



Letter

Omalizumab for the treatment of chronic spontaneous urticaria in clinical practice

Chronic spontaneous urticaria (CSU) is a skin disease that predominantly affects adults, especially women aged 20 to 40 years, and is characterized by the recurrent appearance of localized or widespread wheals, angioedema or both, without apparent external trigger.^{1,2} Severe CSU has a detrimental effect on the quality of life and is a frequent cause of absenteeism from school and work.³ The pathogenesis of CSU is not well understood, and it appears to have an autoimmune cause in approximately one-third of patients.⁴ Guidelines for the management of CSU recommend the use of second-generation antihistamines, with the addition of leukotriene receptor antagonists, cyclosporine, or omalizumab.¹ A short course (10 days maximum) of oral corticosteroids may also be included for acute exacerbations.

Omalizumab is a humanized monoclonal antibody that results in a rapid and substantial reduction in serum levels of IgE with subsequent down-regulation of FcεRI on mast cells and circulating basophils, making these cells insensitive to stimulation by incoming allergens.⁵ It is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of CSU in adults and adolescents (≥ 12 years old) with inadequate response to antihistamine treatment. However, the clinical experience with omalizumab is limited, and data regarding its use in patients with CSU in real-life practice are lacking. We present a case series of patients with CSU refractory to antihistamines and other recommended therapies who initiated omalizumab treatment.

All patients included in the study received 300 mg of omalizumab (Xolair; Novartis, Basel, Switzerland) injection subcutaneously every 4 weeks at 8 dermatology and allergy clinics in southern Italy from July 2014 to November 2015. The response to treatment was evaluated at each monthly visit using the Urticaria Activity Score (UAS) and the Itch Severity Score (ISS). The UAS rated the severity of wheals and pruritus with scores from 0 to 3 (0, none; 1, mild; 2, moderate; 3, intense; total score ranging from 0 to 6), whereas the ISS evaluated pruritus on a 4-point scale (0, none; 1, mild; 2, moderate; and 3, severe) or on an 11-point visual analog scale (0, no itch; to 10, most intense itch). The UAS in the last 7 days (UAS7) evaluated the severity of wheals and pruritus during the past week and was a sum of the scores for each day of the past week (maximum score, 42), which relied on entries in the patient diaries. Adverse events associated with the treatment were recorded, and all patients were followed up for a variable period after treatment discontinuation. The study was conducted in accordance with the ethical standards of the institutional and national committee on human experimentation and the Declaration of Helsinki. All patients included in the study provided a written informed consent.

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Of the 14 white patients (64.3% females; mean age, 45.1 years), 78.6% of patients had a disease duration of 2 years or longer (Table 1). The baseline UAS7 scores indicated moderate to intense CSU (mean [SD], 31.1 [6.9]); the total treatment duration varied between 2 and 7 months, with 64.3% of patients receiving at least 6 injections. One patient had 2 courses of treatment of 6- and 7-month durations. A substantial improvement in symptoms was visible after 1 month of omalizumab initiation, and the overall response to treatment (defined as well-controlled urticaria [UAS7 ≤ 6] or completely controlled [UAS7 = 0]) was generally rapid (2–3 months). At the end of the treatment, 35.7% of patients achieved complete symptom resolution (UAS7 of 0), 50.0% had well-controlled disease (UAS7 ≤ 4), whereas only 14.3% of patients had mild to moderate CSU symptoms (UAS7 of 7–11). Omalizumab was well tolerated, and no treatment-related adverse events were reported. Furthermore, it was observed during follow-up that omalizumab discontinuation led to reappearance of CSU symptoms in all patients within 1 to 4 months; reappearance was generally gradual, with the exception of 1 patient who reported elevated UAS7 scores within 1 month of treatment discontinuation.

The results of this study indicated that once monthly treatment with 300 mg of omalizumab had a substantial benefit in patients with moderate to severe CSU refractory to antihistamines and other available treatments. These findings are consistent with the results of randomized clinical trials that reported that omalizumab had the highest response rate at a dose of 300 mg in patients with CSU and that the median time to reach a UAS7 of 0 is 12 to 13 weeks.⁶ Few case series and real-life studies also report complete resolution of symptoms and improvement in the quality of life with omalizumab in patients with CSU.^{7–9}

In the present study, discontinuation of omalizumab treatment was followed by the reappearance of CSU symptoms, indicating that omalizumab for up to 6 months is unable to modify the underlying disease. Results of a retrospective analysis of 25 patients with CSU, chronic inducible urticaria, or both indicate that omalizumab is highly effective even when readministered after treatment discontinuation,¹⁰ suggesting that omalizumab treatment can be repeated in patients who report an initial benefit. The results of our case series are consistent with this observation, where 1 patient benefited from a second 7-month cycle of omalizumab.

Currently, data on the long-term safety of omalizumab in the treatment of CSU are limited. However, the long-term safety profile of omalizumab is fairly well established in allergic asthma. Our study found that treatment with omalizumab was well tolerated and easy to administer in all patients, including patients with comorbidities and poor tolerability to other CSU medications or for whom other medications were contraindicated. Thus, omalizumab may be a good treatment option in patients with refractory CSU.

Table 1
Characteristics of Patients with CSU Before and After Treatment with Omalizumab (300 mg Monthly)

Patient No./sex/age, y	CSU Baseline Characteristics				Treatment With Omalizumab		
	Disease duration	Manifestations and comorbidities	UAS7	Treatment history (Daily Dose, mg)	Treatment duration, mo	UAS7 (End of treatment)	Outcomes after omalizumab discontinuation
1/M/53	4 y	Recurrent angioedema; metabolic syndrome; hepatic steatosis; COPD; psoriasis; OSAS; insomnia; nocturnal bulimia	37	Bilastine (40), treatment discontinued because of lack of efficacy, prednisone (50), cyclosporine (300), treatment discontinued because of serum creatinine elevation	6	2	Symptom decrease
2/M/27	>7 y	Recurrent angioedema; delayed pressure urticaria; IBS	30–32	Cetirizine (10–30), desloratadine (up to 3 times the licensed dose), cycles of 2–3 mo, lack of efficacy with all treatments	6; 7 (ongoing)	0–3	Slow increase of UAS/UAS7 to baseline levels after 5 wk from discontinuation of first cycle; second cycle of omalizumab ongoing
3/F/62	Approximately 30 y	Allergic contact dermatitis; sialadenitis; dry eye syndrome; periarthritis of the shoulder	22	Prednisone (25, down-titrated to 6.25 for 2 wk), levocetirizine (10), cetirizine (10), 20-d treatments, low efficacy (especially on wheals and pruritus) with all treatments	3	2	No skin symptoms up to 4 mo after discontinuation
4/M/68	Approximately 3 y	Benign prostatic hypertrophy	21	Desloratadine (5), levocetirizine (10), cetirizine (10), 20-d treatments, low efficacy (especially on wheals and pruritus) with all treatments	3	1	No skin symptoms up to 4 mo after discontinuation
5/F/20	Approximately 5 mo	None	25	Prednisone (25, down-titrated to 6.25 during 2 wk), betamethasone (2, down-titrated to 0.5 during 2 wk), levocetirizine (10), cetirizine (10), 20-d treatments, low efficacy (especially on wheals and pruritus) with all treatments	2	11	Mild pruritus 3 mo after discontinuation; no active skin lesions
6/F/28	2 y	Recurrent angioedema; celiac disease; asthma; autoimmune thyroiditis	30	Desloratadine (up to 4 times the licensed dose, treatments of 2- to 4-wk duration), bilastine (up to 4 times the licensed dose, treatments of 2- to 4-wk duration), bilastine (80) and montelukast (10 mg) (4-wk treatment), lack of efficacy with all treatments, asthma treated concomitantly with beclomethasone/formoterol (2 puffs), or fluticasone/formoterol (250/10), with progressive improvement of FEV ₁	6	0	After 2 mo, skin symptoms still absent

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Table 1 (continued)

Patient No./sex/age, y	CSU Baseline Characteristics				Treatment With Omalizumab		
	Disease duration	Manifestations and comorbidities	UAS7	Treatment history (Daily Dose, mg)	Treatment duration, mo	UAS7 (End of treatment)	Outcomes after omalizumab discontinuation
7/F/54	13 y	Atopic diathesis; allergic rhinitis	40	Cetirizine (10) and hydroxyzine (25) and ketotifen (2), short courses of methylprednisolone during acute exacerbations, cyclosporine (200), low efficacy with all treatments, cyclosporine treatment discontinued before initiating omalizumab treatment; antihistamines combination gradually reduced to cetirizine (10) only	7	7	After 2 mo, appearance of mild symptoms; after 6 mo, patient is doing well, with occasional symptom manifestations; UAS7 of 16
8/M/45	10 mo	Atopic dermatitis	31	Cyclosporine (200 for 30 d, 150 for 30 d, 100 for 30 d; 2 cycles with 30-d interval), cetirizine (10, 3 cycles of 1-m duration with intervals), ebastine (10, 1-mo cycles alternating with cetirizine), zafirlukast (40, 2-mo treatment), methylprednisolone (16 mg, down-titrated, 21-day cycles), low efficacy (especially on pruritus) with all treatments	6	0	NA
9/F/32	9 mo	Mild gastritis	28	Cyclosporine (200 for 30 d, 150 for 30 d, 100 for 30 d; 2 cycles with 30-d interval), levocetirizine (5, 1-mo cycles), methylprednisolone (16 mg, down-titrated, 21-d cycles), low efficacy with all treatments	6	0	NA
10/F/39	Approximately 3 y	Atopic diathesis; contact urticaria; mild chronic asthma	35	Cetirizine (10) and hydroxyzine (25) and betamethasone (4, as needed), for 3 mo, desloratadine (10) and ranitidine (300), for 3 mo, unsatisfactory results with all treatments	6	8 (after second administration) 0 (after third administration)	After 3 mo, reappearance of CSU symptoms with angioedema, after insect sting (treated with antihistamines and corticosteroid); UAS7 of 25
11/F/66	11 y	Recurrent angioedema; hypertension; breast adenoma (removed 20 y before)	38–42	Antihistamines (up to 3 times the licensed dose), systemic corticosteroids also combined with antihistamine, cyclosporine (200, discontinued after 2 mo for tolerability problems), antihistamines with occasionally systemic corticosteroids, low efficacy with all antihistamine-based treatments	3	0–2	Immediately after discontinuation; patient resumes treatment with antihistamines and steroids

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Patient No./sex/age, y	CSU Baseline Characteristics				Treatment With Omalizumab		
	Disease duration	Manifestations and comorbidities	UAS7	Treatment history (Daily Dose, mg)	Treatment duration, mo	UAS7 (End of treatment)	Outcomes after omalizumab discontinuation
12/F/48	>2 y	Recurrent angioedema; allergy to NSAIDs	40–42	Antihistamines (up to 3 times the licensed dose), occasionally combined with systemic corticosteroids, cyclosporine (200, 3–4 mo, symptom reappearance on discontinuation), low efficacy with all antihistamine-based treatments	3	0–2	About 40 d free of symptoms; then reappearance of symptoms, occasionally of severe intensity; patient resumes antihistamines and then cyclosporine
13/F/43	2 y	Recurrent angioedema; atopic diathesis; rhinitis; allergic bronchial asthma	32	Fexofenadine (360, continuous), low benefit in terms of UAS7 and pruritus, prednisone (25, 10-d courses, twice monthly), temporary symptom resolution	6	0	Gradual worsening of symptoms already after 2 mo
14/M/37	5 y	Recurrent angioedema; atopic diathesis; rhinitis; allergic bronchial asthma	22	Ebastine (10, continuous, up to 4 times the licensed dose), low or no benefit in terms of UAS7 and pruritus, prednisone (25, 10-d courses, twice monthly), temporary symptom resolution	6	4	After first months, progressive worsening of symptoms

Abbreviations: COPD, chronic obstructive pulmonary disease; CSU, chronic spontaneous urticaria; FEV₁, forced expiratory volume in 1 second; IBS, irritable bowel syndrome; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; OSAS, obstructive sleep apnea syndrome; UAS7, Urticaria Activity Score in the last 7 days.

In conclusion, omalizumab is effective in reducing the symptoms of CSU in patients refractory to other available treatment regimens and may be a valuable drug for the management of CSU in real-world clinical practice. Further studies determining the duration and frequency of treatment in these patients are warranted.

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References

- [1] Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–887.
- [2] Greaves MW. Chronic urticaria. *N Engl J Med*. 1995;332:1767–1772.
- [3] Greenberger PA. Chronic urticaria: new management options. *World Allergy Organ J*. 2014;7:31.
- [4] Greaves M. Autoimmune urticaria. *Clin Rev Allergy Immunol*. 2002;23:171–183.
- [5] Chang TW, Chen C, Lin CJ, et al. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2015;135:337–342.
- [6] Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol*. 2016;137:474–481.
- [7] Lefevre AC, Deleuran M, Vestergaard C. A long term case series study of the effect of omalizumab on chronic spontaneous urticaria. *Ann Dermatol*. 2013;25:242–245.
- [8] Romano C, Sellitto A, De Fanis U, et al. Omalizumab for difficult-to-treat dermatological conditions: clinical and immunological features from a retrospective real-life experience. *Clin Drug Investig*. 2015;35:159–168.
- [9] Sussman G, Hebert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014;112:170–174.
- [10] Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol*. 2014;150:288–290.