

## Omalizumab for the Treatment of Chronic Spontaneous Urticaria: Association Between Body Mass Index and Outcome

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**ABSTRACT** **Introduction:** Omalizumab has been recently registered as a third-line therapy for chronic spontaneous urticaria.

**Objectives:** In this study, we aimed to provide real life data by reporting our experience with omalizumab in the treatment of chronic spontaneous urticaria.

**Methods:** A retrospective data analysis was conducted on 40 patients affected by chronic spontaneous urticaria and treated with omalizumab at the Dermatology Unit of Padova University Hospital. Demographic, anthropometric, and clinical data have been collected.

**Results:** Overall, the majority of patients (23 patients, 57.5%) achieved complete recovery by taking omalizumab and 17.5% (7 patients) had a partial response. The majority of patients who did not have a response to omalizumab had a body mass index (BMI) > 25 kg/m<sup>2</sup>.

**Conclusions:** Our study suggests that omalizumab is a safe and effective treatment for chronic spontaneous urticaria. We identified BMI as a critical biological factor that significantly impacts the outcomes of omalizumab treatment. Our findings also suggest a potential use of BMI as a predictive biomarker for omalizumab treatment. An up-dosing of omalizumab may be proposed in patients with high BMI to achieve a better control of the disease.

## Introduction

Chronic spontaneous urticaria (CSU) is a common disease, however, epidemiological data currently available on CSU prevalence ranging from 0.02% to 1% in different studies [1,2]. It is clinically characterized by the recurrent appearance of itch, wheals and/or angioedema for more than 6 weeks in absence of a known trigger [3]. It is often a self-limiting disease lasting no more than 2-5 years; however in 20% of patients lasts for more than 5 years. Many factors may play a role in the pathogenesis of chronic idiopathic urticaria, including infections, diet, drugs, emotional factors, and stress [1,4]. Chronic spontaneous urticaria highly impacts quality of life of patients affected. Pruritus causes variable discomfort, as well as cutaneous wheals which may harm individual physical appearance and social life. The first line therapy for CSU consists in the use of non-sedating H1-antihistamines. If the response is inadequate after two weeks of treatment, increasing the antihistamine dosage up to four-fold is recommended as second-line therapy [2,4]. Omalizumab, a humanized anti-IgE monoclonal antibody, that was primarily approved for the treatment of moderate/severe asthma has been recently registered for CSU treatment as a third-line therapy [5-8].

## Objectives

In this study, we aimed to provide real life data by reporting our experience with omalizumab in the treatment of CSU.

## Methods

A retrospective data analysis was conducted on 40 patients affected by CSU and treated with omalizumab between 2016 and 2019 at the Dermatology Unit of Padova University Hospital.

All patients provided written informed consent. The patients included were aged over than 18 years with at least 6 months history of chronic idiopathic urticaria. The severity of the urticaria was assessed thanks to the Urticaria Activity Score (UAS) and established both daily and weekly (UAS7), based on the presence of wheals and itching.

All patients received a 300 mg subcutaneous injection of omalizumab every 4 weeks for at least 6 months. Once

a month, follow-up visits were scheduled together with the omalizumab infusions. The following data were collected: birth date, sex, height, weight, date of urticaria diagnosis, severity of the disease, previous urticaria therapies, comorbidities, and concomitant medications. The body mass index (BMI) value was calculated (in  $\text{kg}/\text{m}^2$ ) to classify patients as underweight ( $\text{BMI} < 18.4 \text{ kg}/\text{m}^2$ ), normal weight ( $18.5 \text{ kg}/\text{m}^2 \leq \text{BMI} \leq 24.9 \text{ kg}/\text{m}^2$ ), overweight ( $25 \text{ kg}/\text{m}^2 \leq \text{BMI} \leq 29.9 \text{ kg}/\text{m}^2$ ) and obese ( $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$ ). The date of the first omalizumab administration, the number of therapy cycles and the date of the last infusion were recorded as well as any adverse events during or after omalizumab administration. The outcome of the treatment with omalizumab was evaluated based on the patient's report, any objective improvement or worsening, and reduction of UAS7. UAS7=0 was considered as complete response, while a 90% reduction in UAS7 was considered as a partial response. Benefit achieved after a single course of omalizumab was considered a partial response.

## Results

The study included 40 patients with the following demographic characteristics: 30 females (75%) and 10 males (25%), with a mean age of 49 years (range: 21- 81 years). The minimum BMI detected was  $17.8 \text{ kg}/\text{m}^2$ , while the maximum was  $34 \text{ kg}/\text{m}^2$ , with an average value of  $24.1 \text{ kg}/\text{m}^2$ . The patients were divided in underweight, normal weight, overweight and obese (Table 1). The date of urticaria diagnosis was between 1994 and 2019. The mean age of patients at the time of the diagnosis was 45 years. All patients were affected by severe disease with  $\text{UAS} > 4$  and  $\text{UAS7} > 30$  before starting treatment with omalizumab.

Medications used before omalizumab for the treatment of CSU included three main classes of drugs: antihistamines (85% of patients, mainly desloratadine), glucocorticoids (62.5% of patients, mostly prednisone) and immunosuppressants (27.5% of patients, primarily cyclosporine). Furthermore, 27.5% of patients followed a histamine-free diet, 10% of cases received a supplementation with nicotinamide, while 5% of patients were treated with UVB phototherapy. The majority of patients (80%) presented comorbidities including allergic rhinitis (20%), hypothyroidism (20%), nickel allergy (15%), grasses allergy (12.5%) and atopic dermatitis

**Table 1. Classification of patients based on the BMI value according to the WHO: underweight ( $<18.5 \text{ kg}/\text{m}^2$ ), normal weight ( $18.5- 24.9 \text{ kg}/\text{m}^2$ ), overweight ( $25- 29.9 \text{ kg}/\text{m}^2$ ) and obese ( $>30 \text{ kg}/\text{m}^2$ )**

Patient	Underweight	Normal Weight	Overweight	Obese
Female, N (%)	2 (5%)	17 (42,5%)	7 (17,5%)	4 (10%)
Male, N (%)	0	6 (15%)	4 (10%)	0

(12.5%) were detected. Simultaneously to the omalizumab therapy, many patients have taken various therapies for both CSU and their concurrent diseases including antihistamines (60%), glucocorticoids (55%), levothyroxine (15%). In addition, 15% of patients continued to follow a histamine-free diet and 12.5% were taking nicotinamide.

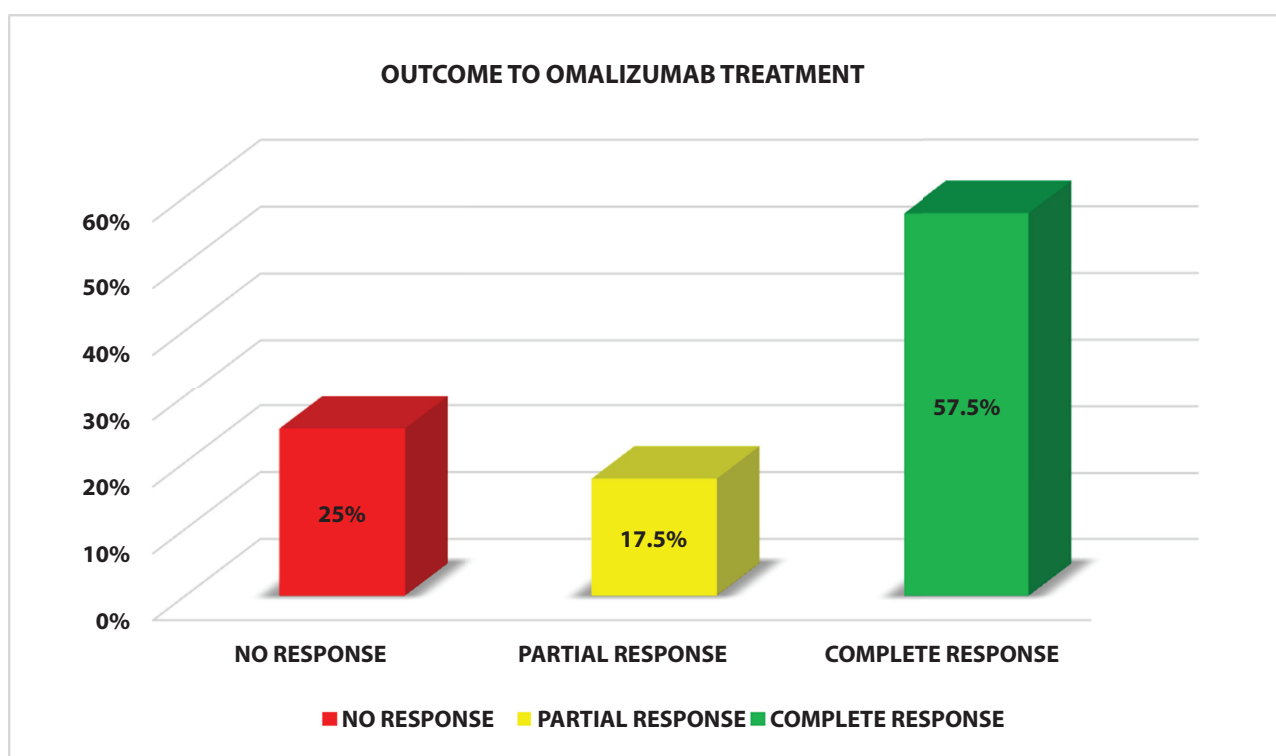
Overall, 30 patients (75%) completed the entire course of omalizumab therapy, while 10 of them (25%) discontinued omalizumab due to acute side effects (discontinuation at the first dose, in 2 patients), other diseases (2 patients) or ineffectiveness (6 patients). Based on the results obtained, patients were classified into three categories: no response (10 cases, 25%), partial response (7 patients, 17.5%), complete response (23 patients, 57.5%) (Figure 1). The majority of

patients who did not have a response to omalizumab had a BMI > 25 kg/m<sup>2</sup>.

Binomial logistic regression enables us to determine which of our independent variables have statistically significant effect on outcome; considering age, sex and BMI as variables, emerged that BMI has a statistically significant effect (P = 0.042), and odds ratio < 1 indicates a positive predictive value of better response to therapy (Table 2).

## Conclusions

In our cohort patients were predominantly female (M:F ratio was 1:3), according to the literature, which reports a prevalence of CSU two times higher among women than man. It may be explained by the role of autoimmunity in CSU



**Figure 1.** Outcome of omalizumab treatment. Complete response: UAS7=0; Partial response: 90% reduction of UAS7 values; 25% of patients (10 patients) had no response; 17.5% of patients (7 patients) reported partial response, while 57.5% (23 patients) had a complete response to omalizumab.

**Table 2.** Model coefficients – outcome

Predictor	Estimate <sup>a</sup>	SE	Z	P	Odds ratio
Intercept	3.8904	2.5292	1.538	0.124	48.930
BMI	-0.2105	0.1037	-2.029	0.042	0.810
Age	0.0458	0.0315	1.452	0.147	1.047
Sex:					
M – F	0.8918	1.0390	0.858	0.391	2.439

BMI = body mass index; F =female; M = male; SE = standard error.

<sup>a</sup>Estimates represent the log odds of “Outcome = yes” versus “Outcome = no”

pathogenesis [3]. Patients aged from 21 to 81 years have been treated, showing omalizumab safety in all age groups, even in the elderly patients which may have comorbidities [9]. The average value of BMI was 24.1 kg/m<sup>2</sup>, which belongs to the category of normal weight but with a tendency to overweight. Although the study population is not large, the distribution of BMI categories was overlapping to the percentage obtained by 2016 ISTAT on the entire Italian population. The most common diseases associated with CSU were hypothyroidism, hypertension, allergic rhinitis, nickel and grass allergy and atopic dermatitis. Several patients included in our case series were also affected by atopic dermatitis, vitiligo, psoriasis, alopecia, SLE, scleroderma, spondylarthritis and/or diabetes suggesting a potential role of autoimmunity.

Our patients continued their concomitant treatments during omalizumab cycles, including antihistamines (60% of patients) and low-dose oral corticosteroids (55% of patients) intake. In addition, 15% of patients continued to follow a histamine-free diet and 12.5% were taking nicotinamide. No pharmacological interactions were observed, confirming literature data [7,10].

Most of patients (57.5%) had a complete response. Moreover, considering partial responses and first cycle benefits, 30 out of 40 patients (75%) had at least a partial favorable response. Given the small number of subjects recruited a statistical analysis has not been performed, but a significant number of patients with a beneficial effect from the use of omalizumab has emerged.

Concerning the occurrence of adverse reactions to omalizumab, only 2 cases out of 40 (5%) were reported. Specifically, a single case of angioedema and 1 case of respiratory crisis have been documented, leading to therapy discontinuation. Other reasons why patients interrupted omalizumab were ineffectiveness or the onset of disease that required hospitalization (breast cancer, atrial fibrillation, splenic aneurysm). The total number of patients who discontinued the first course of omalizumab was 10 (25%).

Recent findings have shown an increased prevalence of metabolic syndrome among patients with CSU, which is characterized by a pro-inflammatory state, increased oxidative stress and alterations in adipokine profile [11-13]. Interestingly, the majority of patients (7/10) who did not have a response to omalizumab had a high BMI (BMI > 25 kg/m<sup>2</sup>), suggesting the potential role of adipokines in mast cells activation leading to CSU worsening. However, the high body weight may also influence the pharmacokinetics of the drugs affecting the apparent volume of distribution of the drugs, as documented in other studies on biological treatments [13-15].

The recommended dose of omalizumab for the treatment of CSU is 300 mg every 4 weeks, but there is no recommendation for patients who do not benefit from this dose. While

for patients affected by asthma the recommended dose of omalizumab changes according to the body weight of the patient, a fixed dose regimen is recommended for CSU regardless of the body weight and total IgE levels. In the recent years, there have been several studies on up dosing of the drug, suggesting that the individualized approach for urticaria treatment with omalizumab is useful [16]. Patients with a higher BMI have been found to require higher doses to control the disease [17]. A step-wise approach starting from 450 mg and then up dosing to 600 mg has been proposed if there is no response after 3 months of treatment in CSU patients [17]. Furthermore intervention on lifestyle through a combination of dietary changing and physical activity should be recommended in patients with high BMI.

Total IgE serum level do not justify an omalizumab dose changing however, it is a reliable biomarker predicting response to omalizumab in CSU since levels are significantly higher in responder than non-responder patients [18].

The main limitation of our study is the small number of patients included. Furthermore, all patients had a high UAS and some patients continued antihistamines and corticosteroids during omalizumab. We know that these may be confounding factors that may have influenced the outcome.

In conclusion, in this study we identified BMI as a critical biological factor that significantly impacts the outcomes of omalizumab treatment. Our findings also suggest a potential use of BMI as a predictive biomarker for omalizumab treatment. An up-dosing of omalizumab may be proposed in patients with high BMI to achieve a better control of the disease.

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