

**Omalizumab updosing allows disease activity control in refractory patients with chronic
spontaneous urticaria**

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Dear editor,

Omalizumab has been shown to be a very effective drug in chronic spontaneous urticaria (CSU) improving patients' quality of life.¹ Phase III clinical trials ASTERIA I/II and GLACIAL showed respectively 58.8-52.4% of patients achieving a twice daily average Urticaria Activity Score 7 (UAS7td) \leq 6 at week 12.² Outside of clinical trials, the response varies between 77-83%.³ However, some patients do not achieve well-controlled activity of the disease with the licensed dose of omalizumab (300mg/4 weeks).

With the hypothesis that omalizumab up dosing may be useful in some patients with partial or non-response, an observational, multicentre study was conducted by the "Catalan and Balearic Chronic Urticaria Network, XUrCB" including 15 hospitals. The medical charts of 286 CSU patients treated with omalizumab were reviewed retrospectively. CSU activity was assessed according to the EAACI/GA²LEN/WAO/EDF guideline recommendations.⁴ We considered control of CSU when once daily UAS7 (UAS7od) \leq 6 [0-42].

In order to look for factors that could predict the need for omalizumab up dosing, the patients were divided into 3 groups: **Group-1**) UAS7od \leq 6 with 300mg (Licenced Dose Responders, LDr), **Group-2**) UAS7od \leq 6 with 450/600mg (High Dose Responders, HDR) and **Group-3**) patients without achieving UAS7od \leq 6 despite up dosing (Non-responders, Nr). The variables

included in the multivariate analysis were: baseline UAS7od, inducible urticaria, angioedema, gender, age, Body Mass Index (BMI), total Immunoglobulin E, D-dimer and previous immunosuppressive treatments. Ethics was granted by the approval of the Committee-Clinical Research (2016/6606/IEUDRAC).

Demographic and clinical features of patients are summarized in **Table 1**. With the licenced dose, 65% of patients (n=187) reached UAS7od ≤ 6 , mostly during the first three months of treatment (83%). In 80% of partial or non-responder patients (n=79) the dose was increased. Seventy-five percent of them (n=59) achieved UAS7od ≤ 6 (55% at 450mg and 20% at 600mg). **(Figure 1)**

Bivariate analysis showed that when the licenced dose was not enough to reach UAS7od ≤ 6 , cyclosporine A (CyA) was previously used more frequently (41% in HDr vs 21% in LDr, p=0.04).

The multivariate analysis comparing Group-1 versus Group-2 showed a significant association of omalizumab up dosing with BMI ([OR 1.14], p=0.004); as well as with age ([OR 1.038], p=0.013). There were no significant statistical differences in the other variables studied. The aggregate analysis comparing Groups 1+2 versus Group-3 did not show any statistically significant association. No serious adverse events were reported at any dose.

In our series, 65% of CSU patients responded very well to 300mg/4w of omalizumab. However, 21% of the global patient population needed the up dosing to reach UAS7od ≤ 6 and 7% did not achieve control of the disease despite increasing the dose. Predictors of partial response to 300mg and good response with the up dosing were previous treatment with CyA, obesity and age > 57 years old. Our data agrees with Ghazanfar et al.⁵ suggesting that previous immunosuppressant treatments are associated with a worse response to omalizumab. The previous use of CyA could alter the responsiveness to omalizumab by modifying patients' immune status or may reflect severity of the disease itself.

Obesity is currently considered a chronic low-grade inflammatory condition since visceral fat is known to be a potential source of proinflammatory cytokines. Long-term efficacy of biologics in other inflammatory cutaneous diseases such as psoriasis is influenced by the BMI, so this

also may be the case of omalizumab in CSU. Although in CSU there is not a requirement to adjust the dose based on the weight, it is considered in asthmatic patients.

Omalizumab has demonstrated to be safe in the elderly but the reason why older patients required higher doses to control the disease is still unknown.⁶

No differences in these predictive factors were found when comparing CSU responders (Group 1+2) versus non-responders (Group-3), suggesting other factors involved such as a low baseline high affinity IgE receptor in blood basophils (FcεRI) that has been shown to correlate with the response to omalizumab.⁷

The decision to increase the dose in patients that shows a partial response to omalizumab could be considered after the third administration based in the experience published by Gericke et al. regarding the time of good control obtained by slow responders to omalizumab.⁸ According to these authors and our data, we suggest periodic evaluation of treatment every 3 months.

Omalizumab up dosing is safe and should be considered in partial or no responder patients (UAS7>6). The predicted likelihood of success is greater when the BMI is 30 or higher, patients older than 57 years old and in those with previous cyclosporine treatment. The main limitation of our study is related to its retrospective nature.

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Table 1. Clinical variables of the study population (n=286)

Variables		n (%) or mean ± SD
Gender	Female	73.8 (211)
	Male	26.2 (75)
Mean age (years old)		44.6 ± 16.4
Body Mass Index		27.0 ± 4.6

Angioedema		47.4 (135)
UAS7 pre-omalizumab (<u>237/286</u>)		26.5 ± 10.1
UAS7 pre-updose to 450mg (<u>45/59</u>)		<u>20.2 ± 9.83</u>
UAS7 pre-updose to 600mg (<u>13/16</u>)		<u>24.6 ± 9.96</u>
Chronic inducible urticaria		33.3 (95)
High IgE levels		45 (98/217)
High Dimer D levels		50 (59/118)
Previous IS treatment	CyA	27.6 (79)
	Others	6.6 (19)
Concomitant antihistamines		90.6 (259)

UAS7: Urticaria Activity score 7; IgE: Immunoglobulin E; DD: D-Dimer; IS:

immunosuppressive drugs; CyA: Cyclosporine A; AH: H1-antihistamines.

Figure 1. Distribution of patients

