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## Letter

## Omalizumab in chronic spontaneous urticaria: patient-tailored tapering or planned discontinuation?

Management of chronic spontaneous urticaria has undergone a paradigm shift in recent years. Several randomized trials have demonstrated the efficacy of anti-IgE monoclonal antibodies in treating refractory disease, with high tolerability and a low incidence of reported side effects.<sup>1–3</sup> Current international guidelines recommend monthly administrations of 300 mg of omalizumab in patients unresponsive to previous medications (nonsedating H<sub>1</sub> antihistamine up to 4 times the standard dosage), which would otherwise require oral systemic corticosteroids for symptom control.<sup>4</sup> Although clinical response is excellent, some open questions need to be addressed. Overall treatment duration is one matter of debate: currently, the indication of pursuing anti-IgE treatment beyond 6 months is limited owing to the lack of clinical trials proving effectiveness and long-term safety in chronic spontaneous urticaria.<sup>5</sup> Tapering or discontinuation of omalizumab therapy is another issue, because the optimal strategy to adopt remains unknown. Several tapering attempts have been documented in real-life clinical settings, namely decreasing the dose and prolonging the dosing interval. Romano et al<sup>6</sup> found that maintenance of remission with progressive dose tapering down to 150 mg per month and lengthening the interval beyond 28 to 30 days was not tolerated. Silva et al<sup>7</sup> reached a maximum 6-week interval in 3 of 7 patients treated with full-dose omalizumab. Uysal et al<sup>8</sup> suggested an individualized treatment algorithm, starting from 150 mg of omalizumab and attempting a symptom-guided interval prolongation until pausing, when feasible; 3 of 27 patients were eventually able to discontinue anti-IgE therapy, although data on clinical monitoring after treatment cessation are lacking.

All these options are feasible and cost effective and achieve similar outcomes in safety and remission maintenance. Therefore, longitudinal studies are necessary to better define the optimal strategy to adopt, the best timing to begin regimen modification, and baseline predictive factors for treatment success.

We present data on long-term management of chronic spontaneous urticaria in our outpatient clinic. Eight patients (4 women, mean age  $47.5 \pm 12.1$  years, mean duration of disease  $6.5 \pm 3.8$  years) were treated with nonsedating H<sub>1</sub> antihistamines up to 4 times the standard dose and more than 3 administrations per year of a short course ( $5 \pm 2$  days) of oral steroid therapy (mean on-relapse equivalent daily prednisone dose  $24.4 \pm 26.6$  mg). In 3 patients oral administration of cyclosporine was attempted, resulting in unresponsiveness (1 patient) and relapse shortly after discontinuation (2 patients). Patients were treated with 300 mg of omalizumab every 4 weeks for 6 months and disease severity was assessed using the 7-day Urticaria Activity Score (UAS7) index. Omalizumab responders were defined as subjects whose UAS7

scores were markedly decreased (decrease  $\geq 90\%$  from baseline values) within 6 months of treatment and did not require oral prednisone for symptom management. At the 6-month end point, we attempted prolonging the dosing interval in responders by applying an on-relapse schedule of treatment, similar to that of the Toronto cohort described by Sussman et al.<sup>9</sup> Patients were trained to fill in their UAS7 scores every week, starting from the date scheduled for their next dose, namely the 29th day from their last injection. If the severity score was above 12, they were instructed to contact our center to arrange for another injection of 300 mg of omalizumab soon thereafter. The number of days exceeding the standard 28-day interval was calculated for each patient. The optimal dosing interval was retrospectively defined as the longest symptom-free period in days (UAS7 score  $< 6$ ) that did not require additional rescue medications. The treatment protocol was approved by our health care ethical committee, before approval for use by the European Medicines Agency; written informed consent was obtained from each patient, and the project was completely funded by our clinic.

Symptoms quickly resolved in 4 to 8 weeks from the first omalizumab dose in 7 of 8 patients and were associated with dramatically lower UAS7 scores, improved self-rated quality of life, and, eventually, complete oral steroid withdrawal (Table 1). Only 1 patient showed a delayed response to treatment, because a UAS7 score lower than 6 and complete independence from on-demand oral prednisone were obtained only after 18 weeks. Seven patients could not discontinue omalizumab after 6 months owing to symptom flareup, which quickly resolved after reintroducing the medication. However, anti-IgE treatment was discontinued in 1 patient whose disease was in remission after a 7-month follow-up and who seldom resorted to antihistamines. Four of 7 patients did not tolerate administrations beyond the monthly schedule (mean  $31.8 \pm 3.3$  days). In contrast, 3 patients tolerated longer dose delays, up to a maximum of 84 days (mean  $67.3 \pm 17.6$  days). Over a 2-year follow-up, there was no decrease in efficacy of omalizumab in any patient, and in 2 patients the current dosing interval is 3 and 4 injections per year, respectively.

Our experience allowed us to explore 2 key points. (1) Anti-IgE therapy discontinuation must be attempted in each patient after the induction of disease remission, although optimal timing and positive predictive factors have yet to be defined. (2) If complete suspension of treatment is not a feasible option, the prompt reversal of symptoms with no apparent loss of efficacy over time suggests that patient-tailored long-term management is possible. Our data are consistent with those of other cases of interval lengthening,<sup>6–8</sup> because most patients did not tolerate administration delays beyond 30 days, albeit with a few exceptions. Hence, in certain patients, monthly administration might be redundant for

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**Table 1**  
UAS7-guided determination of dosing interval for each patient

| Patient number        | Baseline UAS7 | On-relapse equivalent daily prednisone dose (mg/d) | UAS7 score 4 wk after first OMZ dose | UAS7 score at 6-mo end point | Calculated optimal dosing interval (d) |
|-----------------------|---------------|----------------------------------------------------|--------------------------------------|------------------------------|----------------------------------------|
| 1                     | 34            | 5                                                  | 0                                    | 0                            | 69                                     |
| 2                     | 37            | 35                                                 | 0                                    | 0                            | 49                                     |
| 3                     | 37            | 7                                                  | 3                                    | 5                            | 34                                     |
| 4                     | 31            | 50                                                 | 21                                   | 6                            | 28                                     |
| 5                     | 36            | 10                                                 | 0                                    | 0                            | 84                                     |
| 6                     | 35            | 13                                                 | 2                                    | 0                            | 35                                     |
| 7                     | 42            | 75                                                 | 0                                    | 0                            | suspended                              |
| 8                     | 25            | 0                                                  | 5                                    | 0                            | 30                                     |
| Mean                  | 34.6          | 24.4                                               | 3.9                                  | 1.4                          | 47.0                                   |
| SD                    | 4.98          | 26.5                                               | 7.16                                 | 2.56                         | 21.73                                  |
| <i>P</i> <sup>a</sup> | —             | —                                                  | >.00007                              | >.000001                     | —                                      |

Abbreviations: OMZ, omalizumab; UAS7, 7-day Urticaria Activity Score.

<sup>a</sup>Comparing UAS7 scores at baseline vs 4-week and baseline vs 6-month end point.

symptom control, and therefore delaying the dose should be attempted. We could not find any difference in baseline features that could be predictive of suspension or tapering tolerance in patients owing to the small number of observations. Nevertheless, it should be kept in mind that in a larger cohort a small percentage of patients (8%) who became unresponsive to treatment, with no clear biological explanation, was identified<sup>9</sup>; whether this could affect the safety of long-term maintenance strategies and to what extent have yet to be elucidated.

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Chiara Tontini, MD  
Lucia Marinangeli, MD  
Miriam Cognigni, MD  
Maria Beatrice Bilò, MD  
Leonardo Antonicelli, MD  
Department of Internal Medicine, Allergy Unit  
Azienda Ospedaliero-Universitaria Ospedali Riuniti  
Ancona, Italy  
c.tontini@live.com

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