

ORIGINAL ARTICLE

Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: A real life survey

Suna BÜYÜKÖZTÜRK,¹ Aslı GELİNCİK,¹ Mustafa DEMİRTÜRK,¹ Emek KOCATURK,² Bahattin ÇOLAKOĞLU,¹ Murat DAL¹

¹Department of Internal Medicine, Division of Allergy, Istanbul Faculty of Medicine, Istanbul University, and ²Department of Dermatology, Göztepe Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Treatment of chronic urticaria consists of antihistamines as the first-line treatment. For more severe symptoms, combinations can be necessary as well as dose augmentations. The recent guidelines suggest the possibility of using omalizumab in resistant cases, but this therapy is still investigational. We treated two patients with idiopathic recurrent angioedema and 12 patients with chronic spontaneous urticaria (CSU) with omalizumab, who had not benefited from the recommended first-line, second-line and third-line treatments. To evaluate the efficacy of the omalizumab treatment, urticaria activity scores (UAS) and chronic urticaria quality of life (CU-Q2oL) scores were measured at baseline, and at the end of the first and sixth month of the therapy. The dosage and intervals of omalizumab therapy were determined according to the rules suggested for severe asthma treatment. CU-Q2oL scores and UAS displayed significant improvements in all 14 patients. None of the patients reported any adverse effect during the treatment until the submission of this data. Our results show that omalizumab apparently improves CU-Q2oL as well as UAS in treatment-resistant CSU in a real life setting.

Key words: angioedema, chronic urticaria, hives, omalizumab, quality of life.

INTRODUCTION

Chronic urticaria (CU) is a severe skin disease characterized by itchy wheals and/or angioedema. In the current guideline of The European Academy of Allergology and Clinical Immunology (EAACI), the European Union-funded Network of Excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO), chronic idiopathic urticaria in which wheals develop independently from external stimuli is renamed as chronic spontaneous urticaria (CSU).¹

Treatment of CU consists of the use of antihistamines and, at exacerbations, corticosteroids. In mild cases, symptoms easily respond to a once daily dose of antihistamines. The current standard therapy with regular dosed H₁-antihistamines leads to an absence of symptoms in less than 50% of patients with CSU. Increasing the dose improves treatment responses but still every third to fourth patient will remain symptomatic. For more severe symptoms, combinations can be necessary as well as dose augmentations. The severe form of CU needs corticosteroid cures when an exacerbation occurs. In those patients who require frequent corticosteroid cures, other alternatives must be tried.

Cyclosporin is such an alternative and demonstrated to be effective in some patients. The guidelines suggest the possibility of using omalizumab in resistant cases.²

Omalizumab is a recombinant monoclonal antibody that selectively binds to immunoglobulin (Ig)E and inhibits its binding to FcεRI on the surface of mast cells and basophils.³ Treatment with omalizumab is currently included in international guidelines on asthma management, as the fifth step drug. Apart from asthma, in 2007, it was noted by two different groups that omalizumab had been found effective in treatment-resistant CU and recurrent idiopathic angioedema patients.^{4,5} One year later, Kaplan *et al.*⁶ published a placebo controlled study demonstrating the effectiveness of omalizumab in antihistamine unresponsive CU. Eventually, the EAACI/GA²LEN/EDF/WAO guideline in 2009 suggested omalizumab as a fourth-line option in the treatment of CU. Very recently, Groffik *et al.*⁷ published their nine CSU patients who responded well to omalizumab treatment.

In our allergy department, two patients with idiopathic recurrent angioedema and 12 patients with CSU who had not benefited from the recommended first-line, second-line and third-line treatments have been treated with the off-label use of omalizumab. The urticaria activity scores (UAS) and CU quality of life (CU-Q2oL) scores

Correspondence: Aslı Gelincik, M.D., Department of Internal Medicine, Division of Allergy, Istanbul Faculty of Medicine, Istanbul University, Millet Cad., Fatih, Istanbul, 34390, Turkey. Email: gelincik@istanbul.edu.tr

Received 13 October 2011; accepted 16 November 2011.

of the patients meaningfully improved with this treatment. We intend to present our experiences and to discuss the use of omalizumab in the treatment of resistant CSU.

METHODS

Twelve CU patients were suffering from daily wheals for periods ranging from 8 months to 30 years (Table 1). Their clinical situations were evaluated according to the EAACI/GA²LEN/EDF/WAO guideline for the definition, classification and diagnosis of urticaria.¹ Accordingly, two patients were diagnosed as idiopathic recurrent angioedema and 12 patients as CSU. None of the patients experienced other types of urticaria, except one patient with CSU (no. 13) who had occasional angioedema attacks. Clinical and laboratory examinations including differential blood count, erythrocyte sedimentation rate, routine biochemistry and serological tests for autoimmune diseases did not reveal any underlying cause or illness except in two patients. These two patients had positive autologous serum skin test (ASST) results as well as moderately high levels of anti-thyroid peroxidase antibodies. None of the patients gave a satisfactory response either to maximal dose and combined antihistamine therapy or elimination diet for allergenic foods and food additives. Three patients were symptomatic despite cyclosporin treatment for 3 months.

Apart from CU patients, two patients (nos. 1 and 2) had frequent and severe angioedema attacks for many years (10–15 years) despite regular prophylactic antihistamine therapy. During these attacks, which infrequently involved laryngeal mucosa, they had to be treated with high-dose parenteral corticosteroids. All the laboratory examinations including C1 inhibitor, C1q, C4, antinuclear antibodies, antithyroid antibodies and ASST were within normal limits. Patient no. 1 had a cushingoid appearance, osteoporosis and impaired fasting glucose because of the frequent corticosteroid use and also did not get benefit from danazol and colchicine therapy. Treatment with methotrexate, cyclo-

sporin, danazol as well as i.v. Ig was ineffective in the other patient with resistant angioedema.

As this medication is not legally indicated for use in CU, we requested the permission of the Ministry of Health for prescribing omalizumab to our patients. After obtaining the permission for every individual and their informed written consents, omalizumab was started in all the patients. The dosage of the drug was calculated based on the IgE levels and bodyweights as it is suggested for severe asthma treatment. The initial intervals between the drug applications were planned to be 4 weeks, except in three cases (nos. 3, 7 and 8; 2-week intervals). After clinical benefit was achieved in these two patients, the drug application intervals were extended to 4 weeks.

Urticaria activity scores and CU-Q2oL scores of the patients were obtained at baseline, and at the end of the first and the sixth month of omalizumab therapy. The UAS is a composite scoring system based on the patient's diary by using numeric severity ratings from 0 to 3 (0, none; 3, intense) for the number of wheals per 24 h and the intensity of pruritus. The total daily score (sum of the wheal and pruritus scores) could therefore assume any value between 0 and 6.^{1,8} In this study the weekly aggregate score calculated as the sum of the daily UAS self-evaluation scores of 7 individual days was used. CU-Q2oL has been specifically developed for use in patients with CU and encompasses the physical, emotional, social and practical domains that characterize this condition.⁹ The Turkish version of the CU-Q2oL was recently validated by Kocatürk *et al.*¹⁰ It consists of 23 items categorized under the following scales: pruritus, swelling, impact on life activities, sleep problems, limits and looks.

Statistical analyses

Data were analyzed with SPSS ver. 15.0 for Windows. The Wilcoxon rank sum test was used to evaluate the differences between the baseline and after-treatment scores of UAS and CU-Q2oL questionnaires.

Table 1. Demographic and clinical characteristics of the CSU patients

Patient (n)	Age	Sex	Diagnosis	Duration	IgE (kU/L)	ASST	Thyroid Autoimmunity	Omalizumab treatment (mo)	Initial doses
1	34	F	AE	10 yrs	57	–	–	10	300 mg/mo
2	46	M	AE	15 yrs	306	–	–	20	300 mg/mo
3	57	F	CSU + asthma	30 yrs	492	+	+	12	375 mg/2 wk
4	31	F	CSU	2 yrs	46	–	–	6	150 mg/mo
5	50	F	CSU	15 yrs	743	–	–	6	375 mg/mo
6	31	M	CSU	2 yrs	281	–	–	8	300 mg/mo
7	51	F	CSU	8 mo	441	–	–	6	300 mg/2 wk
8	49	F	CSU	6 yrs	283	–	–	12	300 mg/2 wk
9	52	F	CSU	8 yrs	195	–	–	10	150 mg/mo
10	48	F	CSU	1 yr	76	+	+	6	150 mg/mo
11	27	F	CSU	5 yrs	136	–	–	6	300 mg/mo
12	33	M	CSU	7 yrs	180	–	–	6	150 mg/mo
13	44	M	CSU + AE	7 yrs	158	–	–	8	225 mg/mo
14	50	F	CSU + asthma	22 yrs	316	–	–	14	300 mg/mo

AE, angioedema; ASST, autologous serum skin test; CSU, chronic spontaneous urticaria; F, female; IgE, immunoglobulin E; M, male; mo, months; wk, weeks; yrs, years.

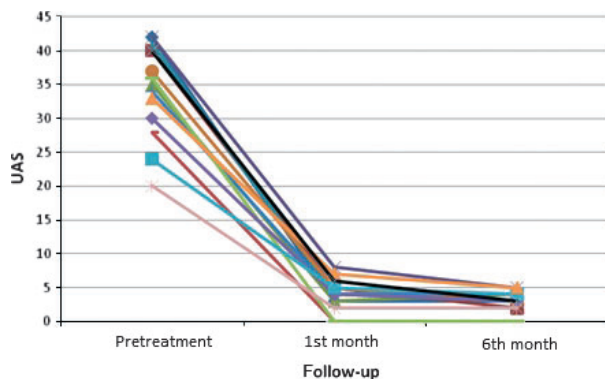


Figure 1. Urticaria activity scores (UAS) of the patients improved obviously with omalizumab therapy.

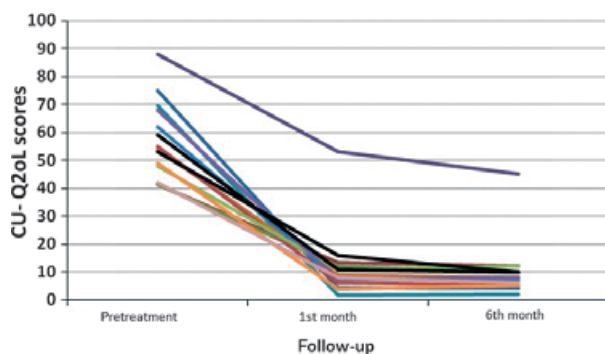


Figure 2. Chronic urticaria quality of life scores (CU-Q2oL) significantly improved with omalizumab therapy.

RESULTS

Angioedema attacks completely ceased immediately after the first injection of omalizumab in patient no. 2, while the symptoms gradually decreased until its disappearance after the fourth dose in patient no. 1.

Twelve patients with treatment-resistant CSU exceptionally responded to omalizumab almost at the first week after the beginning of the first doses. UAS and total CU-Q2oL scores displayed significant improvements at the end of the first month in all 14 patients ($P < 0.000$ for both). These response levels persisted at the sixth month control (Figs 1,2). The differences in the scores of first month CU-Q2oL questionnaires were significant in all subscales compared to the baseline values (Table 2). Beyond the improvement in the scores, most of the patients declared that they did not need to take antihistamines anymore. No patients reported any adverse effect during the treatment until the submission of this data.

DISCUSSION

Patients with CU suffer from strongly impaired quality of life (QoL). In addition to the classical clinical symptoms like pruritus, wheals and the occurrence of angioedema, many other factors such as the unpredictability of the attacks, lack of quality sleep and fatigue

Table 2. Differences in the patients' mean urticaria activity scores and quality of life scores (total and separate domain scores)

Scores	Baseline	1st month	6th month	<i>P</i>
UAS	34.4 ± 6.8	4.0 ± 2.3	2.9 ± 1.5	0.000
Total CU-Q2oL	57.5 ± 13.8	11.7 ± 12.5	10.3 ± 10.4	0.000
Pruritus	9.0 ± 0.8	2.5 ± 0.5	2.7 ± 0.8	0.000
Swelling	6.8 ± 3.1	2.0 ± 0.01	2 ± 0.01	0.013
Impact on life activities	18.8 ± 3.9	7.6 ± 2.4	7.0 ± 0.9	0.001
Sleep problems	17.5 ± 4.5	7.5 ± 1.3	6.8 ± 1.4	0.006
Limits	11.6 ± 2.5	5.1 ± 2.1	5.0 ± 1.2	0.002
Looks	16.6 ± 4.4	8.5 ± 3.9	8.0 ± 2.1	0.002

CU-Q2oL, chronic urticaria quality of life; UAS, urticaria activity scores.

are of major importance for patients with CSU.¹¹ Furthermore, most of the patients avoid a great variety of foods because of the concern of triggering an urticaria attack, which may lead to a further burden. It was demonstrated that CSU patients suffer in many aspects a comparable QoL impairment as patients with severe coronary artery disease waiting for bypass surgery.¹² A great number of studies demonstrated QoL impairments in CU patients and emphasized its importance.^{13–16} We observed very significant QoL improvements in our patients receiving omalizumab therapy. These improvements included all scales of the CU-Q2oL instrument. Previously, similar improvements, especially in the functional capacity and well-being of patients with CU, have been demonstrated by using the daily quality of life index (DLQI)⁶ and Skindex-29 questionnaires.¹⁶ Recently, Vestergaard and Deleuran¹⁷ described two patients with severe CU whose UAS and DLQI had markedly reduced 4 weeks after the omalizumab therapy. Very recently, Maurer *et al.*¹⁸ clearly showed that omalizumab was an effective treatment option for patients with CU with IgE autoantibodies against thyroid peroxidase who are refractory to conventional treatment. They used three different QoL questionnaires (DLQI, Skindex and CU-Q2oL) and found that all three revealed a significantly greater improvement of QoL for patients receiving omalizumab compared with placebo.

Another noteworthy observation was that the benefit of omalizumab treatment emerged markedly as early as the first week after the initial dose in the majority of the patients. Similar observations were reported previously.^{4,18} Maurer *et al.* pointed that a decrease in UAS was observed during the first week of therapy and continued until the end of the study. Equally important, omalizumab had markedly reduced the burden of repeated rescue medication use in their study patients. Although we did not calculate the decrease in medication use, our patients also reported that they had not needed rescue medication since the beginning of the omalizumab therapy.

To explain the efficacy of omalizumab in CSU, Kaplan *et al.*⁶ suggested that omalizumab can reduce the expression of FcεRI on the surface of basophils and prevent both IgG antibody-mediated cross-linking in chronic autoimmune urticaria and the release of mast cell mediators. Noga *et al.*¹⁹ added to this body of knowledge by showing that the anti-inflammatory activity of omalizumab depended on the induction of eosinophil apoptosis and the downregulation of the inflammatory cytokines interleukin (IL)-2 and IL-13.

Iemoli *et al.*²⁰ suggested a new immunomodulator mechanism of anti-IgE therapy characterized by a reduction in B-cell activation and homing and tumor necrosis factor- α and IL-4 production and an increase in γ -interferon synthesis. Recently, downregulation of Fc ϵ RI was observed in association with significant clinical improvement and discontinuation of immunosuppressive medications in a patient with CSU treated by omalizumab.²¹

Omalizumab therapy was very well tolerated by the 14 patients of our series. They were eager to continue to the treatment at subsequent visits. During the follow-up period of therapy, we did not observe any adverse effect. A similar safety profile for omalizumab in CSU was reported by other authors.^{6,7,18}

There is an uncertainty about how long omalizumab therapy should be continued in CU patients. Although in personal communications with experts in CU prolonged time intervals between doses compared with asthma treatment protocol were advised, we could not reach those time periods. When we tried to extend the treatment intervals gradually, only some patients tolerated 6-week intervals while the others needed to take their doses every month at that time. None of the patients tolerated 8-week intervals. Therefore, we can comment that an individual treatment plan must be applied for every patient.

In conclusion, we propose that omalizumab is a promising treatment agent in treatment-resistant CSU and idiopathic angioedema patients who feel hopeless and restricted because of their disease. Although an increasing number of reports demonstrating the utility of omalizumab in patients with refractory CU have appeared recently in the medical published work, this therapy is still investigational. Although placebo control is lacking, our results clearly show that omalizumab therapy is also effective in a real-life setting for refractory CSU and idiopathic angioedema.

REFERENCES

- Zuberbier T, Asero R, Bindslev-Jensen C *et al.* EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417–1426.
- Zuberbier T, Asero R, Bindslev-Jensen C *et al.* EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; **64**: 1427–1443.
- Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med* 2006; **354**: 2689–2695.
- Spector SL, Tan RA. Effects of omalizumab on patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2007; **99**: 190–193.
- Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. *J Allergy Clin Immunol* 2007; **120**: 979–981.
- Kaplan AP, Joseph K, Maykut RJ, Geba ZP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008; **122**: 659–673.
- Groffik A, Mitzel-Kaoukhov H, Magerl M, Maurer M, Staubach P. Omalizumab—an effective and safe treatment of therapy-resistant chronic spontaneous urticaria. *Allergy* 2011; **66**: 298–305.
- Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; **63**: 777–780.
- Baiardini I, Pasquali M, Braido F *et al.* A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy* 2005; **60** (8): 1073–1078.
- Kocatürk E, Aktaş S, Kavala M, *et al.* The Turkish Version of the chronic urticaria quality-of-life questionnaire: cultural adaptation, assessment of reliability and validity. *Acta Derm Venereol* 2011. doi: 10.2340/00015555-1199.
- Maurer M, Weller K, Bindslev-Jensen C *et al.* Unmet clinical needs in chronic spontaneous urticaria. A GA(2) LEN task force report (1). *Allergy* 2011; **66**: 317–330.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; **136** (2): 197–201.
- Baiardini I, Giardini A, Pasquali M *et al.* Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003; **58** (7): 621–623.
- Lennox RD, Leahy MJ. Validation of the dermatology life quality index as an outcome measure for urticaria-related quality of life. *Ann Allergy Asthma Immunol* 2004; **93** (2): 142–146.
- Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol* 2005; **152** (2): 289–295.
- Gober LM, Sterba PM, Eckman JA, Saini SS. Effect of anti-IgE (omalizumab) in chronic idiopathic urticaria (CIU) patients. *J Allergy Clin Immunol* 2008; **121** (Suppl 1): S147.
- Vestergaard C, Deleuran M. Two cases of severe refractory chronic idiopathic urticaria treated with Omalizumab. *Acta Derm Venereol* 2010; **90**: 443–444.
- Maurer M, Altrichter S, Bieber T *et al.* Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011; **128** (1): 202–209.
- Noga O, Hanf G, Kunkel G, Kleine-Tebbe J. Basophil histamine release decreases during omalizumab therapy in allergic asthmatics. *Int Arch Allergy Immunol* 2008; **146** (1): 66–70.
- Iemoli E, Piconi S, Fusi A, Borgonovo L, Borelli M, Trabattini D. Immunological effects of omalizumab in chronic urticaria: a case report. *J Invest Allergol Clin Immunol* 2010; **20** (3): 252–254.
- Saavedra MC, Sur S. Down regulation of the high-affinity IgE receptor associated with successful treatment of chronic idiopathic urticaria with omalizumab. *Clin Mol Allergy* 2011; **9** (1): 2.