H_1-Antihistamines May No Longer Be Necessary for Patients With Refractory Chronic Spontaneous Urticaria After Initiation of Omalizumab

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Omalizumab is indicated for the management of patients with chronic spontaneous urticaria (CSU) who are unresponsive to treatment with antihistamines. A recent meta-analysis of 67 published reports on real-world effectiveness revealed that omalizumab was associated with an average complete response rate of 72.2%, and a partial response rate of 17.8%, thus meeting or exceeding the results obtained in clinical trials [1]. Omalizumab is recommended as add-on treatment of CSU when symptoms are not completely controlled with second-generation antihistamines (sgAHs) [2]. However, the real need for sgAHs once urticaria is controlled with omalizumab is not clear. In a recent review based on available evidence and the experience of urticaria specialists from 4 large urticaria centers in Europe, the authors give suggestions on how to manage sgAHs after treatment with omalizumab is initiated. If a patient shows no benefit from sgAHs before omalizumab, antihistamines can be stopped when omalizumab is started. However, there might be a small, unrecognized benefit, and the risk of worsening of symptoms should be discussed with the patient. If a patient benefits from sgAHs, then this treatment should be gradually stopped as the patient gains complete control with omalizumab [3,4]. In support of this observation, a review of 16 studies revealed that omalizumab was effective without the need for concomitant sgAHs in up to 60% of patients [5]. Considering the high cost of omalizumab, the addition of continuous treatment with high-dose sgAHs could prove expensive. The present study aimed to evaluate the use of antihistamines in CSU patients whose disease was controlled with omalizumab.

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We performed a retrospective analysis using an electronic database of urticaria patients treated with omalizumab in 6 certified UCARE centers in Brazil. Patients with partial or uncontrolled urticaria were excluded. Controlled urticaria was defined as absence of symptoms and/or an Urticaria Activity Score in 7 days (UAS7) ≤6 and/or Urticaria Control Test (UCT) score ≥12. Clinical response and/or UAS7 and/or UCT were assessed at 1, 6, 12, and 24 months of treatment with omalizumab. Use of antihistamines was also evaluated at each visit. Baseline severity was classified according to UAS7 scores and presence of angioedema. Response was considered fast when disease control was achieved after the first dose of omalizumab. The study was approved by the local ethics committees.

We evaluated 162 patients (82.7% female) with a mean (SD) age of 43.3 (14.7) years and CSU that was unresponsive to antihistamines. All patients were receiving sgAHs before starting omalizumab (cetirizine in 48.1%, bilastine in 25.3%, and levocetirizine in 22.8%). Angioedema was reported by 125 patients (78.1%). Median total serum IgE was 90 IU/mL (range, 0.31-1734 IU/mL), and median time from disease onset to initiation of omalizumab was 26 months (range, 2 months to 40 years). UAS7 scores before starting omalizumab treatment were available for 99 patients (61.1%), with a mean score of 28.5 (9.9 [range 9-42]).

Patients were followed for 24 months. At the end of this period, 53 patients (32.7%) were still taking omalizumab. Disease was completely controlled in all 53. The reasons for discontinuation of omalizumab included withdrawal of medication access or disease remission. During the study, 44 patients (27.2%) maintained disease control over 2 years with no need for antihistamines. At the 1-month visit, symptoms were controlled in 87 patients (53.7%), and of these, 10 patients (11.5%) were no longer taking antihistamines. After 6 months of treatment, symptoms were completely controlled in 126 of 135 patients (93.3%); of these, 25 (18.5%) were not taking antihistamines. Among 94 of 96 patients (97.9%) with no symptoms after 12 months, 25 (26.0%) were not taking antihistamines. Finally, symptoms were controlled in 53 patients treated for 24 months; of these, 17 (32.1%) were not taking antihistamines for their urticaria (Figure).

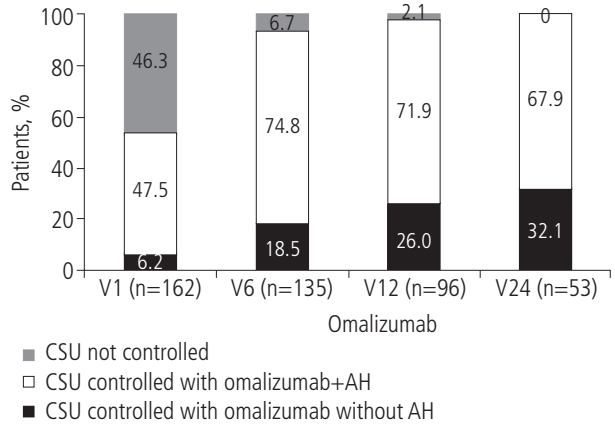

Figure. Patients taking omalizumab at the different monthly visits (1, 6, 12, and 24 months). CSU indicates chronic spontaneous urticaria; AH, antihistamines.

Analysis after 1 year of treatment revealed no significant differences in the use of antihistamines in patients with or without angioedema. Higher baseline UAS7 scores were not significantly associated with intake of antihistamines at month 12 (Table 1, Supplementary Material).

Moreover, no differences in the use of antihistamines were observed when fast responders were compared with slower responders. Interestingly, disease duration was significantly longer in patients who stopped antihistamines before starting omalizumab than in patients who remained on treatment with antihistamines (Table 1, Supplementary Material).

The objective of treatment of urticaria should be complete disease control. Histamine is a central mast cell mediator in this disease, and sgAHs have been recommended as first-line treatment [2]. However, symptoms do not improve with antihistamines in up to 40% of patients, who may be candidates for treatment with omalizumab [5].

In the present study, the complete response rate after 6 months of omalizumab was 93.3%, which is higher than previously reported in real-life data [6,7]. An increasing number of patients stopped taking antihistamines during treatment, despite the fact that some of them were not instructed to do so (44/162 patients [27.2%] over 24 months). Interestingly, urticaria continued to be controlled in these patients when they were taking omalizumab only.

Angioedema has been associated with the severity of urticaria in various studies and was present in most of our patients [8-11]. We hypothesized that patients with more severe disease would be more concerned about stopping medication, although we observed no significant association between presence of angioedema or disease severity and antihistamine use.

While antihistamines continue to be the mainstay of treatment of urticaria, they may be no longer necessary in some patients once the disease is controlled with omalizumab. Identifying patients with appropriate clinical or laboratory biomarkers will help us to decrease the costs of urticaria without worsening the patient's quality of life.

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Conflicts of Interest

LFE reports personal fees and nonfinancial support from NOVARTIS, SANOFI and TAKEDA outside the submitted work. RAC, RFJC, SORV, and LKA report personal fees and nonfinancial support from NOVARTIS and TAKEDA outside the submitted work. SDDJ, JMLM, and RCA report personal fees from NOVARTIS outside the submitted work. JCSO, APCE, and ICCN declare that they have no conflicts of interest.

References

1. Tharp MD, Bernstein JA, Kavati A, Ortiz B, MacDonald K, Denhaerynck K, et al. Benefits and Harms of Omalizumab

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Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of "Real-world" Evidence. JAMA Dermatol. 2019;155:29-38.
2. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73:1393-414.
3. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgereit T, Maurer M. How to treat patients with chronic spontaneous urticaria with omalizumab: Questions and answers. J Allergy Clin Immunol Pract. 2019 Jul 30. pii: S2213-2198(19)30639-7 (ahead of print).
4. Giménez Arnau AM, Valero Santiago A, Bartra Tomás J, Jáuregui Presa I, Labrador-Horrillo M, Miquel Miquel FJ, et al. Therapeutic strategy according to the differing patient response profiles to omalizumab in chronic spontaneous urticaria. J Investig Allergol Clin Immunol. 2019;29(5):338-48.
5. Bernstein JA, Kavati A, Tharp MD, Ortiz B, MacDonald K, Denhaerynck K, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. Expert Opin Biol Ther. 2018;18:425-48.
6. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017;72:2005-16.
7. Ensina LF, Valle SOR, Juliani AP, Galeane M, Vieira dos Santos R, Arruda LK, et al. Omalizumab in Chronic Spontaneous Urticaria: A Brazilian Real-Life Experience. Int Arch Allergy Immunol. 2016;169:121-4.
8. Cherrez-Ojeda I, Maurer M, Bernstein JA, Vanegas E, Felix M, Ramon GD, et al. Learnings from real-life experience of using omalizumab for chronic urticaria in Latin America. World Allergy Organ J. 2019;12:100011.
9. Sanchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F, González-Aveledo L. Biomarkers of treatment efficacy in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol. 2018;50:5-9.
10. Maurer M, Houghton K, Costa C, Dabove F, Ensina LF, Giménez-Arnau A, et al. Differences in chronic spontaneous urticaria between Europe and Central/South America: results of the multi-center real world AWARE study. World Allergy Organ J. 2018;11:32.
11. Maurer M, Nakonechna A, Ortiz de Frutos J, Reynolds M, Sweeney C, Tian H, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: Analyses from ASSURE-CSU. Allergy. 2018;73:1724-34.

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