Predictive Factors and Optimization of Omalizumab in Chronic Spontaneous Urticaria: A Multicenter Study of 257 Patients

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J Investig Allergol Clin Immunol 2025; Vol. 35(3)
doi: 10.18176/jiaci.1053

Key words: Omalizumab. Chronic spontaneous urticaria. Optimization. Biomarkers. Algorithm.

Palabras clave: Omalizumab. Urticaria crónica espontánea. Optimización. Biomarcadores. Algoritmo.

Omalizumab at 300 mg/4 wk is an effective and safe treatment for chronic spontaneous urticaria (CSU). Given the self-resolving nature of CSU, patients eventually discontinue treatment; however, up to 60% relapse and require retreatment [1]. To reduce the relapse rate, therapy can be optimized by decreasing the dosage, prolonging the interval, or both [2-4]. These methods have not been compared to date, and the optimal candidates for down-dosing have not been identified.

Our retrospective, real-world, multicenter study of CSU patients whose therapy with omalizumab was optimized between January 2015 and September 2023 aimed to compare different tapering regimens and assess predictive factors for optimization. The minimum follow-up was 6 months, ensuring that patients received multiple optimized doses and allowing sufficient time for assessment of flares. The timing and method of down-dosing were selected by the clinician. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee of Grupo Hospitalario Quirónsalud-Catalunya (protocol code 2023/03-DER-HUSC, 29/08/2023). The requirement for patient consent was waived owing to the retrospective nature of the study and the use of anonymized aggregated data with no identifying information.

We defined complete response (CR) as an Urticaria Activity Score 7 (UAS7) of 0 and/or and an Urticaria Control Test (UCT) score of 16. A good response (GR) was defined as UAS7 of 1-6 and/or UCT score of 12-15. Flare or loss-of-control (LC) was defined as UAS7 >6 and/or a UCT score <12. Demographic, clinical, and CSU data were retrieved from medical records (Supplementary Table 1). A multivariate analysis was performed using a tree classification method including all study variables.

A total of 257 patients underwent down-dosing after a median (IQR) of 7 (4-13) months of treatment at the licensed dosage. Patients were divided into 2 groups: group 1 (n=135), in which the dosage was initially reduced to 150 mg/4 wk, and group 2 (n=121), who received 300 mg/6 wk. Treatment intervals were subsequently extended in both groups according to the clinical response. One patient underwent both approaches simultaneously. Baseline characteristics between groups were comparable, although group 1 had a longer disease duration (12 vs 9 months, P<.001), a higher erythrocyte sedimentation rate (10 vs 4 mm/h, P=.001), lower antithyroglobulin antibody titers (12 vs 18.25 IU/mL, P=.001), shorter treatment duration at 300 mg/4 wk (6 vs 7 months, P=.012), and a slower time to GR (3 vs 1 month, P<.001) than group 2.

During the first optimization attempt, 47% of patients experienced LC after a median of 4 (2-9) months. Flare rates between groups were similar (47% vs 48.7%, P=.8287), with flares mostly occurring with the initial optimized dose. Flare was associated with longer disease duration (21 vs 13 months, P=.0148), more frequent concomitant chronic inducible urticaria (CIndU; 30% vs 41.94%, P=.0475), and body mass index (BMI) >30 (40% vs 20%, P=.0175). Patients who experienced flares also required more frequent up-dosing (30% vs 15%, P=.0038) and had a lower CR percentage before tapering (84.64% vs 94.75%, P=.0075, Supplementary Table 1). Multivariate analysis revealed a scoring model of successful down-dosing on the first attempt (Figure), with an accuracy of 76%. The most discriminative variables identified included age, C-reactive protein (CRP), baseline total immunoglobulin E (IgE), anti–thyroid peroxidase (anti-TPO), and thyroid-stimulating hormone (TSH). The predicted likelihood of success was greatest in patients aged <75 years with baseline total IgE ≥15 IU/mL, CRP <2 mg/dL, and anti-TPO <10 IU/mL.

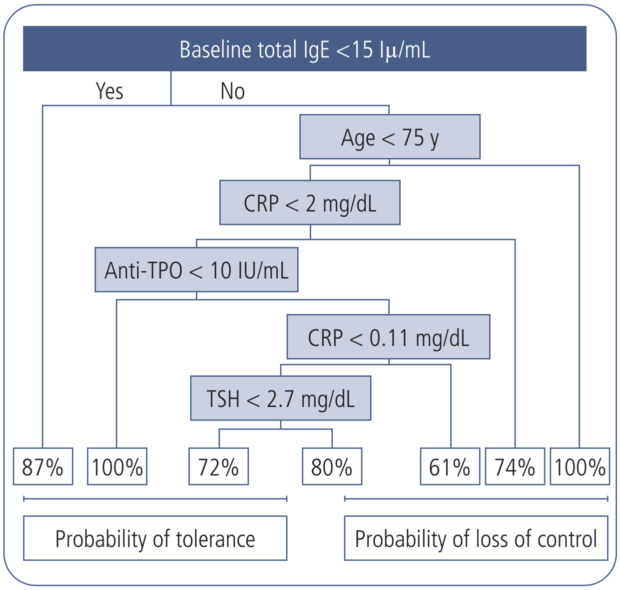

Figure. Phenotypes and probability of successful optimization at the first attempt obtained by the tree classification method. Seven phenotypes were identified based on combinations of age and baseline levels of C-reactive protein (CRP), total immunoglobulin E (IgE), anti–thyroid peroxidase antibody (anti-TPO), and thyroid-stimulating hormone (TSH). Tapering is most likely to be successful at the initial optimization attempt in young patients exhibiting high baseline total IgE, low CRP, and negative thyroid autoimmunity.

Further optimization was performed for patients who flared; 80.6% (n=100) tolerated down-dosing. However, in 9.3% (n=24), optimization failed despite multiple efforts. Compared with patients who tolerated tapering, this refractory group required more up-dosing (45.8% vs 19.8%, *P*=.003), less frequently experienced CR before optimization (75% vs 91.42%, *P*=.011), and had higher CRP levels (1.79 vs 0.61 mg/dL, *P*=.003).

In our study, omalizumab was successfully optimized for 90.7% of patients, thus exceeding the success rate previously reported by Aghdam et al [4]. In contrast to these authors, we found that early response was not associated with better tolerance of optimization. Furthermore, patients without a CR before tapering were more likely to experience flares. Although the groups were not homogeneous, their differing characteristics have not been established as predictive factors of optimization, nor were they relevant in the multivariate model. Given the similar LC rates in both groups, the method used in group 1 may be the most cost-effective option [5-7]. Consequently, tapering seems less important than achieving a CR prior to down-dosing, as CR correlated with successful optimization of both the initial and subsequent attempts.

We did not evaluate adjuvant antihistamine use during optimization. There are no guidelines on how to suspend antihistamines in CSU patients receiving omalizumab. Prior studies indicate that patients with a GR to omalizumab often self-discontinue and that treatment response does not differ significantly between patients receiving omalizumab alone or in combination at the standard dosage with antihistamines [8,9]. Nevertheless, reintroducing antihistamines during optimization may promote a sustained response, in turn improving tolerance to dose reduction. Therefore, we recommend the addition of antihistamines when tapering, although further studies are needed to determine how they can best be managed.

The incidence of CIndU was higher, disease duration longer, and BMI higher among patients experiencing LC during the first attempt. CIndU is linked to prolonged duration of CSU, while duration is associated with an increased risk of relapse following discontinuation of omalizumab [1,4]. Nevertheless, the value of these factors as predictors of optimization has not been addressed. Furthermore, our study aligns with previously published reports suggesting that individuals with low BMI tend to better tolerate tapering [10].

There are no effective biomarkers for identifying patients who can benefit from dose tapering [6], although one study reported higher CRP levels in tolerant patients [11]. In our study, baseline total IgE, CRP, anti-TPO, TSH, and age were most strongly associated with successful optimization during the first attempt. Therapy was more likely to be optimized in patients with type I autoimmunity, whereas those with elevated CRP were refractory to tapering after multiple attempts. Our findings contrast with those of Brás et al [11] but are consistent with evidence linking high CRP levels to activity of CSU, type IIb autoimmunity, and resistance to antihistamines and omalizumab [12].

In conclusion, most patients with CR tolerate optimization regardless of the method. LC during the first optimization attempt should not discourage future efforts, as half of patients require multiple attempts. Tapering is more likely to be successful during the first attempt in young patients with high baseline total IgE, low CRP, and negative thyroid autoimmunity. Upon tolerating an initial dose reduction, patients do not usually experience flares with further tapering.

The limitations of our study include its retrospective nature, the lack of homogeneity between groups, the relatively small sample size, and the absence of data regarding antihistamine use during tapering. Further studies are needed to confirm the efficacy of our predictive model.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

G. Melé-Ninot has been a medical advisor for AbbVie, Leo Pharma, Lilly, Sanofi, and Novartis and has participated in educational activities for Almirall, Avène, AbbVie, Laboratorio Reig Jofre, Leo Pharma, Lilly, Meda, Novartis, Sanofi, and Uriage.

V. Expósito-Serrano has been a medical advisor and/or speaker for and/or has received research funding from AbbVie, Lilly, LEO Pharma, Novartis, and Sanofi Genzyme.

M. Bonfill-Ortí has been a medical advisor and/or speaker for Leo Pharma, AbbVie, Lilly, Novartis, Sanofi Genzyme, Roche, and Sun Pharma.

A.M. Giménez-Arnau is or recently was a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Celldex, Escient

Pharmaceuticals, Genentech, GSK, Instituto Carlos III-FEDER, Leo Pharma, Menarini, Mitsubishi Tanabe Pharma, Novartis, Sanofi–Regeneron, Servier, Thermo Fisher Scientific, Uriach Pharma, and Noucor.

P. Ribó has been a medical advisor and/or speaker for and/or received research funding from Sanofi and Novartis.

J. Spertino has been a medical advisor and/or speaker for and/or has received research funding from AbbVie, Lilly, Leo Pharma, Novartis, Sanofi Genzyme, and Noucor.

The remaining authors declare that they have no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Manuscript received September 29, 2024; accepted for publication November 25, 2024.

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