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Analysis of clinical factors as possible predictors of response to omalizumab and relapse after treatment discontinuation in chronic spontaneous urticaria

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Abstract

Omalizumab is a monoclonal anti-IgE antibody which is effective in chronic spontaneous urticaria (CSU), although clinical response appears to be variable in the real-life setting. The aim of this study was to evaluate whether the response of CSU to omalizumab and disease relapse are associated with individual and/or clinical characteristics of patients. We retrospectively evaluated the clinical records of 124 patients treated with omalizumab for moderate to severe CSU refractory to antihistamines. Disease activity was assessed using the urticaria activity score over the last 7 days (UAS7). After 24 weeks of treatment, 91% of patients showed complete remission (UAS7 = 0) or good control (UAS7 < 7) of CSU. Omalizumab was re-administered in 45 patients because of recurrence of moderate to severe symptoms at week 8 after treatment discontinuation or later, and clinical results achieved with retreatment were similar to those observed in the first course. Among the parameters included in our analysis (age and sex of patients, documented history of atopy or autoimmune thyroid disease, CSU duration and baseline severity, concurrent angioedema, and association with chronic inducible urticaria), none was associated with response to omalizumab in our study population. Similarly, these parameters did not significantly differ between patients who experienced CSU relapse and those without relapse. Predictors of response to omalizumab treatment in CSU patients are still unclear, and further studies are needed to evaluate the presence of baseline factors that can influence treatment outcome.

KEYWORDS

chronic spontaneous urticaria, omalizumab, predictors, relapse, response

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous occurrence of wheals and/or angioedema for more than 6 weeks.^{1,2} CSU corresponds to 66% to 93% of all cases of chronic urticaria and its prevalence in the general population ranges from

0.5% to 1%. The peak age is between 20 and 40 years, with a female to male ratio of 2:1. The duration of the disease ranges on average between 1 and 5 years, but in 11% to 14% of cases symptoms can persist for more than 5 years.³

Because of its unpredictable course and poor response to standard therapies, CSU has a negative impact on the quality of life of

affected patients, who live in a condition of psychological and emotional distress that affects both social relations and work activities.⁴ The chronic nature of this disease and the difficulties in therapeutic management entail a high socio-economic burden, linked to direct medical costs (drugs, laboratory analyses, outpatient medical examinations, and first aid accesses) and indirect costs due to absence from work or reduced working efficiency.³⁻⁵

According to the recent guidelines,^{1,2} the first-line therapy of CSU is represented by second generation anti-H₁ antihistamines at the approved doses. However, in more than 50% of patients this therapy is not successful.³ As a second-line option, daily doses of anti-H₁ antihistamines up to four times the recommended dose can be used; this increases the response to treatment, but up to 30% of CSU patients remain unresponsive.³

In 2014, omalizumab was approved, in association with anti-H₁ antihistamines, for the treatment of CSU in patients aged ≥12 years with inadequate response to anti-H₁ antihistamines. Omalizumab is a humanized monoclonal antibody which selectively binds to free IgE antibodies,⁶ preventing their binding to high-affinity IgE receptors on the membranes of mast cells and basophils, and consequently inhibiting their degranulation and the release of many mediators responsible for the clinical manifestations of urticaria.⁷ Omalizumab is administered subcutaneously at a dose of 300 mg every 4 weeks. The rules defined by the Italian Drug Agency (AIFA, Agenzia Italiana del Farmaco) allow treatment in CSU patients for 24 weeks. In case of relapse, a second course of 20 weeks, at the same dose, can be prescribed after a period of at least 8 weeks. The efficacy and tolerability profile of omalizumab is good, as confirmed by numerous studies.⁸⁻¹⁵

Real-life experience suggests that the clinical response of CSU patients to omalizumab is variable, in terms of efficacy, time required to achieve therapeutic effects, number and magnitude of relapses after drug withdrawal, and need for retreatment. Limited data are available on the possible link between the above-mentioned parameters and characteristics and/or clinical factors of patients.

The aim of this study was to evaluate whether the response of CSU to omalizumab and relapse are associated with individual characteristics and/or clinical factors of patients.

2 | MATERIALS AND METHODS

2.1 | Patients and methods

We retrospectively evaluated the clinical records of patients treated with omalizumab for moderate to severe CSU refractory to antihistamines in two Italian Dermatology centers (Bari and Messina), over a period of 3 years. In accordance with international guidelines, the assessment of CSU activity and response to the treatment was performed using the Urticaria Activity Score over the last 7 days (UAS7), which is the sum of the scores for wheals and itch evaluated daily on the basis of a 0–3 scale for 7 consecutive days.^{1,16}

All patients had been treated in line with international guidelines and AIFA recommendations on the use of omalizumab in CSU patients (300 mg every 4 weeks for 24 weeks, then, after at least 8 weeks,

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria

- Patients with CSU observed at the Dermatology Clinic of the University Hospital of Bari or Messina, Italy
- Age ≥12 years
- CSU resistant to therapy with second-generation anti-H₁ antihistamines, administered according to the international guidelines for at least 30 days
- UAS7 score ≥16 at the enrolment visit

Exclusion criteria

- Positive personal history of cancer
- Treatment with corticosteroids, hydroxychloroquine, methotrexate, ciclosporin, cyclophosphamide and other immunosuppressants, intravenous immunoglobulins or plasmapheresis in the 30 days prior to the start of omalizumab administration

Abbreviations: CSU, chronic spontaneous urticaria; UAS7, urticaria activity score over 7 days.

retreatment at the same dose for 20 weeks in case of relapse with UAS7 values >16). In view of the retrospective nature of the study, we sent a notification to our Ethics Committees.

Inclusion and exclusion criteria are listed in Table 1. From each medical record, different clinical variables were evaluated (Table 2). For each course of treatment, the UAS7 score was evaluated at baseline, week 12, at the end of treatment and at a follow-up visit after 8 weeks. In line with the literature,¹⁷ urticaria was classified as absent (UAS7 = 0), well-controlled (UAS7 = 1–6), mild (UAS7 = 7–15), moderate (UAS7 = 16–27) or severe (UAS7 = 28–42). For each time point, we labeled urticaria-free patients as “complete responders,” and those achieving well-controlled disease as “good responders.”

2.2 | Statistical analysis

Quantitative data were expressed as mean ± SD, minimum, maximum and quartiles, while qualitative data were expressed as absolute and relative frequency of the possible values. Comparison between quantitative data of different subgroups of patients was performed using Student's *t* test, or Mann-Whitney's *U* test when the conditions for Student's *t* test were not met. Similarly, qualitative data of different subgroups of patients were compared using the chi-square test, or Fisher's exact test when one or more values in contingency tables were <5.

For all tests, *p* < 0.05 was considered as threshold for statistical significance, with Bonferroni correction for multiple comparisons.

3 | RESULTS

3.1 | Baseline patients' characteristics and clinical data

The study population included 124 patients (38 males, 86 females), aged between 17 and 89 years (mean, 48.8 ± 18.1 years). In

association with wheals, 40 of them (32%) had also angioedema, and 15 (12%) had concomitant inducible urticaria. Mean CSU duration was 57.9 ± 89.0 months (range, 4–480 months). Atopic subjects were 14 (11%), autoimmune thyroid disease was present in 19 (15%), and other diseases in 27 (22%). Before receiving omalizumab, 70 of them (56%) had been treated with antihistamines only, and 54 (44%) with antihistamines and short courses of corticosteroids. In detail, the antihistamines used were levocetirizine for 43 patients, bilastine for 38, rupatadine for 18, ebastine for 14, fexofenadine for 7, desloratadine and cetirizine for 2 patients each.

As shown in Table 3, all patients had moderate to severe urticaria, and the mean UAS7 score at baseline (T0) was 25.2 ± 6.7 (range, 16–42). Baseline UAS7 was not significantly different in the subgroups obtained after stratification by each of the above-mentioned personal and clinical parameters.

3.2 | First course of omalizumab treatment

After 12 weeks of treatment (T1), about three quarters of patients showed complete remission (59%) or good control of urticaria (Table 3), and the mean UAS7 score decreased to 3.7 ± 6.2

TABLE 2 Variables evaluated in the study

- Age
- Sex
- Documented history of atopy
- Documented history of autoimmune thyroid disease
- Duration of CSU at the beginning of therapy with omalizumab
- Angioedema
- Chronic inducible urticaria
- Severity of CSU (UAS7) at the baseline

Abbreviations: CSU, chronic spontaneous urticaria; UAS7, urticaria activity score over 7 days.

TABLE 3 Severity of urticaria (number of patients for each severity class and mean UAS7) at different time points during and after treatment course(s) with omalizumab

	Urticaria severity class (UAS7 range)					
Time points	Absent (0)	Well-controlled (1–6)	Mild (7–15)	Moderate (16–27)	Severe (28–42)	UAS7 Mean ± SD
First course (124 patients)						
T0 (baseline)	0	0	0	85	39	25.2 ± 6.7
T1 (12 weeks)	73	24	19	8	0	3.7 ± 6.2
T2 (end of treatment)	99	14	9	2	0	1.5 ± 4.0
T3 (8 weeks after T2)	66	12	8	34	4	7.2 ± 9.2
Second course (45 patients)						
T4 (baseline)	0	0	0	42	3	19.4 ± 3.7
T5 (12 weeks)	30	5	9	1	0	2.7 ± 4.7
T6 (end of treatment)	35	4	6	0	0	1.5 ± 3.1
T7 (8 weeks after T6)	30	3	2	9	1	4.9 ± 8.2

Abbreviation: UAS7, urticaria activity score over 7 days.

($p < 0.0001$ vs. T0). Further improvement was observed at the end of treatment (T2), when the sum of complete responders (80%) and good responders was above 90% of patients (Table 3), and a mean UAS7 score of 1.5 ± 4.0 was recorded ($p < 0.0001$ vs. T0 and $p = 0.001$ vs. T1, the latter not significant after Bonferroni correction).

Treatment was well tolerated and no treatment-related adverse events occurred.

Eight weeks after omalizumab withdrawal (T3), a significant overall worsening of urticaria was observed (mean UAS7 = 7.2 ± 9.2 , $p < 0.0001$ vs. T2). However, the mean UAS7 was still significantly lower than the score observed at T0 ($p < 0.0001$) and most patients had no signs or symptoms (53%) or maintained a good disease control (Table 3). Moderate urticaria was present in 69% of patients at the baseline and 27% at week 8 after the end of treatment, whereas the number of severe urticaria patients varied from 31% at T0 to 3% at T3.

In 14 cases, antihistamines were required to achieve good disease control after interruption of treatment with omalizumab.

No statistically significant association was found, at any time point during the treatment period, between UAS7 scores or severity class and patients' characteristics, clinical parameters (reported in Table 2) or disease severity at T0 (data not shown). Complete responders at T1 had a significantly higher probability than the other patients to maintain their status at T2 ($p < 0.0001$). Neither T1 nor T2 results were predictive of status at T3, although complete response at T3 tended to be more frequent among patients who were complete responders at T1 or T2 ($p = 0.003$ and 0.005 , respectively, both not significant after Bonferroni correction).

3.3 | Second course of omalizumab treatment

Retreatment with omalizumab because of recurrence of moderate to severe symptoms refractory to antihistamines was necessary in

45 patients (36% of those who underwent the first course). In detail, 75 out of 78 patients with no or well-controlled symptoms at the follow-up visit (8 weeks after the completion of the first course) did not experience relapses, whereas 42 of the remaining 46 patients had to undergo a new course of omalizumab treatment after 2–6 months from the end of the first one. In 38 of the 45 patients who were retreated, UAS7 values scored >16, suggesting CSU relapse, were already recorded at T3.

Patients who experienced CSU relapse did not significantly differ from the others for any individual characteristic, clinical parameter or

disease severity at T0, T1, or T2 (Table 4). Presence of mild to severe urticaria at T3 was significantly associated with the need for retreatment with omalizumab, whereas complete or good disease control at T3 was significantly associated with the lack of relapses ($p < 0.0001$).

The mean UAS7 before the second course of treatment (T4) was 19.4 ± 3.7 , significantly lower than the score at T0 ($p < 0.0001$). Clinical response at 12 weeks of retreatment (T5) was similar to that of the first course, with 67% of complete responders, 11% of good responders (Table 3) and a significant decrease of UAS7 ($p < 0.0001$).

TABLE 4 Clinical features of CSU patients who experienced relapse and CSU patients without relapse after the first course of omalizumab

Clinical feature	Patients without relapse (n = 79)	Patients with relapse (n = 45)	p value
Sex, n (%)			0.19
Males	21 (27%)	17 (38%)	
Females	58 (73%)	28 (62%)	
Age (mean $\pm$ SD), years	47.39 $\pm$ 18.61	51.33 $\pm$ 17.16	0.24
Disease duration (mean $\pm$ SD), months	48.15 $\pm$ 78.79	75.13 $\pm$ 103.18	0.13
Angioedema, n (%)	23 (29%)	17 (38%)	0.32
Chronic inducible urticaria, n (%)	6 (8%)	9 (20%)	0.04
Atopy, n (%)	11 (14%)	3 (7%)	0.20
Autoimmune thyroid disease, n (%)	15 (19%)	4 (9%)	0.16
UAS7 at T0 (mean $\pm$ SD)	25.22 $\pm$ 6.69	25.20 $\pm$ 6.73	0.97
UAS7 at T1 (mean $\pm$ SD)	2.94 $\pm$ 5.64	5.16 $\pm$ 6.89	0.02
UAS7 at T2 (mean $\pm$ SD)	1.20 $\pm$ 3.40	2.13 $\pm$ 4.80	0.09
UAS7 at T3 (mean $\pm$ SD)	1.22 $\pm$ 3.76	17.76 $\pm$ 5.91	$p < 0.0001^*$
CSU severity at T0, n (%)			0.39
Moderate	52 (66%)	33 (73%)	
Severe	27 (34%)	12 (27%)	
CSU severity at T1, n (%)			0.07
Absent	53 (67%)	20 (44%)	
Well-controlled	13 (16%)	11 (24%)	
Mild	10 (13%)	9 (20%)	
Moderate	3 (4%)	5 (11%)	
Severe	0 (0%)	0 (0%)	
CSU severity at T2, n (%)			0.21
Absent	67 (85%)	32 (71%)	
Well-controlled	6 (8%)	8 (18%)	
Mild	5 (6%)	4 (9%)	
Moderate	1 (1%)	1 (2%)	
Severe	0 (0%)	0 (0%)	
CSU severity at T3, n (%)			$p < 0.0001^*$
Absent	65 (82%)	1 (2%)	
Well-controlled	10 (13%)	2 (4%)	
Mild	3 (4%)	5 (11%)	
Moderate	0 (0%)	34 (76%)	
Severe	1 (1%)	3 (7%)	

Abbreviations: CSU, chronic spontaneous urticaria; UAS7, urticaria activity score over 7 days.

*p values significant after Bonferroni correction.

vs. T4). At the end of the second course (T6), complete responders were 78%, good responders 9%, and mean UAS7 was 1.5 ± 3.1 ($p < 0.0001$ vs. T4, not significant vs. T5). Retreatment was also well tolerated.

Eight weeks after the end of the second course (T7), an increase of mean UAS7 to 4.9 ± 8.2 was detected, but this score was not significantly different from the scores recorded at T5 and T6 and remained significantly lower than the score at T4 ($p < 0.0001$). Patients with complete or good response were still the majority (67% and 7%, respectively), and moderate urticaria was the second most frequent severity class (20% of cases), as observed at the corresponding time point after the first course. In 17 cases, antihistamines were used to control CSU symptoms during the post-retreatment period.

As in the case of the first treatment course, no statistically significant association was found at any time point between UAS7 scores or severity class and patients' characteristics, clinical parameters or disease severity at T4 (data not shown). Patients with complete remission at T5 had a significantly higher probability than the others to maintain their status at T6 ($p < 0.0001$). However, neither T5 nor T6 results were predictive of status at T7. Also, none of the results at different time points of the first phase was significantly associated with results at any time point during and after the second course.

4 | DISCUSSION

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody proved to be safe and effective for the treatment of CSU.^{8–15}

In our study population, 96% of the complete/good responders with UAS7 < 7 at week 8 after the completion of the first course did not experience relapses, whereas 91% of the others had to be retreated. Of all parameters evaluated in our study (Table 2), none appeared to be associated with response to omalizumab. Similarly, these parameters did not significantly differ between patients who experienced CSU relapse and those without relapse (Table 4).

Clinical response at week 8 after omalizumab withdrawal (T3) was the only factor significantly associated with relapses of moderate to severe degree and consequent need for retreatment. Our results indicate that a relevant number of relapses already occurred at T3. Moreover, complete or good disease control at T3 was found to be significantly associated with a non-relapsing course of CSU. This finding might suggest that responders who maintain complete or good disease control at week 8 after treatment discontinuation are unlikely to show CSU relapses with moderate to severe symptoms afterwards.

Several authors tried to analyze biological and clinical predictors of response to omalizumab therapy. Table 5 summarizes the principal clinical and individual factors shown in previous studies to be associated with response to omalizumab and relapse after treatment withdrawal.^{15,18–22}

As concerns previous investigations on the parameters examined in our analysis, a retrospective multicenter study demonstrated that baseline UAS7 was significantly correlated to the first but not to the

TABLE 5 Clinical and individual factors associated with response to omalizumab and relapse after treatment withdrawal in previous studies

Authors	Type of study	Prognostic factors identified
Marzano et al. ¹⁸	Retrospective, multicenter	Baseline UAS7 was correlated with the risk of first relapse. CSU duration was significantly longer in patients who have either first or second relapse.
Ferrer et al. ¹⁹	Phase III randomized controlled trial	High baseline UAS7 and slow decrease of urticaria symptoms after starting omalizumab were associated with higher probability of rapid relapse upon drug withdrawal.
Nettis et al. ²⁰	Retrospective, multicenter	Baseline angioedema, history of angioedema, and (to some extent) duration of CSU were associated with incomplete disease control after 24 weeks of treatment.
Cubirò et al. ¹⁵	Retrospective, single-center	Long duration of CSU was associated with a lower probability of clinical response at week 12 of treatment. A history of angioedema was associated with a higher probability of complete response at week 24.
Curto-Barredo et al. ²¹	Retrospective, multicenter	High BMI and age > 57 years were associated with partial response to the licensed dose of omalizumab and better response with higher doses.
Castagna et al. ²²	Retrospective, single-center	BMI > 30 kg/m ² and CSU aggravation after the first omalizumab injections were linked to non-response.

Abbreviations: BMI, body mass index; CSU, chronic spontaneous urticaria; UAS7, urticaria activity score over 7 days.

second relapse,¹⁸ in line with the study of Ferrer et al. who found that high baseline UAS7 and slow decrease of CSU symptoms after starting omalizumab indicate a higher probability of rapid relapse upon drug withdrawal.¹⁹

Nettis et al. observed a poor treatment outcome in relation to presence of angioedema and longer duration of CSU symptoms.²⁰

The results of another study suggested that the long duration of CSU and history of angioedema may help predict the response to omalizumab, whereas no correlation was found with demographic data and other clinical variables examined in the analysis.¹⁵

Curto-Barredo et al. identified the body mass index (BMI) as a predictor of partial response to the 300 mg dose and better response with higher doses of omalizumab.²¹ The role of a BMI >30 kg/m² as a factor linked to non-response to omalizumab was confirmed by a very recent study.²² Unfortunately, BMI was not included in our analysis as it was not present in our clinical records.

Previous studies highlighted that age and thyroid autoimmunity did not significantly differ between responders and non-responders to omalizumab,^{15,18,20} as well as sex^{18,20,22} and CSU duration.^{18,22} We found that response to omalizumab was not related to age and sex of patients, CSU duration and documented history of atopy or autoimmune thyroid disease. Moreover, chronic inducible urticaria or concurrent angioedema was indifferently present in responders and non-responders. Our results are consistent with those of other authors,^{15,18,23} who found that the clinical response to treatment with omalizumab in patients with CSU is independent of the severity of the disease. The same clinical parameters appeared to have no influence on the association with CSU relapses in our study population. However, the number of patients stratified by each clinical variable was small, and further studies in larger patient samples are necessary.

5 | CONCLUSION

Omalizumab is the preferred treatment for CSU in patients unresponsive to H₁ antihistamines, as it has demonstrated efficacy and safety in both adults and children. Our results confirm the effectiveness of omalizumab in moderate-to-severe refractory CSU, although our study has evident limitations, such as the retrospective nature and the small number of patients. Moreover, response to treatment with omalizumab and subsequent relapse after treatment cessation did not appear to be influenced by any of the individual characteristics and/or clinical factors of patients included in our analysis. Interestingly, clinical response to omalizumab in patients with CSU seems to be independent of the severity of the disease determined by means of UAS7 at baseline.

Since predictors of response to omalizumab treatment in CSU patients are still unclear, further studies are required to evaluate the presence of baseline factors influencing treatment outcome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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