



Omalizumab in elderly patients with chronic spontaneous urticaria: An Italian real-life experience



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ABSTRACT

Background: Omalizumab therapy is effective and safe in patients with chronic spontaneous urticaria (CSU) resistant to non-sedating histamine₁ (H₁) antihistamines (nsAHs).

Objective: To evaluate the efficacy and safety of omalizumab in elderly (aged ≥65 years) patients with non-sedating H₁-antihistamine-refractory CSU in a real-life setting.

Methods: Patients with non-sedating H₁-antihistamine-refractory CSU (n = 322) treated with omalizumab administered every 4 weeks in doses of 300 mg for 24 weeks were divided into 2 groups according to age at omalizumab treatment onset: 15 to 64 years and 65 years or older. Treatment response was assessed using a 7-day urticaria activity score (UAS7). Adverse effects of omalizumab therapy were recorded.

Results: Among patients, 32 (9.9%) were 65 years or older. At baseline, CSU characteristics were generally similar among the groups, although the presence of angioedema was statistically significantly lower in patients younger than 65 years. Any differences in weekly itch severity score, hive score, and UAS7 between the 2 age groups were not significant at weeks 4, 12, and 24, with the exception of the hive score at 24 weeks and the UAS7 at week 24. No significant between-group differences were seen in the proportion of patients with a UAS7 of 6 or lower and with a UAS7 score of 0 at weeks 4, 12, 24, and 40. The proportion of patients with at least one adverse event reported as suspected to be caused by study drug was 10% in the younger group vs 6.3% in the older group (P = .53).

Conclusion: Our study found that omalizumab is a well-tolerated and effective therapy for elderly patients with non-sedating H₁-antihistamine-refractory CSU.

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Introduction

Chronic spontaneous urticaria (CSU) is a common skin disease defined as spontaneous recurrent wheals or angioedema with a duration of at least 6 weeks. The disease is not fatal but is associated with psychiatric morbidity and is responsible for a reduction in patients' quality of life.^{1,2} Although the peak incidence of CSU occurs between 20 and 40 years of age, all age groups can be affected. An

estimated 0.5% to 1% of the general population has this disease at any time in their life.³ Although the duration of CSU can extend to 5 years in 14% of patients,⁴ generally its duration is between 1 and 5 years.

First-line treatment of CSU is based on approved doses of non-sedating, second-generation antihistamines (H₁), and dose levels can be increased 4-fold if required.⁵ Unfortunately, a significant proportion of patients have poorly controlled CSU even with medical treatment, and alternative therapeutic approaches therefore require consideration. Several immune modulator treatments (prednisolone, azathioprine, mycophenolate mofetil, cyclosporine, sulfasalazine, and methotrexate) have been used, with variable outcomes.⁶

Omalizumab, an anti-IgE humanized monoclonal antibody, has proven to be effective in the treatment for CSU and is currently being recommended as the third-line treatment option in the management of CSU by the European Academy of Allergy and Clinical

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Immunology.⁵ The exact mechanism of action of omalizumab in CSU is unknown, although it is hypothesized that omalizumab binds to free circulating IgE, blocking action to target cells.⁷

Efficacy and safety of omalizumab in CSU have been established in several randomized, placebo-controlled trials^{8–13} and confirmed in real-life studies.^{14–21} The specific challenges in the treatment of patients with CSU who are 65 years or older differ significantly from those who are younger. These elderly CSU patients with CSU in fact may have age-related comorbidities that normally require multiple pharmaceutical treatments. Multiple long-term conditions (eg, osteoarthritis, hypertension, kidney failure, type 2 diabetes), age-related immunocellular senescence, and physical and cognitive decline all pose a challenge for effective treatment of CSU in those 65 years or older.²² Polypharmacotherapy implies drug interactions that may cause drug safety problems.²² Furthermore, patients older than 65 years are particularly vulnerable to the adverse effects of prolonged exposure to first-generation H₁-antihistamines (sedation), glucocorticoids (osteoporosis), and cyclosporine (hypertension)—all drugs usually recommended for CSU therapy.⁵ Patients 65 years and older are frequently excluded from clinical trials; therefore, evidence of the efficacy and safety of symptomatic therapy in this target group with CSU is scarce. Accordingly, the safety and efficacy of omalizumab in patients with CSU older than 65 years is still unknown.

In view of these findings, the aim of this study was to evaluate the efficacy and safety of recommended treatment regimens of omalizumab in patients older than 65 years affected by H₁-antihistamine-refractory CSU.

Methods

Patient Population and Study Design

Twenty-three secondary care centers belonging to a task force of the Italian Society of Allergy, Asthma and Clinical Immunology were involved in this observational, retrospective study from September 2015 to August 2017. The study comprised a 4-week pretreatment period, a 24-week first treatment period, and a 16-week follow-up period. The study protocol was approved by the ethics committee of Naples University Hospital. Informed written consent was obtained from all participants.

To be part of this observational study, each center was asked to provide data for patients with refractory CSU, defined as having a history of spontaneous urticaria for more than 6 weeks not responding to treatment for at least 4 weeks with the licensed dosage of nonsedating second-generation H₁-antihistamines and with a daily urticaria activity score (UAS) of 4 or more assessed in clinic on one of the pretreatment checkup days (days –14, –7, or 1) and a 7-day urticaria activity score (UAS7) greater than 16 in the 7 days before the first treatment. UAS7 is a widely used patient-reported CSU measure, capturing intensity of pruritus and number of hives. Daily itch severity score (range, 0 [none] to 3 [severe]) and number of hives rating (range, 0 [none] to 3 [> 50 hives]) are summed to create a daily UAS score (range, 0–6 points per day).⁵ However, most of our patients had remained symptomatic before the start of the present study despite treatment with H₁-antihistamines at up to 4 times the approved dose and/or leukotriene receptor antagonists and/or systemic glucocorticoids and/or cyclosporine. An autologous serum skin test²³ to assess for possible antibodies against Fcε receptor α₁-subunit was performed in all patients during active disease. Total serum IgE was measured by immunofluorometric assay (ImmunoCAP; ThermoFisher, Uppsala, Sweden), according to the manufacturer's instructions.

According to the recommendations of the Italian Drug Agency for CSU,²⁴ omalizumab was administered subcutaneously every 4 weeks in 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 stage. Participants were required to maintain stable doses of their pretreatment therapy with H₁-antihistamines at approved doses throughout the study period. During this time, patients were allowed to take H₁-antihistamines at up to 4 times the approved dose and/or systemic glucocorticoids as needed for symptom relief.

Baseline characteristics, including sex, age, total IgE value, antithyroid autoantibodies, autologous serum skin test result, duration of CSU symptoms, history of angioedema, and type of medication, were collected before the start of omalizumab treatment. Recruited patients were divided into 2 age groups: 18 to 64 years and 65 years or older.

The key efficacy end point was the differences between the 2 age groups in change in UAS7 score, weekly itch severity score (ISS), and hive score at weeks 4, 12, and 24. Another primary objective of the study was to evaluate the safety of omalizumab in patients younger than 65 years compared with those 65 years or older.

Key secondary efficacy outcomes evaluated included the following: change of UAS7 score, weekly ISS, and hive score from baseline to week 4, 12, and 24 in the 2 age groups; differences between the 2 age groups in terms of proportion of patients with well-controlled urticaria (UAS ≤ 6), and proportion of patients with complete response (UAS7 = 0) at weeks 4, 12, 24, and 40. Drug safety across the 24-week treatment period was evaluated in the 2 age groups by recording and monitoring the frequency and severity of adverse events (AEs).

Statistical Analysis

Comparisons of baseline categories were performed by the χ^2 (comparison of proportions) test and z test (comparison of means). Comparisons of health outcomes at different intervals by age group were performed with the Wilcoxon nonparametric test and the t test for comparison of means. A multivariable linear regression model was fitted to investigate the simultaneous effect of age (≥ 65 vs < 65 years) sex (male vs female), and participating center on hive score, ISS, and UAS7 at 4, 12, and 24 weeks, respectively. The level of significance was set at $P < .05$. Missing values were excluded, and complete case analysis was performed. The statistical analysis was conducted with the STATA 14 package (StataCorp, College Station, Texas).

Results

A total of 322 patients with refractory CSU (mean [SD] age, 46.5 [14.3] years; median age, 46.5 years; age range, 15–83 years) received at least one dose of omalizumab and were examined by 56 different physicians. Two hundred ninety patients were between 15 and 64 years old (90.1% of the entire study group; mean [SD] baseline UAS7, 27.9 [8.2]) and 32 were 65 years or older (9.9% of all patients; mean [SD] baseline UAS7, 28.3 [9.5]). Nineteen patients (5.9%) discontinued treatment before the end of the 24-week study: 17 (5.9%) in the younger group vs 2 (6.2%) in the older group. Table 1 compares baseline values among the 2 different age groups. As it can be seen, CSU characteristics were generally similar between the 2 age groups at baseline, although the presence of angioedema was significantly lower in patients younger than 65 years (33.7% vs 60%, $P = .004$). The use of H₁-antihistamines at high dosage, total IgE level, and thyroid autoantibody test positivity were slightly higher in the younger group, whereas the duration of CSU, history of angioedema, and UAS7 were slightly higher in the older group.

The mean change in UAS7 showed a decrease from baseline to week 24 in the 2 age groups (Table 2). Both age bands experienced a reduction of UAS7 scores of 19.5 points from baseline to

Table 1
Comparison of Baseline Characteristics Among the 2 Patient Age Groups

Characteristic	Patients 15–64 years old (n = 290)	Patients ≥65 years old (n = 32)	P value
Age, y			
Mean (SD)	43.8 (12.4)	70.7 (4.7)	<.001
Median (range)	45 (15–64)	70 (65–83)	
Sex, No. (%)			
Female	201 (69.2)	21 (65.6)	.67
Male	89 (30.7)	11 (34.4)	
Duration of CSU, mo			
Mean (SD)	41.6 (63.0)	66.9 (72.2)	.03
Median (range)	22.5 (2–588)	33 (3–240)	
History of angioedema, ^a No. (%)			
No	137/284 (48.2)	10/30 (33.3)	.12
Yes	147/284 (51.8)	20/30 (66.7)	
CSU medication history, No. (%)			
H ₁ -antihistamines at the licensed dosage	290 (100.0)	32 (100.0)	.17
H ₁ -antihistamines at high dosage	206 (71.0)	19 (59.4)	
Leukotriene receptor antagonists	58 (20.0)	8 (25.0)	.51
Systemic steroids	213 (73.5)	24 (75.0)	.85
Cyclosporin	38 (13.1)	5 (15.6)	.69
Total IgE level, kUA/L ^a			
Mean (SD)	234.8 (526.3)	200.4 (271.9)	.78
Median (range)	120 (0.0–5237)	127.3 (19–1257.8)	
Thyroid autoantibody test positivity, ^a No. (%)	55/215 (25.7)	3/21 (14.3)	.25
ASST positivity, ^a No. (%)	70/147 (47.6)	6/13 (46.2)	
In clinic UAS ^b			
Mean (SD)	4.9 (0.8)	4.8 (0.8)	.499
Median (range)	5 (4–6)	4.5 (4–6)	
UAS7 ^c			
Mean (SD)	27.9 (8.2)	28.3 (9.5)	.79
Median (range)	27 (17–42)	28.5 (17–42)	
Weekly ISS ^c			
Mean (SD)	14.3 (4.6)	15.2 (5.0)	.32
Median (range)	14 (3–21)	16 (7–21)	
Weekly hive score ^c			
Mean (SD)	13.4 (5.0)	13.0 (6.5)	.72
Median (range)	13 (4–21)	12 (0–21)	
Presence of angioedema at baseline, ^{a,c} No. (%)	93/276 (33.7)	18/30 (60.0)	.004

Abbreviations: ASST, autologous serum skin test; CSU, chronic spontaneous urticaria; H₁, histamine₁; ISS, itch severity score; UAS, urticaria activity score; UAS7, 7-day urticaria activity score.

^aData regarding angioedema history, total IgE level, thyroid autoantibody test positivity, ASST positivity, and baseline angioedema are missing for 8, 129, 86, 162, and 16 patients, respectively.

^bDefined as the highest value from the day –14 visit, day –7 visit, and day 1 visit.

^cBased on data collected in a patient daily diary in the 7 days before the first treatment date.

week 4, a decrease of 22.6 points (for those aged <65 years) and 23.2 points (for those aged ≥65 years) to week 12, and a reduction of 24.4 points (in patients aged <65 years) and 26.3 points (in patients aged ≥65 years) to week 24. As with the primary efficacy outcome, similar results were observed for ISS and hive scores (Table 2). In patients in the younger age group, the mean weekly ISS decreased by 9.7, 11.5, and 12.2 points from baseline to week 4, 12, and 24, respectively; among those in the older age group, it reduced by 10.1, 12.1, and 13.3 points in the same intervals. The mean changes of hive score from baseline to week 4, 12, and 24 were –9.4, –11.1, and –11.9 points respectively for patients younger than 65 years and –9.1, –11, and –12.8 points in the same intervals for patients 65 years or older. Table 3 reports that all differences in scores (weekly ISS, hive, and UAS7) between the 2 age groups were not significant after controlling for the simultaneous effect of sex and participating center, except for the hive score at 24 weeks (regression coefficient, –1.5; 95% CI, –2.7 to –0.2).

There was no evidence of a difference between the 2 age groups (<65 vs ≥65 years) with respect to the proportion of patients with a UAS7 of 6 or less at week 4 (57.2% vs 68.7%; $P = .21$), week 12 (72.9% vs 78.1%; $P = .52$), week 24 (84.2% vs 83.3%; $P = .90$), and week 40 (62.0% vs 60.0%; $P = .88$). Likewise, no significant differences in the percentage of patients free of both hives and itching (ie, UAS7 = 0) were observed in patients younger than 65 years when compared with those 65 years or older at week 4 (38.3% vs 37.6%; $P = .93$), week

12 (53.2% vs 62.5%; $P = .32$), week 24 (67.8% vs 56.7%; $P = .22$), and week 40 (44.3% vs 33.3%; $P = .41$).

Between weeks 24 and 40, the mean UAS7 in most patients gradually increased; therefore, 119 patients (104 aged <65 years and 15 aged ≥65 years) were re-treated with omalizumab. At week 40, 173 patients remained without restarting treatment (158 aged <65 years and 15 aged ≥65 years).

Safety

During the 24-week treatment period, the proportion of patients with at least one AE potentially attributable to omalizumab was 10% in those younger than 65 years and 6.2% among those 65 years or older ($P = .53$). Nineteen patients discontinued treatment before the end of the 24-week study. Of the patients who discontinued the study, 12 had disease progression (11 in the younger age group and 1 in the older age group), 2 patients (0.6%) in the younger age group experienced AEs (rash and administration-site conditions), 2 were lost to follow-up (in the younger age group), and 3 had personal problems (2 in the younger age group and 1 in the older group). The overall incidence of AEs during treatment was 11.7% in the younger age group compared with 6.2% in the older group ($P = .35$). Migraine, asthenia, and administration-site conditions were the most common AEs (Table 4). No treatment-emergent AEs were observed.

Table 2

Change from Baseline in Hive Score, ISS, and UAS7 at Weeks 4, 12, and 24 in the 2 Patient Age Groups

Score	Patients 15–64 years old		Patients ≥65 years	
	Change	<i>P</i> value ^a	Change	<i>P</i> value ^a
Change in UAS7 from baseline to week 4				
Mean (SD)	–19.5 (10.7)		–19.5 (12.5)	
Median (range)	–19.0 (–42.0 to 9.0)	<.001	–18.0 (–42.0 to 0.0)	<.001
Change in UAS7 from baseline to week 12				
Mean (SD)	–22.6 (10.8)		–23.2 (10.3)	
Median (range)	–21 (–42.0 to 18.0)	<.001	–21.5 (–42.0 to 0.0)	<.001
Change in UAS7 from baseline to week 24				
Mean (SD)	–24.4 (10.0)		–26.3 (8.9)	
Median (range)	–23.0 (–42.0 to 4.0)	<.001	–27.5 (–42.0 to –11.0)	<.001
Change in ISS from baseline to week 4				
Mean (SD)	–9.7 (5.8)		–10.1 (7.6)	
Median (range)	–10.0 (–21.0 to 5.0)	<.001	–10.0 (–21.0 to 5.0)	<.001
Change in ISS from baseline to week 12				
Mean (SD)	–11.5 (6.1)		–12.1 (6.4)	
Median (range)	–12.0 (–21.0 to 13)	<.001	–12.0 (–21.0 to 0)	<.001
Change in ISS from baseline to week 24				
Mean (SD)	–12.2 (5.8)		–13.3 (5.1)	
Median (range)	–12.0 (–21.0 to 6.0)	<.001	–14.0 (–21.0 to –2.0)	<.001
Change in weekly hive score from baseline to week 4				
Mean (SD)	–9.4 (6.1)		–9.1 (6.4)	
Median (range)	–9.0 (–21.0 to –14.0)	<.001	–9.0 (–21.0 to 0.0)	<.001
Change in weekly hive score from baseline to week 12				
Mean (SD)	–11.1 (5.9)		–11.0 (6.0)	
Median (range)	–10.0 (–21.0 to 10.0)	<.001	–10.0 (–21.0 to 0.0)	<.001
Change in weekly hive score from baseline to week 24				
Mean (SD)	–11.9 (5.6)		–12.8 (6.1)	
Median (range)	–11.0 (–21.0 to 3.0)	<.001	–12.0 (–21.0 to 0.0)	<.001

Abbreviations: ISS, itch severity score; UAS7, 7-day urticaria activity score.

^aWilcoxon nonparametric test *P* value.**Table 3**

Multivariable Linear Regression Analysis Adjusted for Age, Sex, and Participating Center

Variable	aRC (95% CI)								
	4 weeks			12 weeks			24 weeks		
	ISS	Hive score	UAS7	ISS	Hive score	UAS7	ISS	Hive score	UAS7
Age, y									
<65	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
≥65	–0.1 (–2.2 to 2.0)	–0.5 (–2.7 to 1.6)	–0.3 (–4.3 to 3.7)	–0.2 (–2.0 to 1.7)	–0.6 (–2.2 to 1.1)	–0.9 (–4.3 to 2.5)	–1.0 (–2.5 to 0.4)	–1.5 (–2.7 to –0.2)	–2.4 (–4.9 to 0.9)
Sex									
Female	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Male	–1.1 (–2.5 to 0.2)	–1.4 (–2.8 to 0.0)	–2.3 (–4.9 to 0.3)	–0.3 (–1.5 to 0.9)	–0.2 (–1.3 to 0.9)	–0.6 (–2.9 to 1.6)	0.0 (–0.9 to 1.0)	0.5 (–0.4 to 1.3)	0.5 (–1.1 to 2.2)

Abbreviations: aRC, adjusted regression coefficient; CI, confidence interval; ISS, itch severity score; UAS7, 7-day urticaria activity score.

Discussion

Drug therapy is essential in caring for patients 65 years or older. These patients often receive several medications because they are frequently affected by several conditions and comorbidities. Unfortunately, polypharmacy positively correlates with an increased risk of adverse drug reactions and drug–drug and drug–disease interactions.²⁵

In addition, polypharmacy can increase the risk of low treatment adherence and, as a consequence, suboptimal therapeutic effectiveness and poor clinical response. Furthermore, the aging process may interfere with pharmacokinetics and pharmacodynamics, resulting in different treatment responses.²⁶ The present study found that omalizumab is as effective and safe in patients with refractory CSU who are 65 years or older as it is in those younger than 65 years. No significant differences between the 2 age groups were detected in the change from baseline to weeks 4, 12, and 24

Table 4

Number (Percentage) of Adverse Events Suspected to be Caused by Study Drug During the Treatment Period

Adverse event	Patients <65 years old (n = 290)	Patients ≥65 years old (n = 32)
Overall	34 (11.7)	2 (6.2)
Migraine	10 (3.4)	0
Asthenia	7 (2.4)	1 (3.1)
Administration-site conditions	6 (2.1)	1 (3.1)
Rash	4 (1.4)	0
Arthralgia	4 (1.4)	0
Nasopharyngitis	1 (0.3)	0
Dyspepsia	1 (0.3)	0
Fever	1 (0.3)	0
Any adverse event leading to discontinuation of study	2 (0.6)	0

(primary end point) in UAS7 score, weekly ISS, and hive score with the exception of a significantly greater difference in hive scores at week 24 in patients older than 65 years compared with the younger age group. Clinically meaningful effects were observed for both age groups in all other efficacy end points, with a similar magnitude in the reduction of symptoms. In fact, almost identical percentages of patients with well-controlled urticaria and with complete symptom control were homogeneously distributed between the 2 age groups throughout the 40 weeks of our study.

A systematic review and GRADE assessment²⁷ as well as a meta-analysis (7 randomized, placebo-controlled studies with 1,312 patients with CSU)²⁸ have provided further evidence to support the efficacy and safety of omalizumab (300 mg every 4 weeks) in patients with CSU. To the best of our knowledge, our study is the first to assess the effects of omalizumab treatment in patients 65 years or older in real-life conditions. Previous studies have considered much smaller numbers of patients in this age group. For example, in 3 randomized, placebo-controlled trials, omalizumab treatment was studied in 6.2% (15 of 243),¹⁰ 4.2% (10 of 238),¹² and 6.8% (3 of 44)¹³ of patients 65 years or older, without comparison with patients younger than 65 years (control group). A few real-life studies on the use of omalizumab in patients with CSU have considered patients aged 64 to 82 years, followed-up for a longer duration than that of randomized clinical trials, providing useful indications for clinical practice.^{14–20} In 2 long-term, real-life studies, omalizumab proved to be safe and effective in the management of patients older than 64 years with severe allergic asthma²⁹ and improved health outcomes in 31 patients 65 years or older with uncontrolled severe asthma compared with those in younger age brackets.³⁰ Nevertheless, in the latter study, omalizumab had a reduced effect among those older than 64 years relative to younger patients with asthma.

In the present study, health improvement was significantly greater only at week 24 in patients younger than 65 years relative to the older age group, and it was limited to hive scores and UAS7 score. Such a tendency (a lower response to omalizumab treatment in those 65 years or older) might be explained by the presence of angioedema at baseline, which was significantly higher in patients older than 65 years. In fact, this decreased response to omalizumab treatment among patients with CSU and angioedema has already been reported.²¹ Other clinical features, including demographic data, abnormal laboratory findings, and medication history of patients with CSU, were not significantly different between the 2 age groups in our study, a similar finding to that of other authors.²⁶ Furthermore, in this study, omalizumab was well tolerated, as previously described.^{8–21} Frequency (11.2%) and severity of AEs probably attributable to the study drug observed in all patients were similar to those in 3 phase 3 clinical CSU trials, in which the percentages of AEs presumably attributable to the study drug were 11.1%,¹¹ 9%,¹⁰ and 17.3%,¹² irrespective of age in the 300 mg of omalizumab groups and, in many aspects, comparable with patients receiving placebo. Furthermore, in our study, there was a statistically nonsignificant tendency for better tolerability to treatment among the population of patients in the older age group compared with the younger group (11.7% vs 6.2%). In the older group, headache and transient injection-site reaction were reported and no patient discontinued the treatment. The good safety profile of omalizumab in patients older than 65 years importantly implies that dose adjustment of this drug is not recommended in case of impaired renal or hepatic function and no dose change seems necessary in older patients.²²

Limitations of this study include the relatively small sample size of patients older than 64 years and the limited availability of omalizumab as long-term treatment for CSU in Italy. Since the study patients were not selected for this study, because all available patients with CSU managed with omalizumab were retrospectively recruited from each participating center, the issue of selection bias

is not applicable to this study. Despite the observational study design, with comparisons of health indicators made between subsets from the same patient population, this study reflects real-life clinical conditions.

In conclusion, the present study specifically focused on patients 65 years or older with refractory CSU, and reported for the first time in a real-life situation that treatment with omalizumab is effective and well tolerated. Large clinical trials with a similar refractory population are warranted to confirm our findings.

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