ORIGINAL ARTICLE

Treating refractory chronic spontaneous urticaria with omalizumab – real life case series

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Recived: 10 August 2022
Revised: 25 September 2022
Accepted: 28 October 2022

Check for updates

Funding information:
The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests:
The authors have declared that no competing interests exist

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Summary

Introduction: Patients with refractory chronic spontaneous urticaria (CSU) may pose a significant challenge to the treating physician. Although many studies have investigated the effects of omalizumab in refractory CSU, many issues remain unanswered.

Aim: To describe our experience in treating refractory CSU with omalizumab in a real-life setting.

Material and methods: We present a series of eight patients with refractory CSU treated with omalizumab during a 2-year period.

Results: The average duration of CSU was 49.9 months (3-180). A high average 7-day Urticaria Activity Score (UAS7) of 31.3 (12-42) and a low average Urticaria Control Test (UCT) score of 4.1 (0-8) had been recorded before omalizumab therapy. Prior to omalizumab, all patients required fourfold dose of H1-anihistamines, montelukast and corticosteroids to achieve at least a partial disease control. Antimalarial was given to two patients and dapsone to three, with no response. Adverse effects of corticosteroids were noted in most patients. Patients received 150 mg or 300mg of omalizumab subcutaneously every 4 weeks, for at least 3 months. All patients responded well to omalizumab and discontinued corticosteroid therapy. There were no significant side effects during omalizumab treatment.

Conclusion: Omalizumab is an effective corticosteroid sparing treatment, enabling disease control in patients with refractory CSU, even in lower doses (150 mg) and when given for a short period of time. This is especially important when the availability of the drug is determined by economic issues.

Key words: chronic spontaneous urticaria, refractory, omalizumab

Cite this article as: Miskovic R, Jovicic Ž, Tomic Spiric V, Stojanovic M, Plavsic A, Raskovic S, Dasic A, Peric Popadic A. Treating refractory chronic spontaneous urticaria with omalizumab – real life case series Medicinska istraživanja 2022; 55(3):13-19 10.5937/medi55-38372

INTRODUCTION

Urticaria is a mast cell-driven disease with heterogenous and insufficiently known activating signals (1). Chronic spontaneous urticaria (CSU) is characterized by recurrent occurrence of wheals, angioedema, or both, for more than six weeks, without an obvious external trigger. It is a highly disabling disease with a major influence on the quality of life and a significant cost for health care system and patients (2). The global prevalence of CSU varies between 0.5 and 1% depending on the population studied (3-4). In the majority of cases it lasts between 2 and 5 years. However, in approximately 20% of patients it can persist for more than 5 years (4). Intensive pruritus, frequent recurrence of symptoms and unpredictive clinical course lead to sleep deprivation and common psychiatric comorbidity (5).

The EAACI/GA²LEN/EuroGiuDerm/APAAACI guideline recommends stepwise therapeutic approach, starting with non-sedating H1-antihistamines once a day and increasing up to the fourfold dose in non-responders. In patients who remain uncontrolled, omalizumab is recommended as a second-line therapy (1). Refractory forms of CSU can be especially challenging for the treating physician and for the patient, causing frustration and uncertainty. Patients with severe active disease frequently receive corticosteroids (CS), developing many CS adverse effects over time. Cyclosporin, another guideline recommended treatment, also carries the risk of serious side effects, especially if taken over a long period of time. However, such patients have been frequently excluded from clinical trials that require strict inclusion criteria, permitting in most cases just the inclusion of patients with severe disease activity treated only with antihistamines.

Omalizumab is the first licensed biological therapy available for CSU. It is a humanized anti-IgE monoclonal antibody that recognizes C3 domain of Fc region of IgE molecule, forming omalizumab-IgE complexes and reducing the level of free IgE. It is hypothesized that this process leads to the down-regulation of high affinity FcƐRI receptor on mast cells and circulating basophils, decreasing mediator release, and consequently reducing the symptoms of CSU. Additional mechanisms of action, independent of the level of IgE have been proposed as well (6). Several studies evaluated the effectiveness of omalizumab in refractory CSU, but many issues remain unresolved. The aim of this study was to describe our case series of patients with refractory form of CSU treated with omalizumab and to discuss some practical issues regarding its use in a real-life settings.

MATERIAL AND METHODS

Patients

We retrospectively reviewed medical records of patients with refractory CSU treated with omalizumab at the Clinic of Allergy and Immunology between January 2018 and December 2019. Main demographical, clinical and laboratory data of the patients were recorded, as well as the clinical evolution of CSU. The Institutional Review Board approved the study (approval number 570/4).

Disease and patient assessment

Disease activity was assessed using the standard 7-day Urticaria Activity Score (UAS7) and the medication scoring system. The UAS7 quantifies the number of wheals (from 0 - none to 3 – severe) and pruritus intensity (from 0 – none to 3 – severe) on daily bases for 7 consecutive days. The total score ranges from 0 to 42, allowing to classify disease activity as a complete response (0), well-controlled (1-6), mild (7-15), moderate (16-27), or severe (28-42). The UAS7 was recorded by each patient during the period of 7 days prior to each visit (7).

The quantitative medication score was calculated before the application of omalizumab therapy and at every subsequent visit. This score is a sum of weighted scores for antihistamines (2 points: regular dose, 8 points: four-fold dose), oral glucocorticoids (5 points: <11mg, 10 points: 11-25mg, 15 points: >25mg), cyclosporine 3.0mg/kg (8 points), hydroxychloroquine (6 points) and montelukast (2 points) (8).

Disease control was assessed using the standard Urticaria Control Test (UCT). This is patient-based, 4-item questionnaire with a 4-week recall period. It assesses the control of physical signs and symptoms of urticaria, impairment of the quality of life, the efficacy of the treatment and overall disease control. The questions are rated from 0 to 4, with the total score ranging from 0 (no control) to 16 (complete control). The patients having score of ≥12 are considered to have well-controlled urticaria (9).

In our study, the patient was considered to have refractory CSU if the disease was uncontrolled despite using non-sedating H1-antihistamines in fourfold dose, leukotriene receptor antagonists (LTRA) and oral corticosteroids or if the patient could not discontinue corticosteroids without losing control over disease.

Total serum IgE was measured by immunonephelometric assay. Measurements were done before (bIgE) and 4 weeks (w4IgE) after the first omalizumab injection. We calculated w4IgE/bIgE ratio and applied the '2x4' rule proposed by Ertas et al. as a predictor of the response to omalizumab. According to this rule, when bIgE fails to double within 4 weeks of treatment, non-response is to be expected (10).

Treatment protocol and the evaluation of treatment response

Patients received 150 mg or 300mg of omalizumab subcutaneously every 4 weeks, for at least 3 months. The response to the treatment and safety were assessed before each application. A 'complete response' was defined as a reduction of 90% or more in the UAS7, 'significant improvement' as a reduction in UAS7 of 90%-30%, and 'no significant improvement' as less than 30% reduction in the UAS7 (11).

We used descriptive statistics to analyze the data considering that due to the small number of patients, it was not possible to apply analytical statistical methods.

RESULTS

Eight patients with refractory CSU were treated with omalizumab during the study period: 3 males and 5 females, mean age 51.12 (23-81) years. Mean disease duration was 49.8 (3-180) months and mean UAS7 was 31.3 (12-42), pointing to high baseline disease activity. All patients had a low UCT score (mean UCT 4.6) indicating poor disease control. Mean serum bIgE was 74.8 (5.8 -273) IU/ml. Patients' characteristics and treatment response are shown in **Table 1**.

Before omalizumab treatment, all patients required fourfold dose of H1-anihistamines and corticosteroids daily (dose range 10 - 40 mg) for symptom control. Three patients were given dapsone and two patients were given antimalarial with no response. One patient received immunomodulatory doses of intravenous immunoglobulins and another high dose of CS therapy (pulse doses), both with only short-term effects. Adverse effects of CS were noted in most patients (cushingoid features, fluid retention, sleep disturbance, anxiety, weight gain, hypertension, hyperglycemia, gastritis, acne).

Mean treatment duration was 5.5 (3-10) months. One patient (No.1) had complete resolution of urticaria (UAS7 0) several hours after his first omalizumab injection, which was maintained thereafter, allowing fast CS tapering and withdrawal. The remaining patients were also fast responders and their UAS7 decreased more than 30% on their second visit. Overall, after 3 doses of omalizumab, 6 patients achieved complete response (UAS7 of 0) and 2 experienced a significant improvement. Medication scores decreased in all patients.

All patients were able to discontinue CS therapy after starting omalizumab, with the time needed for CS withdrawal ranging from 1 to 12 weeks.

The patients were followed-up for at least 6 months after the termination of the treatment. One patient (No.3), with initially good response to omalizumab (UAS7 0), was switched to a lower dose (150mg) after 5 months, but experienced exacerbation of CSU (UAS7 18), although not as severe as at the starting point (baseline UAS7 39). He was not motivated to use cyclosporine, and he was given occasional CS burst for maintaining disease control. Another patient (No. 2) who achieved a significant reduction in UAS7 after 6 doses (300mg) of omalizumab, exacerbated one month after the termination of the treatment and was also introduced to cyclosporine therapy, but with no response. The patient further required prednisone daily (10mg/day). The patient number 5 achieved complete response, but experienced exacerbation three months after the completion of omalizumab treatment. As cyclosporine was not effective, she was given prednisone (15mg/day) to maintain disease control. In these 3 patients reintroduction of omalizumab was not possible due to financial reasons. The remaining 5 patients achieved complete response or a significant improvement and their disease was further maintained with antihistamine therapy only.

Total serum IgE was measured at baseline and 4 weeks after the start of the treatment. An average bIgE was 74.8 IU/ml (5.8-273), increasing to 230.2 IU/ml (10.1-680) 4 weeks after first omalizumab injection. Mean w4IgE/bIgE ratio was 4.2 (1.7-8.3) predicting a good treatment response. Only 2 patients had w4IgE/bIgE ratio lower than 2, but both responded to the treatment.

Overall, the treatment was well tolerated. One patient developed herpes zoster after the third omalizumab injection and was not motivated to continue omalizumab. After thorough literature search, we could not find any case of herpes zoster associated with omalizumab therapy. Furthermore, this patient had other risk factors for herpes zoster (advanced age, diabetes mellitus).

DISCUSSION

Our study describes the efficacy and the safety profile of omalizumab in a case series of patients with refractory CSU in a real-life settings. We included patients with severe disease activity requiring several medications for CSU, including CS daily or every other day to control the disease. All patients had good and fast response to omalizumab. Complete remission was achieved in 5 and a significant improvement in 3 patients at the end of the treatment. This was followed by a significant reduction in medication scores in all cases. Most importantly, all patients discontinued CS therapy.

Several real-life studies evaluated the efficacy of omalizumab in refractory CSU. However, only some of them included patients with a severe form of the disease who used several CSU medications, including CS frequently or daily. In a prospective open-label study, Sussman et al. showed that 150 mg of omalizumab was effective in difficult-to-treat patients with severe chronic urticaria refractory to the recommended treatments who frequently use prednisone (8). Similarly, Kulthanan et al. per-

Table 1. Main demographical, clinical and laboratory characteristics of patients and overall response to the treatment with omalizumab

Patient No/ sex/ age	Duration of CS (months)	AE	Anti-thyroid Abs	Asthma	Previous treatment	bIgE IU/ml	bUAS7	bUCT	Omb dose (mg)	Treatment duration (months)	w4IgE IU/ml	w4IgE/ bIgE	UAS7 end	UCT end	MS end	Time to CS withdrawal (weeks)	Time to serious relaps (weeks)
1/M/23	54	Yes	-	No	4xH1; LTRA; Ket; CS; Dap; AM; IVIG	21.1	42	0	5x150 5x300	10	98	4.6	0	16	2	1	*
2/F/53	12	Yes	-	Yes	4xH1; LTRA; CS	71	18	4	6x300	6	285	4.0	1	16	2	3	4
3/M/55	24	No	-	No	4xH1; LTRA; CS	177	39	2	5x300 2x150	7	680	3.8	19	10	18	2	3
4/F/48	48	No	NP	No	4xH1; LTRA; Ket; CS; MP pulse	6.8	40	7	6x150	6	23.4	3.4	0	15	10	4	*
5/F/45	180	Yes	NP	No	4xH1; LTRA; CS; Dap	273	15	8	3x150	3	477	1.8	0	14	2	12	12
6/F/47	72	Yes	-	No	4xH1; LTRA; CS	34.1	12	8	6x300	6	191	5.6	0	16	2	1	*
7/F/57	6	Yes	+	Yes	4xH1; LTRA; CS; Dap; AM	9.2	42	4	3x150	3	76.8	8.3	0	16	2	12	*
8/M/81	3	No	+	No	4xH1; LTRA; Ket; CS	5.8	42	4	3x150	3	10.1	1.7	6	12	2	3	*

AE – angioedema; Abs – antibodies; end – end of treatment; Dap- dapsone; Ket – ketotifen; MP- methylprednisolone; IVIG – intravenous immunoglobulin; AM – antimalarial; LTRA – leukotriene receptor antagonists; H1- H1 antihistamine; NP – not performed. CS –corticosteroids; b- baseline; Omb – omalizumab; MS – medication score; * - did not experience disease relapse requiring CS during follow up

formed retrospective analysis of omalizumab as an add-on therapy in uncontrolled CSU despite 4-fold dose of non-sedating antihistamines, LTRA, oral CS and cyclosporine, showing efficacy of initial dosage of 150 mg in most cases, with dosing up to 300 mg being effective in the remaining ones. Oral CS and cyclosporin were discontinued in all patients (12). A study from Portugal showed a good long-term efficacy of omalizumab in 6 patients with severe chronic urticaria, allowing discontinuation of CS in all patients. During the median treatment duration of 17.5 months, the main side effect of omalizumab was headache on the administration day (13).

There are currently no official guidelines or recommendations regarding the duration of omalizumab treatment, an optimal dose, or a dose interval in patients with CSU. Many authors suggest an individualized approach when using omalizumab in patients with refractory CSU. This approach considers different aspects of the disease and the patient and is frequently influenced by economic factors. Uysal et al. suggested starting the treatment with 150 mg dose every 2 weeks, prolonging the dose interval for 1 week when the patient achieves UAS7 < 2 up to the maximal dose interval of 8 weeks when the treatment should be paused and the patient further closely monitored for symptom recurrence. In patients with treatment failure, defined as UAS7 > 3 after 2 to 3 doses of 150 mg, they suggest increasing the dose to 300 mg (14). Kasperska-Zajac et al. suggested a treatment algorithm based on their own experience and literature review. They advise starting with 150 mg of omalizumab, and if the symptoms resolve completely, the subsequent dose should be administered on symptom recurrence. In patients with severe symptoms and poor response to CS, a 300 mg starting dose is advised and it can be reduced to 150 mg if remission is achieved. If symptoms recur after dose reduction, it should be increased again to 300 mg. When no remission has been achieved after 8 – 12 weeks of 300 mg dose, the omalizumab treatment should be discontinued (15). Some authors suggest repeating 300 mg dose after 2 weeks before treatment discontinuation in such cases (11). In our group of patients, both doses proved to be effective. Treatment response was visible soon after the first omalizumab dose in most patients. Three patients with good response experienced exacerbation during the follow-up. This is in concordance with other studies, suggesting that in some patients long-term treatment or retreatment with omalizumab is necessary (12, 16-17). It should be noted that dose and treatment duration in our study were significantly influenced by financial factors, and a prolonged or repeated treatment with omalizumab was not feasible in most patients.

The mechanism of action of omalizumab in CSU is not sufficiently elucidated, but it is assumed to be dependent on CSU endotype and reduction of circulating IgE. Binding of omalizumab to free IgE leads to down-regulation of FcεRI on mast-cells and basophils increasing the threshold for cell degranulation. After treatment discontinuation there is a gradual return of serum IgE to baseline values in some patients, which may be followed with CSU relapse. A recent study demonstrated that the clinical effect of omalizumab correlated with the reduction of $FcεRI^+$ cells and IgE^+ cells in the dermis of lesional and non-lesional skin, linking systemic effects of omalizumab to skin changes. Since the clinical response in some patients is much faster than observed histological changes, the authors speculate that an additional mechanism of action might be involved (18). Some of the proposed additional mechanisms include direct stabilization of effector cells, decreased B-cell activation and antibody production and reduction of coagulation activation (15). Although some of these mechanisms overlap with those of CS, they come with a significantly fewer adverse events.

Several biomarkers of CSU have been proposed to help identify disease endotypes and predict response to the therapy. Type I autoimmune CSU is related to the existence of autoreactive IgE antibodies to a wide range of self-antigens and high serum IgE. In patients with type IIb autoimmune CSU mast-cell degranulation is caused by IgG or IgM autoantibodies to the FcεRIα or IgE bound to it and there is a higher rate of low serum IgE, high C-reactive protein, eosinopenia and basopenia (1). Current evidence suggests high D-dimer and C-reactive protein level as predictors of poor response to antihistamines, while cyclosporine response is predicted by a positive basophil histamine release assay (19). There is robust evidence supporting low serum IgE as a predictor of poor response to omalizumab treatment (20). Ertas et al. found that patients with low bIgE level (< 43 IU/ml) have 33% risk of non-response within the first 12 weeks of treatment, as compared to only 5% risk in patients with IgE ≥ 43 IU/ml. However, w4IgE/bIgE ratio was a better predictor of response and patients having at least 2-fold increase of w4IgE responded to treatment (10). It is assumed that this increase in serum IgE is due to formation of omalizumab-IgE complexes, prolonging the half-life of IgE. Most of our patients had low bIgE level which significantly increased 4 weeks after omalizumab injection. We also calculated w4IgE/bIgE ratio and applied the '2x4' rule proposed by Ertas et al. Only two patients had w4IgE/bIgE ratio below 2, but they both responded to the treatment. A recent publication suggests differences in biology and function of IgE between different CSU endotypes. Modifications in glycosylation pattern of IgE molecule are noticed, possibly influencing 3-dimensional folding and lipophilicity of IgE. Whether these modifications are clinically significant and influence treatment response and disease relapse is what remains to be elucidated. If these modifications are clinically significant and weather they influence treatment response and disease relapse are the two things that remain to be elucidated (21).

This study showed that omalizumab is an effective treatment in patients with severe refractory CSU, en-

abling a significant reduction in disease activity parameters and discontinuation of CS therapy. It is limited by a small number of patients. However, the number of patients with this form of disease is relatively small in relation to the total number of patients with CSU. Our experience suggests that a lower dose (150 mg) and shorter treatment duration (3 months) are beneficial for patients. Considering many adverse effects of CS and cyclosporine, such a therapeutic approach seems to be rational from a clinical and economic point of view.

CONCLUSION

In conclusion, real-life experience with omalizumab confirms that it is a safe and effective therapeutic option in the majority of patients refractory to other available treatments. Some patients benefit from a lower dose and shorter treatment duration. We emphasize individualized approach that is based on patient's characteristics, disease manifestations and economic aspects.

Conflict of interest

The authors have no conflict of interest to declare.
We have no funding sources regarding this study to report.

Author contribution

Conception and design of the work: Rada Miskovic, Zikica Jovicic, Aleksandra Peric Popadic
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PRIMENA OMALIZUMABA U TERAPIJI REFRAKTORNE HRONIČNE SPONTANE URTIKARIJE - SERIJA SLUČAJEVA

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Sažetak

Uvod: Pacijenti sa refraktarnim oblikom hronične spontane urtikarije (HSU) predstavljaju značajan izazov u kliničkoj praksi. Iako su brojne studije ispitivale terapijske efekte omalizumaba kod pacijenata sa refraktarnom HSU, mnoga pitanja su još uvek bez odgovora.

Cilj: Prikazati iskustvo primene omalizumaba kod pacijenata sa refraktarnim oblikom hronične spontane koprivnjače.

Materijal i metode: Prikazana je serija od osam slučajeva pacijenata sa refraktarnom HSU koji su lečeni omalizumabom tokom perioda od dve godine.

Rezultati: Prosečno trajanje HSU iznosilo je 49,9 meseci (3-180). Pre započinjanja terapije omalizumabom kod pacijenata su zabeleženi visoka prosečna vrednost sedmodnevnog testa aktivnosti koprivnjače (TAK7) koji je iznosio 31,3 (12-42) i nizak prosečan rezultat testa kontrole koprivnjače (TKK) - 4,1 (0-8). Kod svih pacijenata je pre uvođenja omalizumaba u terapiji bila potrebna primena četvorostruke doze antihistaminika, montelukasta i kortikosteroida za postizanje makar parcijalne kontrole bolesti. Terapija antimalarikom je pokušana kod dva pacijenta, a dapsonom kod tri, bez terapijskog efekta. Kod većine pacijenata zabeleženi su brojni neželjeni efekti kortikosteroidne terapije. Omalizumab je primenjivan u dozi od 150mg ili 300mg subkutano svake 4 nedelje tokom bar 3 meseca. Povoljan terapijski odgovor na omalizumab su imali svi pacijenti, uz obustavu primene kortikosteroida. Nisu zabeleženi značajniji neželjeni efekti terapije omalizumabom.

Zaključak: Omalizumab predstavlja efikasnu terapijsku opciju koja omogućava smanjenje upotrebe kortikosteroida i postizanje kontrole bolesti kod pacijenata sa refraktarnim oblikom HSU, čak i kad se primeni u nižim dozama (150mg) i tokom kraćeg vremenskog perioda. Ovo je od posebnog značaja kad je dostupnost leka određena finansijskim aspektom.

Ključne reči: hronična spontana urtikarija, refraktarnost, omalizumab

Primljen: 10.08.2022. I **Revizija:** 25.09.2022. I **Objavljen:** 27.10. 2022

Medicinska istaživanja 2022; 55(3):13-19