A 47-year-old female had been suffering from atopic dermatitis from her early childhood through puberty. She also had bronchial asthma and pollen allergy. After puberty, her skin condition was in remission until 2013, when it progressed to erythroderma. She was treated with prednisolone for about half a year, which was followed by cyclosporine A treatment (from October 2013 to October 2014), and then again from June 2015. In January 2016 she was referred to our clinic with widespread dry skin with lichenification and multiple excoriations (SCORAD 48), despite cyclosporine A treatment. Subjectively, she felt an unbearable itching that prompted her to scratch continually. Her IgE level was 61,904 IU/ml. Consequently cyclosporine A was gradually phased out, and in March 2016 omalizumab was introduced with a dosage of 450 mg every 2 weeks (SCORAD 45; Fig. 3).

After a 3-month treatment with omalizumab (June 2016), the patient's skin condition slightly worsened (SCORAD 50) and prominent itching persisted as well. The IgE level even increased to 105,000 IU/ml. In September 2016 there was a decrease of IgE level to 53,700 IU/ml, but the skin appearance as well as itching worsened (SCORAD 64; Fig. 4). In December 2016 the omalizumab treatment was terminated due to a lack of efficacy (SCORAD 73), even though the IgE level decreased to 48,600 IU/ml. Treatment with immunoadsorption has recently been introduced.

Figure 3 | Case no. 2 at the initiation of treatment (SCORAD 45).

Figure 4 | Case no. 2 at the termination of treatment (SCORAD 73).

Discussion

The treatment of atopic dermatitis with omalizumab has been subject to great expectations. High hopes were based on the fact that the majority of patients with this condition had a high level of IgE antibodies, which—when reduced—should lead to improvement of eczema. Many authors initially described an improvement of atopic dermatitis with omalizumab therapy (9–11). Sheinkopf et al. conducted a pilot study among 21 patients with atopic dermatitis and asthma (IgE levels varying from 18,2 to 8,396 IU/ml), and all the patients improved significantly (12). Omalizumab also seems to work well in children; Ivengar et al. treated eight children with atopic dermatitis (omalizumab dose 150–375 mg every 2 or 4 weeks) and observed a significant decrease in IgE as well as a SCORAD reduction of 45 to 80% (13). On the other hand, some authors have not recorded any improvement. For example, Heil et al. treated 20 patients with severe atopic dermatitis (mean level of IgE 372.78 IU/ml) with omalizumab for 3 months and observed no significant difference between the omalizumab and placebo group, although the treatment reduced free serum IgE, lowered surface IgE and FcεR I expression, and also improved the results of atopy patch tests (14). Concurring with our experience, Krathen and Hsu did not observe any improvement when three adult patients with severe atopic dermatitis were treated with 450 mg of omalizumab every 2 weeks for 4 months. These patients also had considerably elevated IgE levels (from 5,440 to 24,000 IU/ml) (15); however, their levels were not as high as our patients' levels. The role and efficacy of omalizumab in atopic dermatitis is, realistically, quite complex. Holm et al. performed a systematic literature search in PubMed, Web of Science, EMBASE, and Clinical Trials.gov in 2018 and found 26 studies comprising 174 patients with atopic dermatitis treated with omalizumab, of which 129 (74.1%) experienced a beneficial treatment effect. The authors also noted their own experience with omalizumab in nine patients with atopic dermatitis. They recorded a good or excellent response in 50% of patients, 12.5% had a moderate response, and 37.5% experienced no clinical response or even deterioration of atopic dermatitis during treatment (16). Another extensive literature review was conducted by Wang et al. The authors analyzed 13 studies (103 patients) in PubMed, MEDLINE, EmBase, and the Cochrane library. Most of the patients (60.5%) had severe atopic dermatitis. An excellent clinical response was achieved by 43.0% of the patients, 27.2% showed satisfying results, and 30.1% had an irrelevant response or even deterioration of atopic dermatitis. Multivariate logistic regression among 83 patients verified that IgE levels lower than 700 IU/ml were significantly associated with an excellent clinical response when compared to patients with IgE concentrations between 700 and 5,000 IU/ml and those with IgE more than 5,000 IU/ml. Age, sex, disease severity, comorbidities including asthma, and omalizumab dosage had no significant association with the clinical response to omalizumab (17). The association of more favorable clinical responses among patients with lower concentrations of IgE might be explained by better IgE neutralization in these patients. However, the discrepant results of omalizumab treatment in patients with atopic dermatitis is probably caused by the fact that atopic dermatitis has a much more complex etiopathogenesis, in which not only elevated IgE levels are a significant factor. The damaged skin barrier appears to be crucial in the initial development of atopic dermatitis, and sensitization as well as a gradual increase in IgE levels appears to be secondary. The role of the skin barrier was also proved by a study conducted by Hotze et al., in which 20 patients with atopic dermatitis were treated with omalizumab, and there was a better treatment response in the subgroup with no filaggrin mutation and with higher serum levels of phosphatidylcholines (18). Thus it seems that in patients with extremely high IgE levels treatment with conventional doses of omalizumab results in a certain reduction of IgE levels, which nevertheless still remain significantly elevated. A major reduction of IgE would definitely require significantly higher doses of omalizumab, which would probably unnecessarily increase the risk of anaphylaxis.

To conclude, omalizumab appears to work quite well in pediatric patients, and also in adult patients without extremely elevated IgE levels, and especially in those with no filaggrin gene mutations. However, in patients with extremely elevated IgE concentrations, the effect of omalizumab treatment is not so convincing, as confirmed by our two cases. The solution in such cases might be pre-treatment of patients with immunoadsorption prior to omalizumab treatment (8).

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