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# 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 nonsedating histamine$_1$ ($H_1$) antihistamines (nsAHs).
**Objective:** To evaluate the efficacy and safety of omalizumab in elderly (aged ≥65 years) patients with nonsedating $H_1$-antihistamine–refractory CSU in a real-life setting.
**Methods:** Patients with nonsedating $H_1$-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 nonsedating $H_1$-antihistamine–refractory CSU.


## 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 nonsedating, second-generation antihistamines ($H_1$), 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 $H_1$-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 $H_1$-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 $H_1$-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 $H_1$-antihistamines at up to 4 times the approved dose and/or leukotreine receptor antagonists and/or systemic glucocorticoids and/or cyclosporine. An autologous serum skin test[23] to assess for possible antibodies against Fcε receptor $\alpha_1$-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 $H_1$-antihistamines at approved doses throughout the study period. During this time, patients were allowed to take $H_1$-antihistamines at up 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 $\chi^2$ (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 $H_1$-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