# H1-antihistamines may be no longer necessary for patients with refractory chronic spontaneous urticaria after introduction of omalizumab treatment

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Omalizumabis indicated for the management of patients with chronic spontaneous urticaria (CSU) unresponsive to treatment with antihistamines. A recent meta-analysis of 67 published reports on real-world effectiveness revealed that omalizumab therapy was associated with an average complete response rate of 72.2%, with a partial response rate of 17.8%, 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 (sgAH) [2]. However, the real need for sgAH once the 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 deal with the use of sgAH after treatment with omalizumabe is initiated. According to them, if a patient showed no benefit from sgAH before omalizumab, antihistamines could be stopped when omalizumab is started. However, there might be a small, unrecognized benefit present, and the risk of worsening of symptoms should be discussed with patient. If a patient had some benefit from sgAH, this treatment should be gradually stopped as the patient gain complete control with omalizumab[3, 4]. To support this, a review including 16 studies revealed that omalizumab was effective without the need for concomitant sgAH treatment in up to 60% of patients [5]. Considering the high

 
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cost of omalizumab treatment, additional expenses with high dose sgAH used continuously may have economical impact. The present study aimed to evaluate the use of antihistamines in CSU patients treated and controlled with omalizumab.

We performed a retrospective analysis using an electronic database of urticaria patients treated with omalizumab in six certified UCARE centers in Brazil. Patients with partial or uncontrolled urticaria were excluded from the present study. Controlled urticaria was defined as absence of symptoms and/or Urticaria Activity Score in seven days (UAS7) ≤6 and/or Urticaria Control Test (UCT) ≥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 accordingly 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 Ethics Committee.

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

Follow up of these patients was carried out for 24 months. At the end of this period, 53/162 (32.7%) patients were still taking omalizumab.All presented with



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complete control of the disease. Reasons for discontinuation of omalizumab included withdrawal of medication access or disease remission. During the study, 44 patients (27.2%) maintained disease control over two years without the need for antihistamines. At the one-month visit, 87 of 162 (53.7%) patients had their symptoms controlled, and of those, 10/162 patients (6.2%) were no longer taking antihistamines. After six months of treatment, 126 of 135 (93.3%) patients presented complete control of symptoms; of those, 25/135 (18.5%) were not taking antihistamines. Among 94 of 96 (97.9%) patients with no symptoms after 12 months, 25/96 (26.0%) were not taking antihistamines. Finally, 53 patients were treated for 24 months and had their symptoms controlled; of those, 17 (32.1%) were not taking antihistamines for their urticaria (Figure 1).

Analysis after one year of treatment revealed no significant differences in the use of antihistamines in patients with or without angioedema. Higher baseline UAS7 scores showed no significant association with antihistamines intake at month 12 (Table 1, Supplementary Material).

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

Urticaria treatment should aim at complete disease control. Histamine is a central mast cell mediator in this disease, and sgAHhave 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].



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The complete response rate after six months of omalizumab therapy was 93.3% in the present study, which is higher than previously reported 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. Overall, sgAH antihistamines were stopped in 44/162 (27.2%) of patients throughout the study period of 24 months. Interestingly, urticaria persisted under control in these patients when they were taking omalizumab only.

Angioedema has been associated with urticaria severity in different studies and was present in the majority of our patients [8, 9,10, 11]. We hypothesized that patients with more severe disease would have greater concern in stopping any medication, however no significant association of presence of angioedema or disease severity and antihistamine use was observed.

In the present study, we also observed that patients who presented control of their urticaria with no antihistamines after omalizumab treatment were those who had a more prolonged disease, supporting the relevance of early introduction of omalizumab in antihistamine refractory patients.

Antihistamines are the mainstay of treatment of urticaria, however they may be no longer necessary in some patients after disease control with omalizumab. Identifying those patients with clinical or laboratory biomarkers will help us to decrease urticaria costs without worsening patient's quality of life.





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**Conflict of interest**

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**Figure 1**. CSU, chronic spontaneous urticaria; V1, first month visit; V6, six month visit; V12, twelvemonth visit; V24, twenty-four month visit.