Omalizumab Therapy for Chronic Spontaneous Urticaria: The Israeli Experience

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ABSTRACT: **Background:** Chronic spontaneous urticaria (CSU) is a common, debilitating disease that is frequently resistant to standard therapy. Omalizumab, anti-immunoglobulin-E humanized monclonal antibody, was recently shown to be effective in treating resistant CSU.

Objectives: To investigated the treatment of CSU with omalizumab in Israel.

Methods: We conducted a multicenter retrospective analysis of patients with refractory CSU treated with omalizuamb in Israel during 2012–2013. Complete improvement was defined as resolution of symptoms with no need for other medications, or satisfactory when patients' condition improved but required regular or intermittent doses of antihistamines.

Results: Forty-three patients received omalizumab off-label for refractory CSU. Their mean age was 45 ± 12 years and CSU duration was 4.3 ± 4 years. In this cohort, 98% were unsuccessfully treated with high dose H(1)-antihistamines, 88% with systemic glucocorticoids and 30% with cyclosporine and/or other immune-modulators. Fourteen patients received only one injection of omalizumab, while the other 29 received on average of 4.3 ± 3.2 injections; 30 patients received 150 mg/month and 13 received 300 mg/month. Following omalizumab therapy, disease remitted within weeks in 86% of patients, of whom half achieved complete remission. The latter was associated with usage of high dose omalizumab, 300 mg/month vs. 150 mg/month ($P = 0.02$) and repeated therapy (i.e., multiple injections vs. a single injection) ($P = 0.0005$).

Conclusions: Omalizumab is an effective and safe treatment for refractory CSU with rapid onset of action for inducing and maintaining remission. Treating CSU patients mandates an individual approach, because while low dose omalizumab will suffice for some patients others might need higher doses and prolonged therapy.

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KEY WORDS: omalizumab, urticaria, autoimmune, allergy, anti-histamine

Chronic spontaneous urticaria is a common disease, affecting 1%–1.3% of the population, and is characterized by a typical and severe itching rash lasting for more than 6 weeks [1,2]. This disease may be associated with comorbidities. It may persist for years and adversely affects quality of life, sleep, daily activities, school and work life, as well as social interactions.

The current revised and unified guidelines of the European Academy of Allergy and Clinical Immunology and Global Allergy and Asthma European Network, as well as the World Allergy Association committees (EAACI/GALEN/EDF/WAO) suggest a step-wise approach to the management of CSU [3,4]. This approach aims to achieve complete symptom control, using a three-step process. The first step is the use of a standard-dose non-sedating H1 antihistamine [4]. These drugs are efficacious but increasing the dose fourfold (step 2), above the licensed doses, is frequently required and still leaves a substantial proportion of patients symptomatic. Hence, short-term corticosteroid therapy (3–7 days) may be required. Unfortunately, for most unresponsive CSU patients longer periods of corticosteroid therapy are needed and are associated with numerous undesired side effects [1-4]. Refractory disease requires further interventions (step 3), using cyclosporine A, omalizumab, or montelukast. Low dose cyclosporine A is efficacious in 70% of patients with glucocorticoid-dependent CSU; however, this response generally lasts in only 50% of responders [5]. Furthermore, toxicity associated with cyclosporine A therapy, although less common following the use of low doses as required for CSU, still raises concern. Hence this therapy may not be suitable for all CSU patients.

Omalizumab, an anti-immunoglobulin E humanized monoclonal antibody, is becoming increasingly recognized as an effective therapy for difficult-to-treat CSU. Before 2013 its use was off-label for this condition. Omalizumab is an anti-IgE antibody that binds only circulating free IgE and not cell-bound IgE. It

CSU = chronic spontaneous urticaria
IgE = immunoglobulin

was originally designed to treat allergic asthma and rhinitis [6]. In these conditions the postulated mechanisms by which omalizumab exerts its effects are decreased free IgE and down-regulation of IgE receptors (FcεRI) on mast and other cells, occurring within 12–16 weeks [6-9]. In the last few years, several clinical studies reported that omalizumab therapy was highly effective for resistant CSU as well. Notably, in some studies even a single injection of omalizumab was beneficial, while in others the response was dose-dependent [7-11]. Since omalizumab was used worldwide as off-label therapy for refractory CSU, there is currently a lack of data regarding the length of therapy required, tapering-down protocols, as well as concomitant therapy use. The present study investigated the efficacy and tolerability of omalizumab for CSU in a 'real-life' scenario in Israel.

PATIENTS AND METHODS

We conducted a multicenter retrospective review of all patients with CSU who were treated with omalizuamb from January 2012 to December 2013. CSU was defined as episodes of hives with or without angioedema and occurring either intermittently or continuously for 6 weeks or longer. Patients were excluded if they had drug-related urticaria or angioedema exclusively. Demographic data were recorded, including age, gender, and prior and concurrent therapy. Omalizumab was administered off-label, when available, and in the amount available (i.e., once or more in doses of either 150 mg or 300 mg monthly). Due to the retrospective nature of this study, response was recorded as a categorical result (complete, partial, none) based on the patients' subjective evaluation and on their need for additional treatment with H1-antihistamines. Complete response was defined as complete resolution of symptoms and no need for further medications (other than omalizumab). A satisfactory (partial) response was defined as an improvement in the patient's condition, with the patient still requiring regular or intermittent doses of antihistamines.

STATISTICAL ANALYSIS

Microsoft Excel version 2003 (Microsoft Corp., Seattle, WA) and the statistical program SPSS 13.0 (SPSS, Chicago, IL, USA) were used for statistical analysis. Results are presented as means and standard deviations. Findings were compared between the groups using the Student *t*-test or Fisher's exact test as appropriate. *P* values < 0.05 were considered statistically significant

RESULTS

The study group consisted of 43 CSU patients treated with omalizumab [Figure 1]. In this cohort 30 (70%) were females, their mean age was 45 ± 12 years (range 20–64), and the duration of CSU prior to omalizumab therapy was 4.3 ± 4 years [Table 1]. While all patients were treated with antihistamines, at initiation of omalizumab therapy 42 patients (98%) received high dose (fourfold) H(1)-antihistamines. In addition, 38 (88%) received systemic glucocorticoids, and 13 (30%) were treated with other immune modulating agents: namely, cyclosporine A (26%), montelukast (9%), and others, such as methotrexate (14%). All were unresponsive. Since at the time of the study omlizumab was prescribed off-label for the indication of CSU, 14 patients received only one injection while the other 29 received an average of 4.3 ± 3.2 injections (range 2–12). Of those receiving multiple injections, 7 were given more than one injection but only once every 2–12 months, and the other 22

Figure 1. Response of chronic spontaneous urticaria to therapy with omalizumab

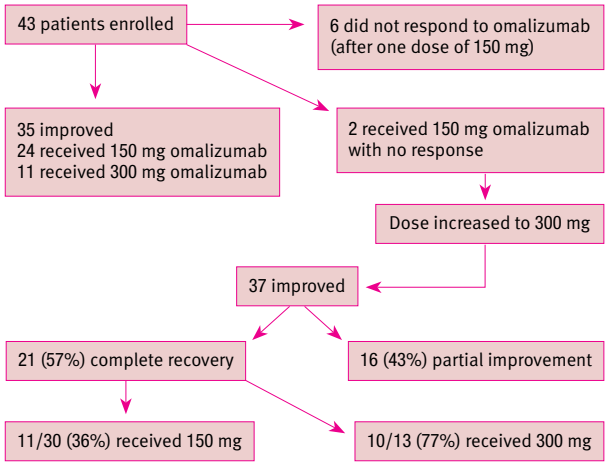

Table 1. Clinical parameters of 43 urticaria patients treated with omalizumab for CSU

	Patients (n=43)
Gender (female %)	30 (70%)
Age (yr)	45 ± 12
Duration of disease (yr)	4.3 ± 4
IgE mean levels (IU/ml)	151 ± 255
Other diseases	
Allergic rhinitis	4 (9%)
Asthma	6 (14%)
Other therapies	
High dose anti-H1-histamines	42 (98%)
High dose corticosteroids	38 (88%)
No. of corticosteroids courses (in the previous year)	2.3 ± 2
Cyclosporine	11 (26%)
Monetelukast	4 (9%)
Other immunosupressants (methotrexate, mycophenolate mofetil, azatioprine, etc.)	6 (14%)
Treatment with omalizumab	
150 mg/month	30 (70%)
300 mg/month	13 (30%)
Responded	37 (86%)
Adverse events (within 2 hours)	1 (2%)

patients were treated regularly each month. In this cohort 13 patients received 300 mg omalizumab/month while 30 patients received 150 mg once or more.

Following treatment with omalizumab CSU subsided in 37 patients (86%) of whom 21 (57%) showed complete response and 16 (43%) a satisfactory improvement. In 35 of the 37 responders to omalizumab, the effect was documented within the first few weeks after the first injection, while in the other 2 patients a dose increment to 300 mg was required to achieve response. It is noteworthy that complete recovery occurred in 11 of 30 patients (36%) treated with 150 mg omalizumab as compared to 10 of 13 (77%) who were finally treated with 300 mg ($P = 0.02$).

Treatment failure was observed in six patients, all of whom received only one dose of 150 mg. In other words, treatment failure was diagnosed in 6 of 14 patients (43%) who received one dose vs. none of 29 who received multiple doses ($P = 0.0005$). One patient experienced palpitations and weakness during the first 2 hours of the first course of omalizumab therapy; further courses were uneventful.

DISCUSSION

We found omalizumab to be efficacious in the vast majority of patients with severe and resistant CSU, following failure of high dose H1-antihistamines and other immune modulating agents. The overall response rate to omalizumab in our cohort was impressively high: 86%, with 57% of responders showing complete response and 43% a partial remission. Only 14% of patients showed no response, most of whom received low dose and/or a single injection of omalizumab, mainly due to the low availability of the drug.

This biologic drug recently emerged as an effective and safe alternative for treating CSU patients [7,13-16]. However, unlike omalizumab dosing for moderate-severe asthma, which is based on IgE levels and body weight, the effect of omalizumab on CSU seems to be unrelated to these parameters [7-12]. Moreover, even a single injection was found to be beneficial in some of our patients, as noted also in other observational and small clinical studies [8,12]. In contrast, in phase III studies of omalizumab for CSU a fixed dose of 300 mg/month was the most efficacious [7,10]. In the study by Maurer et al. [7], the proportion of patients completely free of hives was 10%, 23% and 53%, in those receiving placebo, 150 mg omalizumab, and 300 mg omalizumab, respectively. In another study, even higher doses of 450 mg/month were needed for some patients [8]. In our cohort the doses were limited by the availability of omalizumab, thus the initial dose was either 150 or 300 mg thereafter if plausible therapy was continued. For non-responders who received the 150 mg dose, a higher dose of 300 mg/month was used. We observed that omalizumab was most effective for CSU when higher doses were used and for a prolonged period. Therefore, it seems that a higher dose of omalizumab is more efficacious, although lower doses may suffice for some patients. These findings support the need for tailored use of omalizumab for CSU.

Our cohort of CSU patients included patients diagnosed with autoimmune chronic urticaria as well as patients with no autoimmune features. Few studies have investigated the response of various CSU phenotypes to the available medications, especially omalizumab. In a selective cohort of 12 patients who were designated as having an autoimmune basis for their urticaria, improvement was noted in 11 of 12 patients [14]. Similarly, efficacy was shown in a cohort of patients with IgE autoantibodies to thyroperoxidase [2]. On the other hand, a case series of eight CSU patients with no autoimmune features also showed improvement following omalizumab therapy [17]. A more recent study of a mixed cohort of CSU patients examined whether any specific autoimmune marker or clinical characteristics would serve as predictor(s) of responsiveness to omalizumab. The results showed that indeed all phenotypes of CSU are responsive to omalizumab therapy [18]. Finally, a retrospective study of patients with both spontaneous and inducible urticaria documented a high rate of response in both groups [8]. Therefore, it appears that omalizumab may benefit patients with chronic urticaria, regardless of the immune process underlying this condition.

CSU is a disease of spontaneous remission and exacerbation; thus, the length of therapy with omablizumab or other immune modulators is yet to be determined. In the randomized clinical studies published so far, recurrence of symptoms following termination of 3–6 months therapy was common [7,11]. However, in the current study some patients achieved a long-standing remission (months or a year) after treatment with omalizumab, with no need for further medication. On the other hand, prolonged therapy of up to 12 months in our study and 37 months in other studies was both beneficial and safe [8,19,20].

Consequently, although omalizumab is remarkably effective for patients with different CSU phenotypes (and probably for other types of chronic urticaria), the dose and length of therapy with this drug has yet to be determined and will probably be individually based. Omalizumab is an expensive drug that may have adverse events (e.g., anaphylaxis). Thus, it remains prudent to consider this therapy only after a full assessment by a specialist who is experienced both in treating moderate-severe CSU and in using omalizumab.

The mechanisms whereby omalizumab ameliorates CSU symptoms are currently uncertain and are under investigation. Previous studies have shown that omalizumab decreases free IgE levels and down-regulates receptor ($Fc\varepsilon R1$) expression on mast cells and basophils within 12–16 weeks after initiation of therapy [21,22]. These mechanisms of action, while also playing a role in CSU, cannot be the sole explana-

tion for the effect of omalizumab in this condition since most patients, in this study and others, experienced rapid improvement (within 1–3 weeks) [12,14]. Recent studies showed that omalizumab may intervene in immune mediated processes through direct basophil stabilization [12], effects on pathogenic IgE antibodies [23], or a decrease in IgE synthesis by targeting membrane IgE-positive B cells [24].

There are some limitations to our study, such as its retrospective design, small study population, and the lack of a standard protocol for the assessment and management of CSU.

CONCLUSIONS

We found omalizumab to be an effective and safe treatment for moderate to severe CSU, with a rapid onset of action for inducing and maintaining remission. A tailored regimen of omalizumab, considering dose and length of therapy, is required, as are step-down protocols regarding concomitant medications.

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