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Anti IgE Therapy in Chronic Urticaria

Ragıp Ertaş

Abstract

The crucial position of IgE within the pathogenesis of allergic diseases made it a key target for therapy. The inhibition of the allergic inflammatory cascade by anti-immunoglobulin E (IgE) therapy is a new and promising concept in the treatment of these diseases. Currently available anti-IgE agent omalizumab has been started to be used in past 3 years in the cases of chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU), resistant to the first-, second-, and some third-line treatments. The use of omalizumab as an effective and safe biological therapy for inadequately controlled severe, persistent patients with CSU and CINDU provided a valuable new treatment option for these patients. However, the data about possible mechanisms of anti-IgE therapy in these patients, treatment strategies and dose regimens of anti-IgE therapy are different, and special patient groups and possible side effects are still insufficient. Also, studies about possible future anti-IgE treatment options are ongoing in CSU.

Keywords: chronic urticaria, anti-IgE therapy, omalizumab, management, new anti-IgE agents

1. Introduction

Chronic spontaneous urticaria (CSU) is defined as the spontaneous occurrence of itchy wheals, angioedema, or both for more than 6 weeks [1, 2]. More than 5 million people only in Europe suffer from CSU, especially its negative effects are on quality of life and sleep, school and work performance and daily life activities, and social relationships [3]. Recently, inside the EAACI/GA(2) LEN/EDF/WAO Guideline, it has been endorsed that nonsedating H1 antihistamines ought to be used for the first-line treatment of CSU and doses of H1 antihistamines can be increased by four-fold as the second-line treatment till symptoms can be kept under control completely [1, 4]. When these increased doses of H1 antihistamines fail,

one of the recommended therapies as the third-line treatment is omalizumab. It is the only available agent of anti-immunoglobulin E (IgE) at the current time [3, 4].

2. Role of IgE in CSU

IgE has an important role in the pathogenesis of many allergic disorders including asthma, allergic rhinitis, latex allergy, hyper-IgE syndrome, chronic rhinosinusitis, atopic dermatitis, food allergy, drug allergy, and CSU. However, the role of IgE levels has different mechanisms in pathogenesis and diagnosis of the leading allergic disorders. In support of this, IgE levels are not correlated with CSU severity [5].

Measurements of total IgE levels during anti-IgE therapy with conventional methods show increases by nearly 3- to 11-fold [6]. The increase in monthly IgE levels is explained by the fact that total IgE measured during therapy is made up of free IgE and IgE binds free IgE and forms a complex and that, daily IgE production continues [3]. This is explained in the literature that commercial kits used to determine IgE levels measure both free IgE and IgE-anti-IgE complex together [3, 7]. Therefore, it is recommended that total IgE should not be used for measurement of free IgE during omalizumab treatment [8].

It is known that immunocomplexes do not cause tissue damage or complement fixation. In addition, it is proposed that accumulation of immunocomplexes in the extravascular space (mucosal epithelial lining) and the inability of anti-IgE forming a complex with IgE to go back to capillary space creates a local space, protective against allergens [7].

The role of IgE measurements in planning treatment for chronic urticaria and adjustment of the dose of omalizumab is not clear yet [9]. A recent study has shown that basal IgE levels do not play a role in responses to treatment [3].

Serum total IgE levels are regulated by several factors in the absence of anti-IgE therapy. It is known that the baseline IgE can predict the clearance and rate of production of IgE [10], and baseline IgE levels have a greater dependence on IgE production than IgE clearance [11]. Thus, in patients with high IgE levels and high IgE production, separately omalizumab, relevant IgE levels will come back after omalizumab loses its action as compared to patients with low IgE production and low IgE levels [6, 12]. Also, it was shown that, during the therapy, decrease in the serum concentration of free IgE is negatively correlated to the baseline IgE [6].

On the other hand, Lowe postulated that longer administration of omalizumab (1 year) decrease 56% of the IgE production [13]. Further studies with longer omalizumab administration may be highlighted in this topic.

The clearance of IgE is dependent on serum levels itself [10]. The half-life of serum free IgE is short (1 day) and changes in half-life of IgE are probably not very common and more likely an insignificant effect on regulation of IgE levels [14].

In a study, a different anti-IgE antibody (CGP 51901) was assessed in patients with another allergic disease rather than CSU. The half-life of the drug was negatively correlated to the free

baseline IgE levels. Also, the time for free IgE to return to baseline after anti-IgE treatment was negatively correlated with baseline IgE levels [15]. This issue may be summarized as higher IgE levels predict shorter half-life of anti-IgE antibody. However, the overall results from the studies are difficult to interpret in terms of their relevance because the administration of anti-IgE was different, the observation period was different, and many other aspects of the subjects and the protocols were different. Also, Casale showed that serum concentration of free IgE is correlated to administrated doses of omalizumab. It was claimed that high doses administration of omalizumab, decreases the free IgE to the most stable levels [6].

3. Omalizumab therapy in CSU

It has been known since 2005 that omalizumab, a humanized immunoglobulin G1 (IgG1) monoclonal antibody which binds IgE, is well tolerated by patients with severe atopic asthma [16]. In 2014, as a first anti-IgE agent, omalizumab's marketing authorization for CSU was approved first by European Medicines Agency and then by Food and Drug Administration [17].

Before 2014, there were few case reports on effects of omalizumab used; although not indicated in patients with chronic urticaria, few studies on patients' experiences with omalizumab and omalizumab phase studies in larger groups of patients; however, there is still a limited number of studies on the use of omalizumab for the treatment of CSU in a real life context [4].

The characterization of the response to omalizumab treatment has been previously reported both in the controlled trials and in the case series [3, 4, 18]. But it is still unclear about the long-term management of anti-IgE therapy and possible side effects for the clinician. And, it is also unclear that when will patients show relapse after discontinuation of omalizumab treatment. Omalizumab discontinuation must be taken into consideration every 3–6 months [3, 19]. Patients who have relapsed after discontinuation of omalizumab, the reinitiation of omalizumab therapy is primarily based on modifications in medical factors and doctor's discretion [20]. Metz et al. have reported that, in the case of possible retreatment, resistance to omalizumab does not develop readily in most patients with CSU [20, 21].

It is not often found that an external trigger or any factors that can initiate the symptoms of CSU patients. Most patients with CSU have an autoimmune cause; therefore, autoimmunity can be considered firstly [22]. Some patients produce IgE autoantibodies (against thyroperoxidase or double-stranded DNA) and IgG autoantibodies (against FcεRI and/or IgE), which lead to activate mast cells and basophils. Current reports have demonstrated that IgE, by means of binding to FcεRI on mast cells without FcεRI cross-linking, can boost the proliferation and survival of mast cells [23, 24]. Also, IgE and FcεRI engagement can also lower the release of mast cells and cause high sensitivity to various stimuli through both FcεRI and other receptors. Eventually, in a case of stimuli, this process can give rise to degranulation of mast cells [23]. It is known that anti-IgE therapy shows its effect on urticaria through lowering unfastened IgE levels and mast and basophil cell activations. It also downregulates an IgE receptor FceR1 in the mast, basophil, and dendritic cells [23].

Finally, there are three different mechanisms of omalizumab in patients with CSU [22, 23];

   i. Omalizumab sequesters monomeric IgE to lessen its priming effect on mast cells;

  ii. In CSU patients with IgG autoantibodies in opposition to IgE or FcεRI, the depletion of mast cell IgE with the aid of omalizumab and the following downregulation of FcεRI on mast cells and basophils might lead to their reduced state of hyperexcitability;

 iii. In those sufferers with IgE autoantibodies against autoallergens, the inhibition of IgE binding to FcεRI via omalizumab and the downregulation of FcεRI would represent a significant mechanism of omalizumab.

However, it is quite difficult to explain the mode of action of omalizumab based on elimination of IgE and the other three mechanisms. It is clear that further studies are needed to elucidate its mode of action in CSU.

3.1. The usage of omalizumab in chronic inducible urticaria (CINDU)

Chronic urticaria can also be spontaneous and/or inducible, though the triggers of inducible urticaria [25]. CINDU emerges when triggered by physical stimuli including scratch, cold, heat, pressure, friction, exercise, sun exposure, water exposure, and exercise [19]. The term CINDU includes cold urticaria, delayed pressure urticaria, heat urticaria, solar urticaria, symptomatic dermographism, vibratory angioedema, aquagenic urticaria, cholinergic urticaria, and contact urticaria [19, 25].

The suggested dosing and indications of therapy are not different from that used for CSU in the patients with CINDU. It is either 150 or 300 mg/4 weeks given subcutaneously [3]. Even though, there are many large studies currently underway for CINDU [25], there are individual cases and smaller studies assessing the efficacy of omalizumab in various types of CINDU, while the number of overall cases is low. The results of these studies have shown that efficacy of omalizumab treatment is similar in CSU and CINDU patients [3, 9, 20, 21]. All recent studies and case reports have shown notable and optimistic outcome results in patients with CINDU [9].

3.2. The selection of patients and indications of omalizumab therapy

CSU patients who are planning to use omalizumab should meet the following conditions [1, 3, 19]:

1. Patients who are older than 12 years of age.

2. Patients who are underneath expert care (dermatologists and/or immunologists).

3. Cause of urticaria is not identifiable with the aid of further investigations and CBC, ANA, and urine analysis outcomes are not abnormal.

4. Patients are recognized with the aid of professionals as moderate to severe CSU that is not responsive to standard treatment.

5. Disease period is longer than 3 months and the symptoms stay persistent notwithstanding using guideline primarily-based treatment.

3.3. Dose regimens and assessment of patients

The preliminary and continuation dosing is not similar to that used for asthma. Doses of omalizumab for asthma are adjusted based on weight and serum IgE levels [7]. The role of basal IgE levels in planning treatment for CSU and adjusting doses of omalizumab are not yet clear [26, 27]. Metz et al. have noted that basal IgE levels do not play a part in response to treatment [3]. Also in CSU patients, omalizumab is given 300 mg or 150 mg (sc) every 4 weeks and is not decided with the baseline serum IgE levels or patient's weight [1].

Two doses of omalizumab (150 mg or 300 mg/4 weeks) have been accepted by the USA Food and Drug Administration (FDA) for CSU refractory to H1 antihistamines. Uysal et al. introduced an algorithm for defining dose, dose interval, and clinical response in CSU patients. Due to this set of rules, it is affordable to start omalizumab with a dose of 300 mg every 4 weeks, and if the patient is good enough, taper to a lower dose (e.g., 150 mg every 4 weeks), or much less frequent injections (every 6 weeks) [27] (**Figure 1**). However, in a current meta-analysis, wherein seven randomized, placebo-controlled studies determined substantial proof
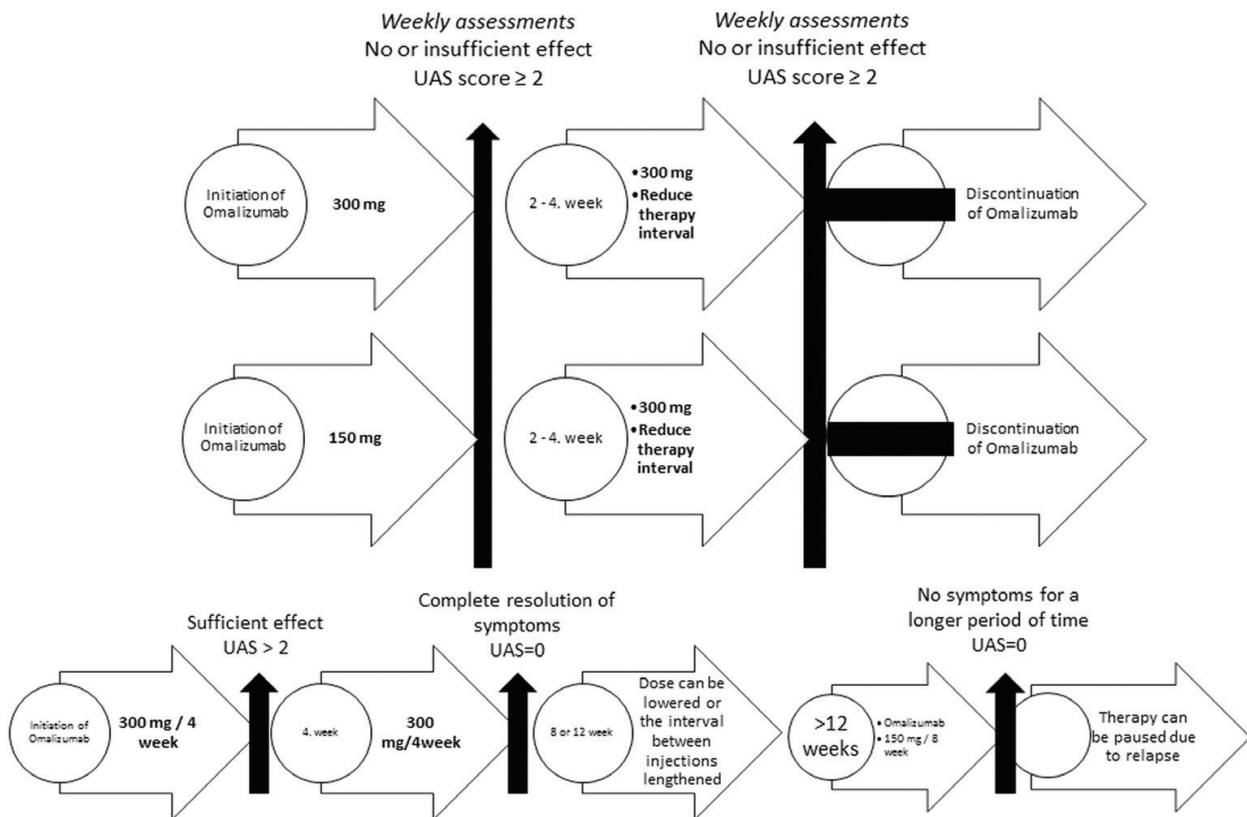

Figure 1. A practical individualization of omalizumab doses during the therapy.

for the efficacy and safety of omalizumab in patients with CSU and to treat patients with CSU with 300 mg of omalizumab for 4 weeks [18].

3.4. Omalizumab therapy in special populations

Current guidelines of CSU consist of tips for special populations, especially children, the elderly, and pregnant or lactating women [1]. They suggest the similar management and treatment algorithms as adults but pay attention to factors such as age, dosage, and availability of toddler-pleasant approaches [1].

3.5. Omalizumab therapy in children and elderly patients

Omalizumab is available as a third-line treatment for CSU in adolescent sufferers (≥12 years) with an insufficient response to antihistamine therapy, and is likewise approved for kids aged ≥6 years with severe persistent allergic asthma [27]. Its efficacy and safety profile have been also shown in a case study in patients with CU aged <12 years [28]. There are no safety warnings about omalizumab in the geriatric population [29].

3.6. Omalizumab therapy in pregnant and lactating women

There are limited posted records at the safety of omalizumab in pregnant women with CSU [30], despite the fact that available data about anti-IgE therapy are reassuring with other diseases; however, the research in asthma patients showed no obvious increase or major anomalies have been observed [31, 32]. The results have been now not distinct from those in women receiving placebo and other asthma therapies [33, 34].

The initiation of omalizumab in the course of pregnancy is not recommended, although if a woman turns into pregnant even as receiving omalizumab, it's far recommended that treatment can persevere if the advantages are estimated to outweigh the possible harms [34]. Immunoglobulin G molecules, along with omalizumab, are known to pass the placenta. IgG is also excreted in human milk, so it would be predicted that a breastfeeding baby might be uncovered to omalizumab. Data in human beings are not available [34].

3.7. Adverse effects of omalizumab therapy

The most common unfavorable reaction derived from omalizumab is injection site reactions, including induration, itching, pain, and bruising. The package insert contains warnings concerning about parasitic infections. While there are not any reports of fatal anaphylaxis due to omalizumab, a few cases have been serious and doubtlessly life-threatening [17].

Available information on the safety profile and tolerability of omalizumab therapy in patients with CSU has been mainly derived from the phase III trials in patients with CSU. ASTERIA I, ASTERIA II, and GLACIAL trials showed a good tolerability profile, which was similar to those with placebo and without any anaphylactic reactions [4, 5, 35].

Limb et al. evaluated anaphylaxis and angioedema profiles of patients with asthma receiving omalizumab [36]. Polysorbate, a part of the drug used to increase its solubility, is very likely to be responsible for adverse reactions [36, 37]. In a report on two cases of atopic asthma on the long-term omalizumab therapy, the intradermal test showed that anaphylaxis is developed due to omalizumab [38]. Anaphylaxis due to omalizumab can be diagnosed; there should be at least two of the following symptoms: angioedema in the throat or in the tongue, broncho-spasm, hypotension, syncope, and/or urticaria [39].

In a study performed by omalizumab joint task force (OJTF) in 2006, 0.09% of the asthmatic patients administered omalizumab had anaphylaxis. They reported that anaphylaxis due to omalizumab developed within 2 h of the administration, and after three injections of the drug in most of the patients (78%). Based on this finding, they recommended that patients should be monitored in the clinic for 2 h after the first three injections of omalizumab administration and for 30 min after the following injections [37].

Due to exacerbation of urticaria or angioedema normally appearing in the course of the CSU, the diagnosis of an adverse reaction can be overlooked. Therefore, possibilities of an adverse reaction, lack of a response to omalizumab, and exacerbations due to discontinuation of other medications should be kept in mind because a decision about whether the treatment is effective and should be continued has to be made.

In addition, since delayed adverse reactions due to omalizumab can appear, patients may think that these reactions are independent of the drug. They may not tell their doctors about them due to clinical benefits they receive from their treatment. Therefore, it is necessary that patients should be informed about possible adverse reactions before treatment and observed for a long time after treatment.

According to data we collected in the dermatology clinic in Education and Research Hospital, from 2014 to 2016, about 100 patients diagnosed as CSU were treated with omalizumab. One of these patients, after a long period of time without angioedema, had the first angioedema attack on the tongue within 30 min of omalizumab administration. The reaction appearing was regarded as an adverse effect or flare-up of urticaria. One patient had urticarial exacerbation and angioedema; hypotension, 30 min after the first omalizumab administration, and lack of any other symptoms were proposed to be a nonspecific adverse reaction. Exacerbation of urticaria and angioedema occurring after the second administration in the same patient were indicative of an adverse reaction. One patient had urticarial exacerbation; late-onset urticaria exacerbation after the first dose in was thought to be a delayed adverse reaction due to omalizumab or exacerbation of the disease because the previous cyclosporine therapy was discontinued [17]. Except those, two patients had localized urticarial plaque on the site of omalizumab application. One patient had a mild and one had a moderate headache, three patients had acneiform eruption and two patients had widespread foot pain and myalgia, which can be considered as the flu-like syndrome. One patient had dizziness. Omalizumab changed into discontinued within the patients experiencing urticarial exacerbation and/or angioedema, but the treatment became persevered within the patients located to have other adverse reactions and necessary precautions toward the side effects had been taken.

4. Newly introduced anti-IgE therapies

As a third-line therapy in patients with CSU, omalizumab is an effective and safe biological therapy option for both antihistamine-resistant CSU patients and physicians dealing with CSU [40]. However, there are nonetheless many patients who do not tolerate or benefit from existing and the other third-line therapies including omalizumab [41].

MEDI-4212, ligelizumab (QGE031), and mAbs targeting the extracellular segment (M1′) of membrane IgE: quilizumab is a new anti-IgE reagents that is currently undergoing phase II trial testings [42, 43].

4.1. Ligelizumab (QGE031)

Ligelizumab is a completely humanized IgG1 monoclonal antibody directed in opposition to human IgE that binds with excessive affinity to the Cε3 area of IgE. It also binds to Cε3 area of IgE with much more affinity than omalizumab [41]. Compared to omalizumab, ligelizumab suggests sixfold to ninefold more suppression of allergen-induced skin prick exams *in vivo*. It also affords more and longer suppression of free IgE and IgE on the surface of circulating basophils compared to omalizumab [44].

Current findings suggest that ligelizumab can be more potent than omalizumab within the treatment of CSU. The advent of an even stronger anti-IgE mAb-ligelizumab is developing; in addition, possibilities for anti-IgE therapy to improve the symptoms and life quality of patients with chronic urticaria [40, 41].

4.2. Quilizumab

Quilizumab is a humanized monoclonal antibody that targets the M1 prime of membrane-expressed IgE on IgE-switched B cells and plasmablasts. Quilizumab is in the medical development for the remedy of allergic diseases. By inflicting the depletion of IgE-switched B cells and plasmablasts, it reduces serum IgE [45].

A currently achieved multicenter, double-blind observe with 32 CSU patients showed that there was no significant difference between quilizumab and placebo group in terms of decreases in disease scores [46]. But its longer period use in CSU patients or its combination with omalizumab may enhance treatment effects and lead to sustained responses. This has to be revealed in future studies [41].

These findings suggest that quilizumab may be an effective treatment of CSU. Quilizumab and ligelizumab are still under investigation in CSU [41].

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