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Omalizumab in Chronic Spontaneous Urticaria Refractory to Conventional Therapy: An Italian Retrospective Clinical Analysis with Suggestions for Long-Term Maintenance Strategies

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ABSTRACT

Introduction: Omalizumab is indicated for the treatment of patients affected by chronic spontaneous urticaria (CSU) refractory to antihistamines. The aim of this study was to assess the efficacy, safety, and recurrence of symptoms in a real-life experience of omalizumab as an add-on therapy for H_1-antihistamine-refractory CSU patients (refractory CSU).

Methods: A retrospective review of the clinical records of all refractory CSU treated with omalizumab at our dermatology center from June 2014 to April 2017 was performed. Patients previously treated with second-generation antihistamines at a fourfold increased dose without clinical responses at 4 weeks of treatment were selected. Omalizumab was administered at a single dosage of 300 mg every 4 weeks for 6 months. Disease severity was assessed using the 7-day Urticaria Activity Score (UAS7).

Results: Eighteen patients (14 women; mean age 51 years, range 25–74) were enrolled. Mean UAS7 at baseline was 27.3 (range 15–38). Symptoms improved in all patients at 4 weeks (UAS7 = 16.1, range 0–36). Treatment was completed in 17 patients (94.4%), and among these, a complete response (UAS7 = 0) was registered in 10 patients (58.8%). Adverse events included thrombocytopenia in 1 patient (5.6%) at 16 weeks; therapy was suspended after 20 weeks and the complication was resolved, resulting in a freedom from major adverse events of 94.4%. Symptom recurrence occurred in 3 patients (17.6%) at 4, 5, and 7 months from the end of the primary therapy. Retreatment with omalizumab was successful without any adverse effects. Mean follow-up was 9.5 months (range 1–28).

Conclusion: Add-on omalizumab therapy for refractory CSU in a real-life setting seems to be effective and safe with a relatively low incidence of symptom recurrence. Further research should investigate personalized omalizumab treatment dosages and administration intervals, and the identification of biomarkers for future treatment algorithms.

Keywords: Angioedema; Chronic spontaneous urticaria; Omalizumab; UAS7; Urticaria treatment; Wheal

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INTRODUCTION

Chronic spontaneous urticaria (CSU), also called chronic idiopathic urticaria, affects around 0.5–1% of the global population at any given time [1]. H_1-antihistamine-refractory CSU (refractory CSU) has been previously defined as uncontrolled symptoms (persisting of pruritus and wheals) for at least 6 weeks [2]. CSU more commonly affects women and is characterized by the spontaneous appearance of itchy hives, with or without angioedema, persisting for at least 6 weeks [2]. Generally, this chronic disease has a duration of 1–5 years, rarely persists for up to 50 years, and it is associated with patient referred reduced quality of life [1, 2].

The EAACI/GA^{2}LEN/EDF/WAO urticaria guidelines' treatment objective is the complete resolution of signs and relief of symptoms as quickly as possible, improving patients' quality of life in a three-step treatment algorithm [2]. The first choice treatment is second-generation H_1-antihistamines in a single administration, and in the cases of inadequate responsive, guidelines suggest a second-line treatment of increasing dosages, up to four times the recommended primary dose (currently an off-label treatment) [2]. The recommended third-line treatment includes add-on therapy of cyclosporine or montelukast (currently unlicensed for CSU) [2] or omalizumab, a humanized monoclonal anti-immunoglobulin E (IgE) antibody, which is the only approved add-on therapy for refractory CSU [3, 4]. In the ASTERIA I, ASTERIA II, and GLACIAL pivotal randomized clinical trials, omalizumab, at various single doses (ranging from 75 to 300 mg) every 4 weeks for 3 or 6 months, demonstrated its efficacy and safety for the treatment of CSU, with significant improvements in the Itching Score and 7-day Urticaria Activity Score (UAS7), compared to placebo [5–7]. Current EAACI/GA^{2}LEN/EDF/WAO urticaria guidelines recommend a 300 mg dose [2].

In clinical settings, the treatment of refractory CSU with omalizumab has been shown to be similar to, or in some cases even better than, those reported by the pivotal randomized controlled trials [5–11]. Many previous studies have included CSU with other forms of urticaria, various dosages, and high variability of evaluation instruments. We present a retrospective clinical analysis of the effects of omalizumab in a homogeneous cohort of CSU patients, following a strict protocol of a single dosage of 300 mg every 4 weeks, measured according to the UAS7.

METHODS

A retrospective analysis selected all consecutive refractory CSU, subsequently treated with omalizumab, at our dermatology center from June 2014 to April 2017. All patients selected in this study provided written, informed consent and were previously treated with second-generation antihistamines at a fourfold increased dose without clinical responses at 4 weeks of treatment. The study was conducted in accordance with the Declaration of Helsinki, good clinical practice, and all applicable laws and regulations. Exclusion criteria included all patients who tested positive to the FricTest$^®$ (Moxie GmbH, Berlin, Germany) and TempTest$^®$ (Khazaka Electronic, Köln, Germany) for the evaluation of physical/inducible urticaria. Data analyzed included patient demographic and clinical variables. A complete laboratory investigation including immunologic tests (immunoglobulins, rheumatoid factor, antinuclear factor, and organ-specific antibodies), IgE, serum tryptase, D-dimer, and vitamin D was performed at baseline. Further, autologous serum skin test (ASST), a simple in vivo clinical test for the detection of basophil histamine-releasing activity, was also performed at baseline, following suspension of antihistamine therapy for at least 7 days.

According to current guidelines, omalizumab was subcutaneously administered at a single dose of 300 mg (independent of patient body weight or serum IgE level), and repeated every 4 weeks for 6 months. Disease severity was assessed using the UAS7 at baseline (prior to omalizumab administration) and at 1, 4, 12, 16, 20, and 24 weeks during the treatment cycle, and every 8 weeks after the final therapy administration. Routine laboratory

investigations were also repeated at 4, 12, 16, 20, and 24 weeks after treatment initiation.

The UAS7 is the sum of the average daily UAS, which is a composite score of itch severity and hive count, over 7 days (range 0–42) [2, 12]. Response was classified according to UAS7 as complete (UAS7 = 0), good ($1 \leq UAS7 \leq 6$), partial ($6 < UAS7 < UAS7$ at baseline), and no response ($UAS7 \geq UAS7$ at baseline) [2, 12].

Patient relapse was considered a new increase in UAS7 compared to the UAS7 recorded at 24 weeks of treatment with omalizumab. Patients with relapse were prescribed a second omalizumab add-on therapy cycle, of a single administration of 300 mg, repeated every 4 weeks for 5 months, according to the national protocol from the Ministry of Health. UAS7 was repeated prior to the second therapy cycle at baseline and 1, 4, 12, 16, and 20 weeks, while routine laboratory investigations were performed at 4, 12, 16, and 20 weeks.

Statistical analysis was performed using STATA® software version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). Analysis included the Student's t test to compare continuous variables. Margin statistics was used to estimate adjusted predictions and marginal effects after a linear regression based on a previously fitted model. The model considered that the values of UAS7 were fixed among patients during the first and second cycles of omalizumab administration. For all tests, a $p < 0.05$ was considered statistically significant.

RESULTS

The study population comprised 18 patients with refractory CSU. Mean age of our patient population was 50.9 years (range 25–74) and the majority were female (14 cases, 77.8%). All patients had persistence of symptoms for at least 12 months (in two cases for over 10 years) and none reported angioedema. One patient had a history of breast cancer (3 years prior) treated with total mastectomy and chemotherapy. Demographic data, comorbidities, and concomitant and previous medications of the patients are reported in Table 1.

Table 1 Demographic, comorbidities, and concomitant and previous medications

Age, years (range)	50.9 (25–74)
Age at urticaria onset, years (range)	45.4 (12–72)
Gender, n (%)	
Female	14 (77.8)
Male	4 (22.2%)
Time from onset to omalizumab assumption, months (range)	65 (8–228)
Comorbidities, n (%)	
Hypertension	2 (11.1)
Hypercholesterolemia	1 (5.6)
Hashimoto thyroiditis	3 (16.7)
Breast cancer	1 (5.6)
Obesity	1 (5.6)
β-thalassemia minor	1 (5.6)
Concomitant medications, n (%)	
Antihypertensive	2 (11.1)
Statin	1 (5.6)
Levothyroxine	3 (16.7)
Medications prior to omalizumab assumption, n (%)	
Second-generation H_1-antihistamines, increased fourfold dosage	18 (100)
First-generation H_1-antihistamines	11 (61.1)
Leukotriene receptor antagonists	11 (61.1)
Orally administered corticosteroids	12 (66.7)
Cyclosporine	3 (16.7)

Antihistamine therapy was prescribed according to protocol to all patients during the omalizumab therapy; 11 patients (61.1%) adhered to the antihistamine therapy, while 7 patients (38.9%) reported spontaneous interruption of antihistamine therapy, without any modification to treatment response.

The mean serum levels were IgE 174.2 IU/ml (range 1–1560), serum tryptase 5.7 µg/l (range 2.7–9.4), D-dimer 385.3 ng/ml (range 66–1823), vitamin D 15.5 ng/ml (range 7–25.7). ASST was positive in only 2 patients (11.1%) who achieved the latest and worst partial response, while anti-thyroglobulin antibodies (anti-Tg) and anti-thyroid peroxidase antibodies (anti-TPO) were detected in 3 patients (16.7%) with known Hashimoto thyroiditis. The values of all other laboratory investigations performed at baseline were within normal ranges.

Almost all patients had improved symptoms after the first dose of omalizumab at 4 weeks, with UAS7 16.1 (range 0–36) compared to baseline 27.3 (range 15–38), and orally administered prednisone for symptom management was therefore not required. The average UAS7 continued to improve during the first treatment cycle, which was completed in 17 patients (94.4%) with UAS7 8.3 (range 0–35) at 24 weeks. Among these patients, a complete response was registered in 10 (58.8%), a good response in 1 patient (5.9%), a partial response in 4 patients (23.5%), and no response in 2 patients (11.8%) (Fig. 1).

A major adverse event was registered: the routine laboratory investigations revealed at 16 weeks the progressive onset of thrombocytopenia in 1 patient (5.6%) with a history of breast cancer. A complete response to CSU was registered at 20 weeks, and omalizumab drug administration was interrupted. The thrombocytopenia resolved and the patient dropped out of the study. Freedom from major adverse events was 94.4%. During the treatment period, three minor adverse events were registered in three patients: asthenia, slight arthralgia, and mild hypertransaminasemia. These events did not provoke omalizumab therapy interruption.

Symptom recurrence was registered in 3 patients (17.6%) at 4, 5, and 7 months following initial omalizumab therapy, respectively. Retreatment was successful with a complete response for all patients without any reported adverse effects or laboratory alterations (Fig. 2).

The average follow-up was 9.5 months (range 1–28).

Demographic data, comorbidities, laboratory investigation at baseline, adverse events, and UAS7 at first and second cycles of omalizumab
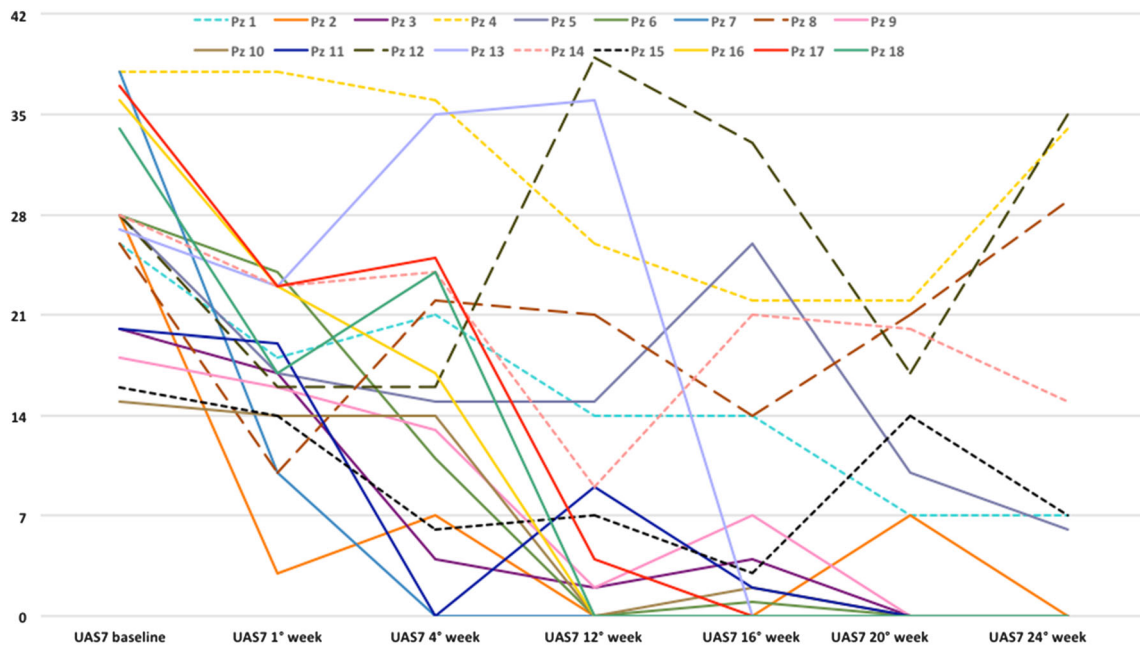

Fig. 1 UAS7 of patients treated with the first cycle of omalizumab. Complete (UAS7 = 0) and good responders (1 ≤ UAS7 ≤ 6) are indicated by continuous lines, partial responders (6 < UAS7 < UAS7 at baseline) by short-dashed lines, and non-responders (UAS7 ≥ UAS7 at baseline) by long-dashed lines
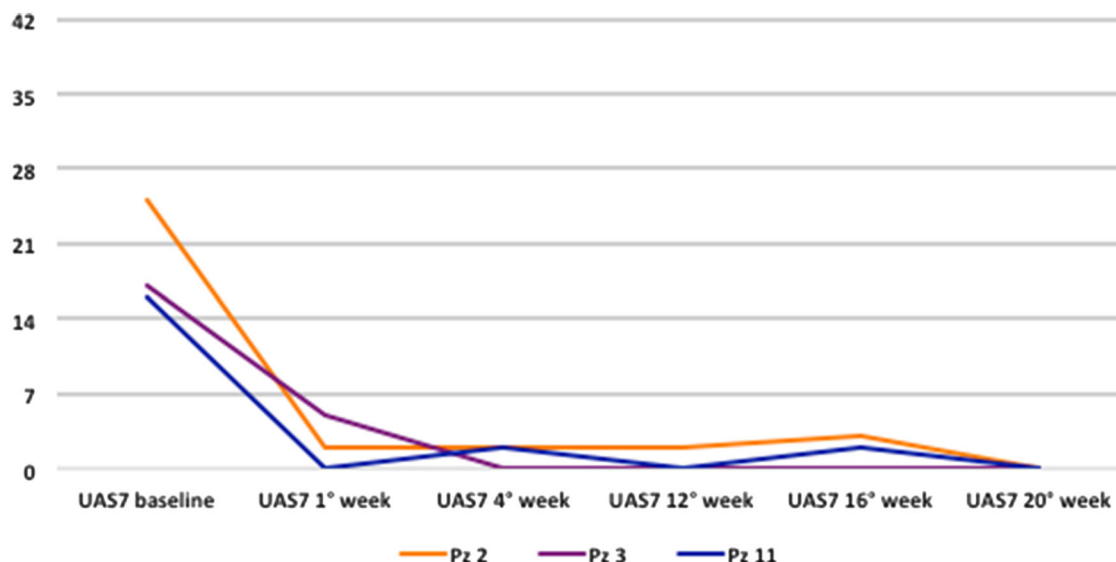
Fig. 2 UAS7 of patients treated with the second cycle of omalizumab

administration are reported in Table 2, while the mean UAS7 values during treatment and retreatment are outlined in Table 3. The linear prediction of the mean UAS7 for the first and second cycles illustrates that patient response to the second cycle treatment is effective more quickly compared to the first cycle response (Fig. 3).

DISCUSSION

Omalizumab has an established safety profile, approved for treatment of asthma in the USA (2003) and in the European Union (2005), and for the treatment of CSU in 2014 in both continents [3, 4]. Large multicenter, randomized, double-blind, placebo-controlled phase III trials (ASTERIA I, ASTERIA II, and GLACIAL) have shown that omalizumab significantly improved urticaria outcomes compared with placebo in patients with CSU [5–7]. However, none of the currently theories, alone or in combination, fully account for the pattern of symptom improvement seen with omalizumab [13] and, therefore, additional research seems justified in order to understand its definitive mechanism of action and to further clarify its involvement in relieving CSU symptoms.

The licensed dosage for omalizumab for refractory CSU in Europe is 300 mg every 4 weeks [3], while in the USA is either 150 or 300 mg every 4 weeks [4]. In the case of angioedema, only the dosage of 300 mg every 4 weeks has been proven to be effective [6]. Currently, the licensed dosage in Italy is 300 mg every 4 weeks over a 6-month period, and in the case of disease recurrence, a minimum of 8 weeks suspension from omalizumab is obligatory, and then it can be prescribed again for a further 5 months only. This schedule (6 months treatment, 8 weeks suspension, and 5 months therapy) can be repeated for eventual relapses; however, this de novo treatment is considered off-label.

Response patterns following omalizumab treatment of CSU patients in the three clinical trials (ASTERIA I, ASTERIA II, and GLACIAL) were investigated in a retrospective analysis, which demonstrated earlier and more sustained response in patients receiving 300 mg dose compared to patients receiving 75 or 150 mg doses or placebo [14]. Some CSU patients respond to treatment more quickly than others and for this reason two different categories of "omalizumab responders" have been described [14]. Proposed classifications included "fast responders" for those who responded within 4–6 weeks, while "slow responders" are those who respond more gradually, from 12 to 16 weeks of treatment. However, an analysis of response patterns revealed that "slow responders" may still respond even after 24 weeks,

Table 2 Demographic data, comorbidities, laboratory investigation at baseline, adverse events, and UAS7 at first and second cycles of omalizumab administration

ID (cycle)	Sex	Age of onset (years)	Comorbidities	ASST	IgE (IU/ml)	Serum tryptase (µg/l)	D-dimer (ng/ml)	Vitamin D (ng/ml)
1 (1st)	F	50	Hypertension	Negative	15	5	1823	19.6
2 (1st)	F	59	None	Negative	128	6.9	282	12.6
3 (1st)	M	58	None	Negative	97	3.3	66	18.7
4 (1st)	F	44	Hashimoto thyroiditis	Negative	125	5.3	463	25.7
5 (1st)	F	37	None	Negative	122	9.4	75	18.5
6 (1st)	F	45	None	Negative	106	4.9	276	18.5
7 (1st)	F	72	None	Negative	1560	6	296	7
8 (1st)	F	45	None	Positive	152	5.3	111	20.5
9 (1st)	F	49	Previous breast cancer	Negative	84	7.6	356	12.5
10 (1st)	F	49	Hashimoto thyroiditis	Negative	187	3.4	256	16.2
11 (1st)	F	36	β-thalassemia minor	Negative	168	2.7	111	13.2
12 (1st)	F	31	Hypertension and obesity	Positive	47	7.5	688	12.3
13 (1st)	F	62	None	Negative	47	6.1	376	19.4
14 (1st)	M	47	None	Negative	125	6.7	155	8.7
15 (1st)	M	12	None	Negative	83	5.8	230	7.6
16 (1st)	F	36	Hypercholesterolemia	Negative	46	4.6	295	20.6
17 (1st)	F	34	Hashimoto thyroiditis	Negative	42	6.2	656	13.9
18 (1st)	M	52	None	Negative	1	6	421	12.6
2 (2nd)	F	59	None	–	–	–	–	–
3 (2nd)	M	58	None	–	–	–	–	–
11 (2nd)	F	36	β-thalassemia minor	–	–	–	–	–

ID (cycle)	Adverse events	UAS7 baseline	UAS7 week 1	UAS7 week 4	UAS7 week 12	UAS7 week 16	UAS7 week 20	UAS7 week 24
1 (1st)	None	26	18	21	14	14	7	7
2 (1st)	None	28	3	7	0	0	7	0
3 (1st)	None	20	17	4	2	4	0	0
4 (1st)	Asthenia (minor)	38	38	36	26	22	22	34

Table 2 continued

ID (cycle)	Adverse events	UAS7 baseline	UAS7 week 1	UAS7 week 4	UAS7 week 12	UAS7 week 16	UAS7 week 20	UAS7 week 24
5 (1st)	None	28	17	15	15	26	10	6
6 (1st)	None	28	24	11	0	1	0	0
7 (1st)	Slight arthralgia (minor)	38	10	0	0	0	0	0
8 (1st)	Hypertransaminasemia (minor)	26	10	22	21	14	21	29
9 (1st)	Thrombocytopenia (major)	18	16	13	2	7	0	Drop out
10 (1st)	None	15	14	14	0	2	0	0
11 (1st)	None	20	19	0	9	2	0	0
12 (1st)	None	28	16	16	39	33	17	35
13 (1st)	None	27	23	35	36	0	0	0
14 (1st)	None	28	23	24	9	21	20	15
15 (1st)	None	16	14	6	7	3	14	7
16 (1st)	None	36	23	17	0	0	0	0
17 (1st)	None	37	23	25	4	0	0	0
18 (1st)	None	34	17	24	0	0	0	0
2 (2nd)	None	25	2	2	2	3	0	–
3 (2nd)	None	17	5	0	0	0	0	–
11 (2nd)	None	16	0	2	0	2	0	–

ASST autologous serum skin test, *UAS7* 7-day Urticaria Activity Score

while some "fast responders" may respond even within 1 week of treatment [14]. In a retrospective analysis of patients treated in a clinical setting, a complete response was reported in 57% of patients within 1 week, escalating to 86% of patients within 4 weeks [8]. We suggest that the response patterns of patients to omalizumab therapy may contribute to the understanding of the actions and pathophysiological mechanisms of the disease, providing essential information for future personalized therapeutic approaches. Currently, there are no established biomarkers available to predict the extent and course of changes in urticaria disease activity in response to therapy.

The current study reports a complete and good response (UAS7 ≤ 6) in 64.7%, which compares well with the values from the ASTERIA I and II studies of 58.8% and GLACIAL of 52.4% [5–7]. Complete response achieved in 58.8% in the current study was considerably higher than the ASTERIA I and II 40% rates, and the GLACIAL 33.7% [5–7]. A study of 110 patients also provided strong evidence for the efficacy of omalizumab, reporting outstanding results of a complete or significant response in 81.8%, with 60% interrupting concomitant medications, and recurrence in 80.9% [11]. However, different doses and administration protocols were used in this study.

Song et al. reported a similar complete response rate (62.5%) to the current study in their study of 16 patients [15]. Comparison with other retrospective studies is difficult given the use of subjective methods of evaluation to show categorical responses to omalizumab [9, 11, 16], many

Table 3 UAS7 at first and second cycles of omalizumab administration

Omalizumab administration	Initial therapy	Retreatment therapy	p value
Patients, n (%)	18 (100)	3 (17.6)	–
7-day Urticaria Activity Score (UAS7), mean, standard deviation (range)			
Baseline	27.3 ± 7.4 (15–38)	19.3 ± 4.9 (16–25)	0.091
Week 1	18.1 ± 7.4 (3–38)	2.3 ± 2.5 (0–5)	0.002
Week 4	16.1 ± 10.5 (0–36)	1.3 ± 1.2 (0–2)	0.028
Week 12	10.2 ± 12.6 (0–39)	0.7 ± 1.2 (0–2)	0.215
Week 16	8.3 ± 10.6 (0–33)	1.7 ± 1.5 (0–3)	0.306
Week 20	6.6 ± 8.5 (0–22)	0	0.207
Week 24	8.3 ± 12.4 (0–35)	–	–
Drop out, n (%)	1 (5.6)	0	–
Response based on UAS7 at end of treatment, n (%)[a]			
Complete (UAS7 = 0)	10 (58.8)	3 (100)	–
Good (1 ≤ UAS7 ≤ 6)	1 (5.9)	0	–
Partial (6 < UAS7 < UAS7 at baseline)	4 (23.5)	0	–
No response (UAS7 ≥ UAS7 at baseline)	2 (11.8)	0	–

[a] 17 patients completed the treatment
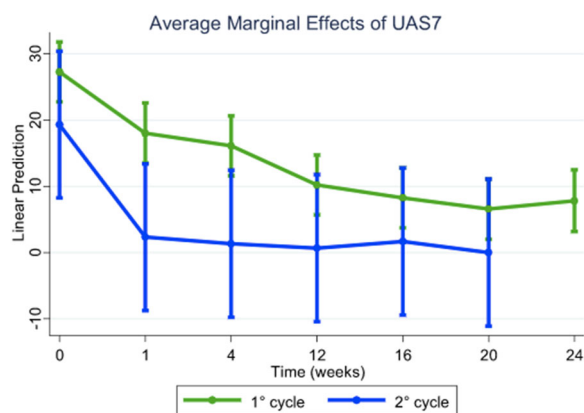
Fig. 3 Linear prediction of UAS7 among patients during the first and second cycles of omalizumab administration. Means (dots), 95% confidence interval (whiskers), samples between baseline (week 0) and the end of treatment (week 24) or retreatment (week 20)

physicians rely on their own experience and clinical judgment to assess disease activity [16], and differing outcome presentations [12]. Despite the EAACI/GA²LEN/EDF/WAO urticaria guideline recommendation of UAS7 for disease assessment [2], a systematic review referenced the use of UAS7 in only 6 of the included 26 randomized controlled trials dedicated to CSU [17]. The most common tools used by physicians to assess treatment response include the UAS7 [2], Angioedema Activity Score (AAS) [18], the Urticaria Control Test (UCT) [19], and specific disease quality of life questionnaires [Chronic Urticaria-Quality of Life Questionnaire (CU-Q₂oL) and Angioedema-Quality of Life Questionnaire (AE-QoL)] [12]. We suggest that future guidelines should propose UAS7 for the assessment of CSU patients with wheals, AAS for CSU patients with angioedema, and both scores for CSU patients with wheals and angioedema. Further, in many CSU patients disease activity and quality of life impairment are poorly correlated [12]. Therefore, UAS7 and/or AAS should be used together with specific disease quality of life questionnaires.

Successful alternative dosages of omalizumab have also been reported in small case

series: low dosages of omalizumab (150 mg every 4 weeks) for long-term management of refractory CSU following initial therapy [20], and high dosages (450 or 600 mg every 4 weeks) for partial or non-responders [12, 21, 22]. Moreover, some authors suggest that long-term omalizumab treatment may not alter the natural history of the disease and could increase the chance of spontaneous remission [22, 23].

The omalizumab clinical trials were all designed with a standard interval of treatment of 4 weeks, irrespective of serum immunoglobulin E level or body weight [5–7]. Some studies have experimented with personalized dosage intervals, concluding that some patients may tolerate dosage intervals longer than 4 weeks, while others may require reduced dose intervals in order to avoid relapse of the disease [20, 21, 23, 24]. We suggest that future patient therapies should consider both individualized dosages and optimal intervals.

Evidence suggests that following successful omalizumab treatment, eventual relapse can be again successfully treated with omalizumab [24]. In one study, all patients reported a rapid and complete response within the first 4 weeks of retreatment with omalizumab, and often even during the first week, without relevant adverse events [24]. Our study confirmed the data of literature showing a complete response, without adverse effects, in the three patients with relapse. Moreover, a good response was obtained in all these patients within the first week of retreatment.

Interestingly, in all responding patients in the current study, until they achieved a complete response, we observed a slight enhancement of daily UAS a few days prior to the next administration of omalizumab. This phenomenon may be due to the biological half-life of omalizumab, which is about 26 days, or may be due to a psychological effort of upcoming treatment.

Currently, there is only limited evidence for the long-term use of omalizumab for CSU, as completed clinical trials only provide data up to 6 months [5–7]. Some ongoing trials are investigating treatment for up to 1 year (XTEND-CIU; NCT02392624) and retreatment effectiveness (OPTIMA; NCT02161562) [12]. In our study, at a relatively long follow-up, only one major adverse event (thrombocytopenia) was reported, confirming the safety profile into the long term of omalizumab for CSU patients.

It still remains unknown for how long omalizumab may be administered continuously and if longer treatment duration or retreatment will induce earlier remission. Moreover, it is not known whether an immediate effective treatment will contribute to quick, complete, and permanent disease control.

The limitations of our retrospective study include the small number of enrolled patients and the absence of history of angioedema among this selected population.

CONCLUSIONS

Add-on omalizumab therapy for homogeneous refractory CSU in a real-life setting following a strict protocol of a single dosage of 300 mg every 4 weeks seems to be effective and safe. We propose that further research should investigate personalized omalizumab treatment dosages and administration intervals, based on UAS7 results, and the identification of biomarkers able to predict changes in disease activity in response to therapy for the development of treatment algorithms for use in clinical practice.

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