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Omalizumab chronic spontaneous urticaria: efficacy, safety, predictors of treatment outcome and time to response

Omalizumab in patients with chronic spontaneous urticaria: an Italian multicentric real life study

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Introduction

Chronic spontaneous urticaria (CSU) is the most common subtype of urticaria, and is characterized by recurrent episodes of spontaneous wheals and/or angioedema with unknown triggers, lasting for more than six weeks.[1] CSU generally affects 0.5–1.0% of people 20–40

years of age, with a disease duration of 1–5 years.[2] Patients with CSU often experience sleep deprivation and psychiatric comorbidities like anxiety and depression, which compromise the health-related and overall quality of life of the affected individuals.[2, 3]

Treatment of CSU can be challenging in most cases as it is often difficult to identify the underlying cause of the disease, and symptomatic therapies remain mainstay of treatment in these patients. First-line treatment of CSU includes second-generation non-sedating antihistamines.[1, 4, 5] However, the licensed doses of these drugs relieve symptoms in only 50% of cases, and the current guidelines suggest updosing of H1-antihistamines up to fourfold. [1] Both clinical experience and clinical studies support this approach showing a higher efficacy in many, but not all, patients.[6] Patients refractory to antihistamine therapy are generally treated with up to four times the recommended dose of second-generation antihistamines plus omalizumab, or cyclosporine A in severe cases.[1, 5]

Omalizumab is a recombinant anti-IgE antibody approved for the treatment of CSU refractory to antihistamines.[7, 8] It is administered subcutaneously at the recommended doses of 150 or 300 mg every 4 weeks. [9]"The mechanism of action is still unclear, although omalizumab seems to block the binding of IgE to the FcεRI receptor on the surface of target cells, including mast cells and basophils, thus reducing receptor expression and the release of inflammatory mediators[9]".

Since predictors of response to omalizumab treatment in CSU patients are still unclear, this study aims to evaluate efficacy and safety of this drug in patients with H1 antihistamine-

refractory CSU, investigating also baseline factors influencing treatment outcome as well as time lag to response to omalizumab by serum auto-reactivity.

Methods

Study design and patients

This multicentric retrospective observational study involved 23 Italian allergy and clinical immunology secondary care centers. The study comprised a 4–week pre-treatment period, followed by a 24–week treatment period, and a 16-week follow-up period. Patients aged 12-85 years included in the study had a history of spontaneous urticaria for more than 6 weeks, not responding to treatment with licensed doses of non-sedating second-generation H1-antihistamines for at least four weeks, with a daily urticaria activity score (UAS) ≥4 assessed in clinic on one of the pre-treatment check-up days (days –14, –7, or 1), and a 7-day urticaria activity score (UAS7) >16 assessed during 7 days before first study treatment. Baseline autologous serum skin test (ASST) was performed as per standard guidelines. ASST was considered to be positive if the wheal induced by serum was ≥ 1.5 mm larger in diameter than that induced by saline.[10] The total IgE serum levels were also measured using immunofluorometric assay (ImmunoCAP; ThermoFisher, Uppsala, Sweden) and were expressed in KUA/L, according to the manufacturer's instructions.

The key exclusion criteria were as follows: patients with serious psychological disturbances; history of malignancy or hypersensitivity to omalizumab; or treatment with omalizumab within the previous six months.

All procedures complied with the Helsinki Declaration of 1964, subsequently revised in

2013. The study protocol was approved by the ethical committee of Naples University Hospital, Italy. Informed consent was obtained from all patients who agreed to participate to this study.

According to the recommendations of the Italian Drug Agency (AIFA) for CSU, omalizumab was administered subcutaneously every 4 weeks at doses of 300 mg for 24 weeks in total (first treatment course) and was administered again (second treatment course) at least 8 weeks after the end of the first treatment course if the UAS7 score showed values similar to those at pretreatment.[11]

Throughout the study period, patients were required to maintain stable doses of their pre-treatment therapy with H1 antihistamines at approved doses. During this time, patients were therefore allowed to use up to four times of the licensed dose of H1 antihistamines and/or systemic glucocorticoids, as needed, for symptomatic relief.

Study end points and statistical analysis

The primary efficacy end points included mean and median change in UAS7 score, weekly itch severity score (ISS) and hive score from baseline to respective values at weeks 4, 12, and 24. The t-test was employed for comparison of means.

Secondary efficacy outcomes included the proportion of patients with well-controlled urticaria (UAS7≤6) and complete response to omalizumab treatment (UAS7=0) at week 4, 12, 24, and 40. Safety was evaluated by monitoring and recording the frequency and severity of adverse events (AEs).

Various factors were then investigated as predictors of response to omalizumab treatment, contrasting patients with UAS7 score of >6 (non-responders[12]) to those with UAS7 ≤6

(responders[12]) at week 24. Logistic regression analysis was employed to investigate treatment response as binary endpoint (UAS7 >6 vs. UAS7 ≤6) by different baseline characteristics. Total level of pre-treatment IgE were categorized into quartiles. A multivariate logistic regression model was fitted by selecting factors significant at the univariate analysis. The results of the multivariable logistic regression model, expressed as odds ratio (OR) with 95% confidence interval (95% CI), were also adjusted for the effect of participating centers. Patients responding within 8 days since omalizumab administration were considered "*fast responders*", those responding between 8 days and 6 months were considered "*slow responders*".[13]

The speed of response to omalizumab (*fast responders* vs. *slow responders*) was tested against serum reactivity based on ASST results (positive vs. negative) in an univariable exact logistic regression analysis. Results were expressed as odds ratio (OR) with 95% confidence interval (95%CI).

Statistical analyses were performed using Stata 14.2 package (Stata Corporation, College Station, Texas, USA). Level of significance was set at <0.05. Missing values were excluded and complete case analysis was performed.

Results

The study was conducted at 23 allergy and clinical immunology secondary care centers in Italy, all of which were members of the Italian Society of Allergy, Asthma and Clinical Immunology task force. A total of 322 patients with refractory CSU who received at least one dose of omalizumab at the study centers from September 2015 to August 2017 were included in the study, and were examined by 56 different physicians.

The mean age of patients was 46.5 ± 14.3 years, 222 patients (68.9%) were female and the mean total IgE at baseline was 231.4 ± 506.6 KUA/L (Table I). Mean duration of CSU was 44.1 ± 64.3 months and 167 patients (53.2%) had history of angioedema. The mean baseline UAS7 score was 27.9 ± 8.3 and in-clinic UAS was 4.8 ± 0.8; the baseline hive score was 13.3 ± 5.2, whereas baseline ISS was 14.4 ± 4.7. Angioedema was reported by 111 (36.3%) patients in the week before treatment.

Efficacy

As it can be seen from Table II, UAS7 scores diminished from baseline to week 4 (mean change = –19.5), up to week 12 (mean change = –22.7) and week 24 (mean change = –24.6), with a significant decreasing trend over time (p-trend <0.001). Similar mitigated trends from baseline to week 4, 12 and 24 were also observed for mean values of weekly hive scores (p-trend <0.001) as well as ISS (p-trend <0.001).

Nineteen patients (5.9%) discontinued the study during the 24-week treatment period; 12 patients had disease progression, three had personal problems, two had AEs, and two were lost to follow-up. Eleven patients (3.4%) discontinued treatment between week 24 and week 40 and were lost to follow-up.

During the follow-up period, 119/292 (40.8%) patients repeated treatment with omalizumab (second treatment course) due to an increase in the mean UAS7 score. At the end of the study, 173/292 (59.2%) patients did not repeat omalizumab treatment.

At the end of the 40-week study, 107 out of 173 patients (61.8%) reported well-controlled urticaria (UAS7 score ≤6), and complete response to omalizumab treatment (UAS7 score=0) was observed in 75 out of 173 treated patients (43.4%) (Table II).

Based on the above, factors significantly associated with UAS7 score >6 after 24 weeks since treatment start with omalizumab at univariable analysis were baseline angioedema, cyclosporine use, angioedema history, IgE levels and (to some extent) duration of CSU (Table III). At multivariate analysis only higher pre-treatment IgE values – categories (48-119) KUA/L and (120-236) KUA/L – were significantly less likely to be associated with a UAS7 score >6 at the end of the 24-week treatment period (Table III).

ASST was performed on 160 patients only. The results of ASST performed on the 135 patients who responded to omalizumab treatment (out of 255 responders) were analyzed. Sixty-six patients responding within 8 days of omalizumab administration were categorized as "*fast responders*", the remaining 69 patients were classed as "*slow responders*". Nineteen out of the 66 (28.8%) "*fast responders*" were ASST positive compared with 44 of the 69 (63.8%) "*slow responders*" (P <0.001) (Table IV). ASST-positive patients were 4.30 times more likely to have a slow response to omalizumab treatment as compared with ASST-negative patients.

Safety

The overall incidence of AEs during the 24-week treatment phase was 11.2%, and 31 patients (9.6%) reported at least one AE. Migraine, asthenia and administration site conditions were the most common AEs (Table V). No treatment-emergent AEs were reported during the study.

Discussion

The results of this study showed that omalizumab effectively reduced the symptoms of CSU in antihistamine refractory patients. After 24 weeks of treatment, omalizumab significantly

decreased the mean UAS7, ISS and weekly hive scores. Furthermore, 84.2% of patients reported well-controlled urticaria at the end of the 24-week treatment period, and complete response to treatment was seen in 66.7% of patients. Overall, the treatment was well tolerated.

UAS7 is a validated and widely used patient-reported measure of CSU that captures the intensity of pruritus and number of hives.[14] Studies with omalizumab have reported a reduction in UAS7 scores with treatment in patients with CSU.[15, 16] A randomized, double-blind, placebo-controlled study of omalizumab in patients with CSU reported that treatment with omalizumab decreased the UAS7 scores during the 24-week treatment period.[15] Another prospective open-label study with omalizumab reported a reduction in the UAS7 scores from baseline (5.7 vs 32.2) with treatment.[16] The results of the present study are in line with these reports and show that omalizumab treatment effectively reduced the UAS7 scores in patients with CSU over the 24-week treatment period, thus improving the overall symptoms in these patients.

Currently, the predictors of response to omalizumab treatment in CSU are not well known. A study by Ghazanfar and colleagues reported that favorable response to omalizumab treatment can be predicted by the presence of CSU, no angioedema, negative histamine release test, older age, shorter duration of symptoms, and no history of treatment with systemic immunosuppressant drugs.[17] Another prospective study with omalizumab reported that patients with lower baseline IgE values showed poor response to treatment and that the ratio of IgE values after treatment to baseline IgE levels of patients can help in predicting the treatment response in patients with CSU.[18] Similarly the present study confirmed poor

treatment outcome in relation of some baseline characteristics as cyclosporine administration, presence of angioedema, longer duration of CSU symptoms and low level of IgE. The above results are in line with previous reports identifying markers of response to omalizumab treatment in patients with CSU, which may be of significant value in clinical settings. However, after controlling for the simultaneous effect of all factors, the only important predictor of efficacious treatment response in our study was higher levels of pre-treatment IgE.

ASST is a simple *in vivo* clinical test for the detection of basophil histamine-releasing activity. ASST has a sensitivity of approximately 70% and a specificity of 80%, and it may be used as a reasonably predictive clinical test to indicate the presence of functional circulating anti-FcεRIα and anti IgE autoantibodies [10], but it can cause false positive results, because of the formation of a large amount of bradykinin and secretion of tryptases from neutrophils during the coagulation process[19].

Our study also showed that patients who were ASST positive were less likely to be "*fast responders*" (i.e. response within 8 days of omalizumab administration) to omalizumab treatment than those who were ASST negative. This result confirms the findings of Gericke et al. who also identified a significant association between ASST positivity and slower time lag to symptom relief with omalizumab in CSU patients[13], suggesting that omalizumab reduced the number of FcεRI receptors on mast cells and basophils in these patients.

Treatment with omalizumab was well tolerated in the present study. The most common AEs were migraine, asthenia and administration site conditions, which were not related to

omalizumab treatment. The main limitation of this study is its design, being observational and retrospective, without controls. In addition, although current guidelines for the diagnosis of CSU still recommend the *in vivo* ASST to define a CSU subgroup as having autoreactive urticaria,[1] concerns have been raised regarding its interpretation and specificity [10].

In conclusion, omalizumab was well tolerated and effective in the treatment of patients with CSU refractory to second-generation non-sedating antihistamines. Monitoring the baseline characteristics of patients before introduction of omalizumab therapy may help to predict treatment outcome in CSU patients.

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Table I. Baseline characteristics of patients included in the study

Baseline characteristics	**N**	
Age, years		
Mean ± SD	322	46.5 ± 14.3
Median (range)		46.5 (15–83)
Sex, n (%)	322	

Male		100 (31.1)
Female		222 (68.9)
Duration of CSU, months		
Mean ± SD	322	44.1 ± 64.3
Median (range)		24 (2–588)
History of CSU medications, n (%)		
H1 antihistamines at regular dose	322	322 (100.0)
H1 antihistamines at high dose		225 (69.9)
Leukotriene receptor antagonists		66 (20.5)
Systemic steroids		237 (73.6)
Cyclosporines		43 (13.3)
History of angioedema, n (%)	313	167 (53.2)
Presence of angioedema*, n (%)	306	111 (36.3)
Total IgE levels, KUA/L		
Mean ± SD	193	231.4 ± 506.6
Median (range)		120 (0–5237)
Positive thyroid autoantibody test, n (%)	236	58 (24.7)
Positive ASST, n (%)	160	76 (47.5)
In clinic UAS		
Mean ± SD	322	4.8 ± 0.8
Median (range)		5 (4–6)
UAS7*		
Mean ± SD	322	27.9 ± 8.3
Median (range)		27 (17–42)
Weekly ISS*		
Mean ± SD	322	14.4 ± 4.7
Median (range)		14 (3–21)
Weekly No. hive score*	322	
Mean ± SD		13.3 ± 5.2

Median (range)	13 (0–21)

*Based on data collected in patient's daily diary in the week before first treatment.

ASST, autologous serum skin test; *CSU*, chronic spontaneous urticaria; *ISS*, itch severity score; *SD*, standard deviation; *UAS*, urticaria activity score; *UAS7*, 7-day urticaria activity score.

Table II. Efficacy of omalizumab treatment during the study (n=322)

Endpoint	Week 4	Week 12	Week 24	Week 40
Change from baseline in UAS7 score				
Mean ± SD	–19.5 ± 10.9*	–22.7 ± 10.7*	–24.6 ± 9.9*	-
Median (range)	–19 (–42, 9)	–21 (–42, 18)	–23 (–42, 4)	-
Change from baseline in ISS				
Mean ± SD	–9.7 ± 6.0*	–11.6 ± 6.1*	–12.3 ± 5.8*	-
Median (range)	–10 (–21, 5)	–12 (–21, 13)	–12 (–21, 6)	-
Change from baseline in hive score				
Mean ± SD	–9.4 ± 6.2*	–11.1 ± 5.9*	–12.0 ± 5.7*	-
Median (range)	–9 (–21, 14)	–10 (–21, 10)	–11 (–21, 3)	-
Proportion of patients with well-controlled urticaria (UAS7 ≤6)	58.4% (188/322)	73.4% (232/316)	84.2% (255/303)	61.8% (107/173)
Proportion of patients with complete response (UAS7=0)	38.2% (123/322)	54.1% (171/316)	66.7% (202/303)	43.4% (75/173)

*t-test: *P* <0.001 vs baseline

ISS, itch severity score; *SD*, standard deviation; *UAS7*, 7-day urticaria activity score.

Table III. Logistic regression analysis for UAS7 scores as binary endpoint (>6 vs. ≤ 6). Odds ratios crude (OR) and adjusted (aOR) with 95% confidence interval (95%CI) and likelihood ratio test p value

Variable	Univariate analysis		Multivariate analysis
	OR (95% CI)	*P*-value	aOR (95% CI)
Age, years			
<65	reference	0.685	–
>65	0.81 (0.27, 2.41)		
Sex			
Female	reference	0.971	–
Male	1.01 (0.52, 1.97)		
Duration of CSU, months	1.01 (1.00, 1.01)	0.011	1.00 (1.00, 1.01)
History of angioedema			
No	reference	0.010	reference
Yes	2.36 (1.20, 4.62)		1.50 (0.38, 5.96)
Presence of angioedema			
No	reference	0.002	reference
Yes	2.77 (1.46, 5.27)		1.70 (0.48, 6.01)
Thyroid antibodies			
No	reference	0.937	–
Yes	1.04 (0.42, 2.58)		
ASST			
No	reference	0.371	–
Yes	1.52 (0.60, 3.85)		
Cyclosporine use			
No	reference	0.012	reference
Yes	2.81 (1.31, 6.05)		2.60 (0.70, 9.66)
Steroid use			
No	reference	0.058	
Yes	2.08 (0.93, 4.66)		
High dose antihistamine therapy			
No	reference	0.587	–
Yes	1.21 (0.61, 2.41)		
Total IgE, KUA/L			
<48	reference	0.011	reference
48–119	0.12 (0.03, 0.50)		0.11 (0.02, 0.69)
120–236	0.28 (0.09, 0.89)		0.24 (0.06, 0.92)

≥237	0.58 (0.22, 1;55)	0.33 (0.09, 1.21)

OR, odds ratio; *αOR*, adjusted odds ratio; *ASST*, autologous serum skin test; *CSU*, chronic spontaneous urticaria.

Table IV. Patients responding to omalizumab by ASST result

ASST result	Slow responders (Total=69) N (%)	Fast responders (Total=66) N (%)	OR (95% CI)	*P*-value
Negative	25 (36.2)	47(71.2)	*reference*	
Positive	44 (63.8)	19 (28.8)	4.30 (1.99- 9.60)	<0.001

"*Slow responders*" = patients who responded to omalizumab between 8 days and 6 months after omalizumab administration.

"*Fast responders*" = patients who responded to omalizumab within 8 days of omalizumab administration.

Exact logistic regression analysis.

ASST, autologous serum skin test; *CI*, confidence interval; *N*, Number; *OR*, odds ratio.

Table V. Summary of adverse events (AEs) reported during the 24-week treatment period

AEs, n (%)	**N=322**
Overall	36 (11.2)
Migraine	10 (3.1)
Asthenia	8 (2.5)
Administration site conditions	7 (2.2)
Skin rash	4 (1.2)
Arthralgia	4 (1.2)
Nasopharyngitis	1 (0.3)
Dyspepsia	1 (0.3)
Fever	1 (0.3)
Any AE leading to discontinuation of study	2 (0.6)