

The Real-Life Effectiveness and Safety of Omalizumab Updosing in Patients With Chronic Spontaneous Urticaria

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Abstract

Background: Omalizumab is a third-line treatment for chronic spontaneous urticaria (CSU). Studies investigating the use of higher doses of omalizumab in patients unresponsive to regular doses are limited.

Objectives: This study aims to investigate the effectiveness and safety of omalizumab 450 mg in CSU.

Methods: A retrospective cohort study was conducted. The response to therapy was evaluated using the Urticaria Activity Score over 7 days (UAS7) and the Urticaria Control Test (UCT). Patients showing complete response (CR) (UAS7: 0-1) to omalizumab 300 mg (Group 1) and patients receiving at least 3 doses of omalizumab 450 mg (Group 2) between 2016 and 2018 were included.

Results: A total of 72 patients (Group 1: 59; Group 2: 13) were included. In Group 2, the mean UAS7 score decreased from 18.6 to 5.1 and the mean UCT score increased from 8.6 to 12 after a mean 4.3 courses of 450 mg omalizumab treatment. Of the 13 patients in Group 2, 6 had CR and 3 had good disease control (UAS7: 2-6). The rate of patients with low baseline IgE levels (< 43 IU/mL) was significantly higher in Group 2.

Conclusions: Higher doses of omalizumab are effective and safe in patients with CSU that is unresponsive to omalizumab 300 mg. Lower baseline total IgE levels might be used as a predictor of nonresponse to omalizumab and the need for higher doses.

Keywords

chronic spontaneous urticaria, omalizumab, updosing

Introduction

Chronic spontaneous urticaria (CSU) is characterized by the occurrence of wheals and/or angioedema for > 6 weeks. The prevalence of CSU is 0.5% to 1.0% among people age 20-40, with an average duration of 1-5 years. It has a high burden on affected individuals, impairing sleep as well as physical and emotional well-being.^{1,2} According to current treatment guidelines, the first-line treatment option for CSU is a second-generation H1-antihistamine at standard doses. In patients unresponsive (UR) to these doses, updosing up to 4-fold is recommended.^{2,3} Despite the regular use of upodosed H1 antihistamines, many patients still suffer from CSU.

Omalizumab is an anti-IgE antibody, and it is a third-line treatment option in patients with CSU recalcitrant to antihistamines. The recommended dose is 300 mg every 4 weeks administered subcutaneously.²

RCTs have repeatedly demonstrated the efficacy and safety of omalizumab in CSU, with 52.4% to 58.8% of patients achieving a Urticaria Activity Score over 7 days (UAS7) ≤ 6 at week 12.⁴ Real-life studies suggest an even higher response rate, with an average complete response (CR) rate of 72.2%.⁵

Despite the high response rates obtained in studies, there is still a subset of patients who do not show any improvement with the licensed dose of omalizumab. In this group of patients, updosing of omalizumab might be a viable alternative before switching to immunosuppressive drugs. However, studies investigating the effectiveness and safety of higher doses of omalizumab in patients with CSU and predictors of the need for updosing are sparse.⁶⁻⁹ Thus, we aimed to evaluate the use of higher doses of omalizumab in our cohort of patients with CSU using validated scores. Another objective of the study was the identification of clinical predictors of patients in whom updosing would be required earlier in the treatment course.

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Patients and Methods

A retrospective cohort study was conducted. The study was approved by our institution's ethics committee (approval number: 09.2018.724). The medical charts of patients with CSU who had been followed up and had received at least 3 doses of omalizumab in our specialized urticaria outpatient clinic between 2016 and 2018 were reviewed. Of them, the patients showing CR to omalizumab 300 mg comprised Group 1. Group 2 consisted of patients UR to 300 mg omalizumab and who had at least 3 courses of omalizumab 450 mg. Medical charts of the patients were reviewed and the patients' demographic, clinical, and treatment characteristics (gender, age, BMI, atopy, comorbidities, disease duration, coexisting chronic inducible urticaria/angioedema, previous treatments, baseline levels of total IgE, D dimer, erythrocyte sedimentation rate (ESR), high-sensitivity CRP, omalizumab dose, frequency, maximum dose interval for omalizumab, concomitant treatments, adverse effects (AEs), UAS7, and Urticaria Control Test [UCT] scores) were recorded. Baseline and follow-up UAS7 and UCT scores of the patients in Group 2 were compared to assess the effectiveness of the omalizumab at higher doses. The baseline demographic, disease, and treatment characteristics of Group 1 vs 2 were also compared.

In our specialized outpatient clinic, demographic information, disease characteristics, and baseline laboratory tests of all patients are recorded using a standardized form at the initial visit. The patients with CSU UR to antihistamines up to 4-fold of standard doses for ≥ 6 months are administered omalizumab. The standard protocol for omalizumab treatment is 300 mg every 4 weeks administered subcutaneously. The patients are followed up every 4-8 weeks depending on the severity of disease and control of symptoms. Following the first 3 treatments, the dosing interval is increased gradually in patients with CR or good disease control (GDC). In case of a partial or no response after 6 months of treatment or any worsening during follow-up, we either combine omalizumab with immunomodulatory agents, such as colchicine and dapsone, or increase the omalizumab dose to 450 mg every 4 weeks or switch to treatment with cyclosporine. The patients are asked to complete the UAS7 in-between follow-up visits to evaluate disease severity. The daily UAS is the sum of scores for intensity of itch and number of wheals. Thus, the daily UAS ranges between 0 and 6, and the UAS7 from 0 to 42.¹⁰ Treatment response is categorized as CR (UAS7 ≤ 1), GDC ($1 < \text{UAS7} \leq 6$), partial response (PR; UAS7 > 6 , but ≥ 10 points of decrease from baseline), or UR (no change or increase in UAS7).¹¹ Moreover, at every follow-up visit, patients are asked to complete the UCT for the assessment of disease control. The UCT is an easy-to-administer, self-reported questionnaire assessing disease control in patients with CSU, and it provides a final score between 0 and 16. A score of 12 or more indicates a well-controlled disease.¹²

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA), v21.0. Descriptive data were shown as n (%) and mean $\pm$ SD (range) for categorical variables and quantitative variables, respectively. The chi-squared test and Student *t*-test were used for the comparison of 2 categorical variables and means between 2 independent samples, respectively. The comparison between 2 measurements within the same sample was performed with a paired-samples *t*-test.

Results

The medical records of 136 patients who had been followed up in our urticaria outpatient clinic during the study period were reviewed. Of them, 59 patients showing CR to omalizumab 300 mg (Group 1) and 13 patients treated with omalizumab 450 mg (≥ 3 courses) following unresponsiveness to omalizumab 300 mg (Group 2) were included in the study.

The comparison of the 2 groups' demographic, clinical characteristics, and mean baseline laboratory tests failed to reveal any statistically significant differences. The patients were grouped according to baseline total IgE levels as high or low IgE, based on a previously reported threshold (43 IU/mL).¹³ The rate of patients with low IgE levels was significantly higher in Group 2 (60% vs 18.2%, $P = .006$). Of note, the percentage of active smokers was higher in Group 2 (46.2% vs 21.2%, $P = .067$).

The baseline characteristics of the groups are summarized in Table 1.

In Group 2, up dosing was administered following a mean number of 8.2 treatments with omalizumab 300 mg. Following a mean number of 4.31 treatments with 450 mg, mean UAS7 decreased from 18.69 to 5.15 and the mean UCT scores increased from 8.62 to 12 ($P = .003$ and $.031$, respectively) (Figure 1). Treatment with 450 mg omalizumab led to CR in 6 patients (46.2%) and GDC in 3 patients (23.1%). Two patients had PR and 2 patients had no response. The treatment characteristics of group 2 are detailed in Table 2. No AEs were observed during the study period.

Discussion

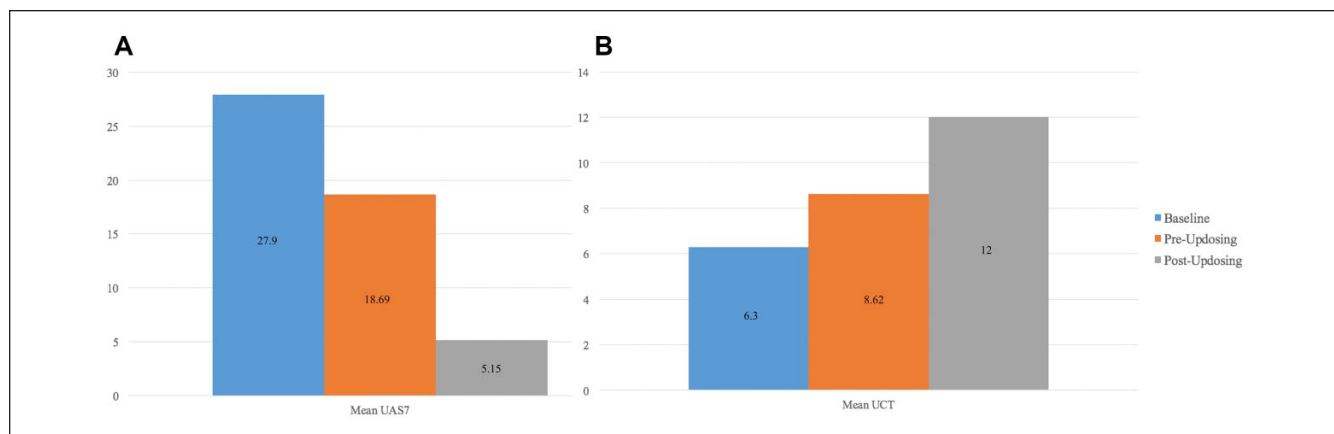
The results of the present study have demonstrated an additional benefit of up dosing of omalizumab to 450 mg in patients with inadequate response to licensed doses of omalizumab.

Omalizumab is a third-line treatment option for antihistamine-resistant CSU with high response rates reported in RCTs and real-life studies.^{4,5,14,15} A good safety profile, even on long-term use up to 4 years, has also been demonstrated.¹⁶⁻¹⁸ Treatment with omalizumab is recommended to be continued for 3-6 months because in some patients, so-called "slow responders," achieving CR or GDC might take a longer time.¹¹ In patients partially or not responding to omalizumab 300 mg

Table 1. Demographic, Clinical, and Disease Characteristics of the Study Groups at Baseline.

Characteristics		Group 1 (n=59) Mean $\pm$ SD (Min to Max)/n (%)	Group 2 (n=13) Mean $\pm$ SD (Min to Max)/n (%)	P
Age (years)		44.2 $\pm$ 15.6 (17-81)	40.2 $\pm$ 15.6 (18-65)	.392
Gender	Female	39 (66.1)	11 (84.6)	.190
	Male	20 (33.9)	2 (15.4)	
BMI (n=51, n=13)		28.4 $\pm$ 5.7 (20.3-45.8)	28.6 $\pm$ 6.8 (19.1-41.5)	.931
Presence of atopy		2 (3.4)	0	.797
Smoking status	Smoker	11 (21.2)	6 (46.2)	.067
	Nonsmoker	41 (78.8)	7 (53.8)	
Duration of disease (months)		49.1 $\pm$ 58.1 (6-240)	66.6 $\pm$ 101.7 (6-360)	.401
Angioedema		40 (67.8)	10 (76.9)	.518
Baseline UAS7		25.2 $\pm$ 7.4 (14-42)	27.9 $\pm$ 10.5 (10-42)	.275
Baseline UCT		6.1 $\pm$ 2 (1-10)	6.3 $\pm$ 3.2 (2-12)	.809
Mean total IgE (n=44, n=10)		205.4 $\pm$ 368.4 (9-2284)	261.2 $\pm$ 459.1 (0-1446)	.681
Mean D-dimer (n=32, n=10)		0.72 $\pm$ 0.81 (0.09-3.41)	1.18 $\pm$ 1.94 (0.27-6.6)	.290
Mean hsCRP (n=33, n=8)		7.34 $\pm$ 9.17 (0.16-37)	3.71 $\pm$ 4.45 (0.16-11.7)	.287
Mean ESR (n=46, n=8)		18.4 $\pm$ 14.2 (2-68)	17.7 $\pm$ 9.8 (7-35)	.901

Abbreviations: ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; max, maximum; min, minimum; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

**Figure 1.** Change in A, Mean Urticaria Activity Score Over 7 Days (UAS7) and B, Urticaria Control Test (UCT) Scores of Group 2 During Treatment.

monthly, switching to immunosuppressive or immunomodulatory drugs might be considered. In addition, despite the limited number of studies, the literature data suggest that the use of omalizumab at shorter intervals or higher doses in this group of patients might be of additional benefit.

In our study, the mean change in the UAS7 and UCT scores were -13.53 and $+5$ points, respectively. In addition to a statistically significant change in the UAS7 and UCT scores with treatment, the mean changes were over the minimal important difference of 10 points and 3 points for UAS7 and UCT, respectively.^{19,20} Overall, we observed a CR (UAS7 ≤ 1) or GDC ($1 < \text{UAS7} \leq 6$) in 69.3% of patients treated with omalizumab 450 mg monthly, indicating better

control of CSU with updosing of omalizumab to 450 mg. Consistent with our findings, in 2 multicentre studies investigating the effect of updosing in patients not responding to omalizumab 300 mg monthly, an additional beneficial effect was obtained in 64% and 71% of the patients treated with 450 mg or 600 mg monthly.^{6,8} In another study, shorter intervals and/or updosing led to CR in 8 patients partially responding to licensed doses.⁷ More recently, a UCT score > 12 was achieved with updosing to 450 mg and 600 mg in 76.4% and 59% of patients.⁹ In line with the existing data, updosing was well tolerated in all patients without any AEs.

The decision to updose was made after a mean number of 8.2 treatments in our patients. Similarly, the mean number of

Table 2. Treatment Characteristics of Patients in Group 2.

Characteristics	Mean $\pm$ SD (Min to Max)/n (%)	P
Mean number of treatments with 300 mg Omalizumab	8.23 $\pm$ 5.27 (4-24)	
Mean number of treatments with 450 mg Omalizumab	4.31 $\pm$ 1.79 (3-8)	
Mean UAS7 score before updosing	18.69 $\pm$ 11.92 (6-35)	.003
Mean UAS7 score at final follow-up visit	5.15 $\pm$ 8.38 (0-30)	
Mean UCT score before updosing	8.62 $\pm$ 2.56 (4-12)	.031
Mean UCT score at final follow-up visit	12 $\pm$ 4.02 (5-16)	
Response to treatment at final follow-up visit	Complete response Good disease control Partial response Unresponsive	6 (46.2) 3 (23.1) 2 (15.4) 2 (15.4)

Abbreviations: Max, maximum; min, minimum; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

treatment courses was 6 in previous studies.^{7,9} These findings are consistent with the recommendation of waiting 6 months to evaluate the response to omalizumab.¹¹

The demographic and clinical predictors of better disease control with updosing were also investigated in this study. The rate of patients with low IgE levels (<43 IU/mL) was significantly higher in the updosing group, in accordance with the existing literature suggesting that low baseline IgE levels have a high negative predictive value for response to omalizumab.^{13,21,22} Although these findings should be confirmed in larger, prospective studies, we believe updosing earlier, or even starting treatment with higher doses, might be a reasonable option in patients with low baseline IgE levels (<43 IU/mL). Also, albeit not statistically significant, the higher rate of smokers among patients requiring updosing for disease control is worth mentioning. Although baseline IgE levels were not different between smokers and nonsmokers in our cohort, smokers have been reported to have higher levels of total IgE compared to nonsmokers.^{23,24} However, higher levels of total IgE are linked to a better response to omalizumab.^{25,26} Thus, it is unlikely that IgE elevation in smokers would be a contributing factor to the need for higher doses of omalizumab. Moreover, previous studies failed to show any effect of smoking on the prognosis or exacerbation of CSU.^{27,28} It can be speculated that inflammation and coagulation induced by smoking might have resulted in more severe disease and a need for a higher omalizumab dose for adequate disease control.^{29,30} We think it would be of interest to investigate the effects of smoking on treatment outcomes in a larger group of patients.

In contrast to our findings, patients with a shorter duration of disease, lower baseline UAS7/UCT scores, or a higher BMI were more likely to improve with updosing in previous reports.^{6,8,9} The discrepancy between these results might be attributed to the relatively small sample size in the present study.

The use of omalizumab with intervals shorter than 4 weeks has previously been evaluated in 2 studies reporting better control of symptoms, particularly in patients experiencing recurrence during the last days of 4-week intervals.^{31,32}

The current study is limited by its retrospective nature and relatively small sample size. Nevertheless, the use of validated methods (UAS7 and UCT) to evaluate treatment effectiveness provides valuable information on a subject that has not been studied in detail.

In this study, updosing of omalizumab provided disease control in patients who remained symptomatic with omalizumab treatment at the licensed dose. Moreover, our results support the predictive value of baseline IgE levels for response to omalizumab. We believe updosing is an effective and safe treatment option in patients with PR or no response to omalizumab after 6 months. Prospective RCTs investigating the effectiveness and safety of updosing in larger populations are needed.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A. S. has served as a medical advisor and speaker for Novartis. E. C. has nothing to declare.

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