

Planned omalizumab discontinuation in CSU management as a sustainable strategy: A 2-year real-life study

To the Editor:

Successful treatment of antihistamine-resistant chronic spontaneous urticaria (CSU) with omalizumab is reported at increasing frequency in the literature.¹⁻⁶ Randomized controlled trials (RCTs) provided evidence on efficacy of omalizumab administered for 24 to 48 weeks.^{1-3,51} Efficacy and safety of longer duration treatment were reported in observational studies.⁴⁻⁶ Some National Regulatory Agencies, but not all, consider the strength of evidence from observational studies on omalizumab insufficient to make strong recommendations. This is the reason why the licensed doses and treatment duration vary between different countries. In Italy, for example, based on RCT results, omalizumab can be administered for 24 weeks (300 mg subcutaneously every 4 weeks) in eligible patients with CSU (urticaria activity score [UAS] and UAS in the last 7 days [UAS7] higher than 3 and 16, respectively). Then, after a 8-week discontinuation period, a second course of 20 weeks can be prescribed with the same eligibility criteria in case of relapse.⁷ Notably, according to the Italian Regulatory Agency (AIFA), a third course of treatment cannot be prescribed in relapsing patients, since evidence from RCTs in patients treated for more than 48 weeks is missing.

Here, we show the results of a 2-year large multicenter observational study (Bari University Hospital; Foggia University Hospital; Parma University Hospital), including 195 adults (mean age 46.3 ± 15.1 years; 64.1% female) affected by CSU (median duration, 15 months, interquartile range [IQR], 7 to 36 months) refractory to antihistamines (UAS7, 24.9 ± 7.1). Ninety-eight patients (44.6%) had a history of angioedema. Laboratory findings showed normal or slightly increased serum IgE values (median 124 [IQR, 56.5-315] KUA/L) and positive thyroid autoantibody test in 17.1% of patients. Autologous serum skin test was positive in 35 patients (18.8%). See Table 1.

Reduction of UAS7 below 16 was regarded as the efficacy end point, according to AIFA.⁷ Patients with a post-treatment UAS7 = 0 were considered complete responders; those with UAS7 > 0 and ≤ 16 were considered responders; those with a UAS7 > 16 were considered nonresponders. Among nonresponders, only those who showed a UAS7 reduction of at least 20% compared to the baseline underwent an additional omalizumab course. Informed consent was obtained from participants.

Thus, patients received 2 omalizumab courses, according to regulatory agency.⁷ After the second omalizumab course, patients who

relapsed received an additional treatment courses. Patients with UAS7 ≤ 16 during the 8-week discontinuation period were considered sustained responders and stopped omalizumab. Patients who relapsed (UAS7 > 16 after an initial response during the 8-week discontinuation period) received an additional omalizumab course. Antihistamines were taken as continuous or rescue medication by the patients as needed.

TABLE 1 Baseline characteristics of patients included in the study

Baseline characteristics	Patients (N = 195)
Age, years	
Mean $\pm$ SD	46.3 ± 15.1
Sex, n (%)	
Female	125 (64.1)
Duration of CSU, months	
Median (IQR)	15 (7-36)
History of angioedema, n (%)	87 (44.6)
Current angioedema ^a , n (%)	28 (14.3)
History of CSU medications, n (%)	
H1 antihistamines at regular dosage	195 (100)
H1 antihistamines at high dosage	96 (49.2)
Leukotriene receptor antagonists	6 (3.1)
Systemic steroids	101 (51.7)
Cyclosporine	5 (2.6)
Total IgE levels, KUA/L	
Median (IQR)	124 (56.5-315)
Positive ASST, n (%)	35/186 (18.8)
Positive thyroid autoantibody test, n (%)	30/175 (17.1)
UAS7 ^a	
Mean $\pm$ SD	24.9 ± 7.1

Abbreviations: ASST, autologous serum skin test; CSU, chronic spontaneous urticaria; IQR, interquartile range; SD, standard deviation; UAS7, 7-day urticaria activity score.

^aBased on data collected in patient's daily diary in the week before first treatment.

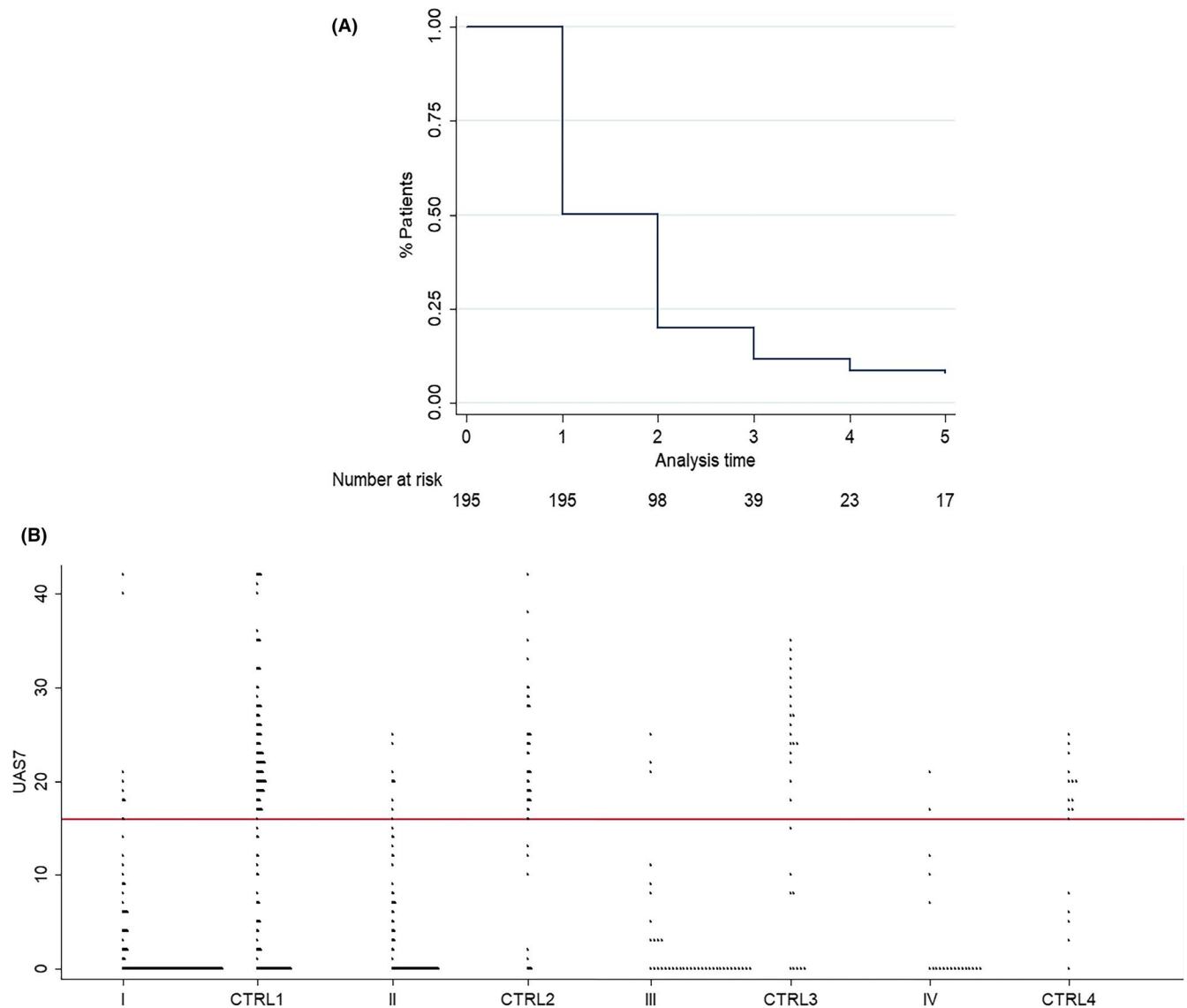


FIGURE 1 A, Fraction of patients under treatment (number at risk) at each omalizumab course (1, 2, 3, 4, 5). B, Patients' UAS7 values at the end of each treatment course (I, II, III, IV) and the respective 8-week observation period (CTRL 1, CTRL 2, CTRL 3, CTRL 4). A reference line (red) indicates the UAS7 value of 16

One hundred seventy-five patients experienced a clinical improvement after the first course of treatment (89.2%) (Figure S1, Figure 1), the majority of whom with a complete response (UAS7 = 0; 74.1%). Six patients (3.1%) stopped treatment (2 patients because of lack of efficacy; 2 for pregnancy; 1 for cancer occurrence; 1 for side effects). During the programmed 8-week discontinuation period, 46.7% of patients remained asymptomatic, whereas 50.2% experienced a CSU relapse and, therefore, underwent a second omalizumab course (Figure S1, Figure 1A,B).⁷ The vast majority of the re-treated patients (93.4%) showed a clinical improvement (Figure S1, Figure 1B). Again, the majority of these had a complete response (more than 70%). Two patients withdrew because of inefficacy. After the established planned 8-week discontinuation, a third course was started only for relapsing/non-responder patients at 2 of the three centers involved. The Parma

Center did not receive the necessary authorization for prescription. Of the 39 re-treated patients, 36 (92.4%) had a clinical response, complete in 27 patients (72.8%). One patient withdrew for pregnancy. During the planned 8-week omalizumab discontinuation, again more than 50% of these patients relapses and were, thus, re-treated (4th course), with a symptom improvement (UAS7 ≤ 16) in more than 80% of them. This improvement was sustained in about 50% of cases (Figure S1, Figure 1).

The cumulative percentage of patients with a sustained response was 75.9% after the recommended 2 treatment courses⁷ and raised to 83.6% and 86.7% after the 3rd and the 4th course, respectively (Figure S1).

No significant safety issues were identified, except for the occurrence of angioedema (facial, throat, lip, and tongue swelling) in one patient.

Compared to other approach for omalizumab discontinuation, such as tapering attempts, decreasing dose, and prolonging dose intervals, individualized discontinuations, periodic attempts to discontinue omalizumab, explored here, not only is a safe and effective strategy for control of CSU, but also seems economically sustainable. Planned discontinuation after a 6-month course identifies a subgroup of patients with rapid and sustained response. Actually, about 50% of the patients did not need a second course of treatment, or delayed intervals, or reduced doses, thus a stopping rule at this time-point (6 months) would lead to an early identification of patients who may safely cease omalizumab, with a 50% of cost saving, compared to a strategy with continuous treatment or patient individualized dose/interval.^{8,52}

The second 20-week course of omalizumab led to a similar percentage of sustained response (about 60%). Therefore, 2 consecutive courses led to a cumulative remission rate of 75.9%. The chance of stable remission decreased in patients undergoing the fourth omalizumab course, though symptoms ameliorated during additional courses (Figure S1, Figure 1). This means that re-treating with omalizumab may control symptoms in patients resistant in initial courses, as previously reported,⁴ but the chance of CSU remission remains low (ie, we selected a population fraction possibly requiring prolonged omalizumab treatment).⁹

The risk of nonresponse to the first 2 omalizumab courses was higher in subjects with a positive ASST (OR 2.49; 95% CI 0.9, 6.8; $P = .04$), but was not significantly associated to total IgE levels (OR 0.5; 95% CI 0.2, 1.3; $P = \text{NS}$).

Regarding the long-term benefit of omalizumab, 129 out of the 169 patients (75.3%) who stopped omalizumab (after the 8 week observation period; sustained responders) were contacted in order to assess the persistency of treatment efficacy (censored in February 2020 by telephone interview). Notably, of these 129 patients, 77 (59.7%) remained asymptomatic or with a UAS7 ≤ 16 (sustained response). As of February 2020, 37 of these 77 patients (48.3%) had stopped omalizumab for 1 year, 24 patients (31%) had stopped omalizumab for 2 years, and 16 patients (21%) had stopped omalizumab for 3 years.

In contrast, 52 out the 129 patients relapsed (45 of whom after the first and the second course). Of these, 27 (51.9%) were re-treated with omalizumab. The remaining patients were not re-treated because of prescription limitations,⁷ or because they declined a new treatment course.

Successful omalizumab discontinuation has been reported for severe asthma, too.⁵³⁻⁵⁶ Disease control (eg, no exacerbation in the last year) is critical for discontinuation, as in urticaria. However, urticaria has a higher chance of spontaneous remission than asthma. Therefore, an approach based of planned discontinuation at definite time-points over a short period of time (every 6 months) is conceivable, whereas in severe asthma, discontinuation after a longer period of control (years) seems more appropriate.

Considering omalizumab cost and that CSU may undergo spontaneous remission, we believe that periodical treatment discontinuation is an effective and cost-saving strategy. The cost-saving obtained with this strategy may, thus, permit to prolong the treatment in

those patients who require it (despite regulatory recommendations). In these patients, the chances of achieving sustained response decrease over time. However, a significant symptom relief may be achieved during treatment.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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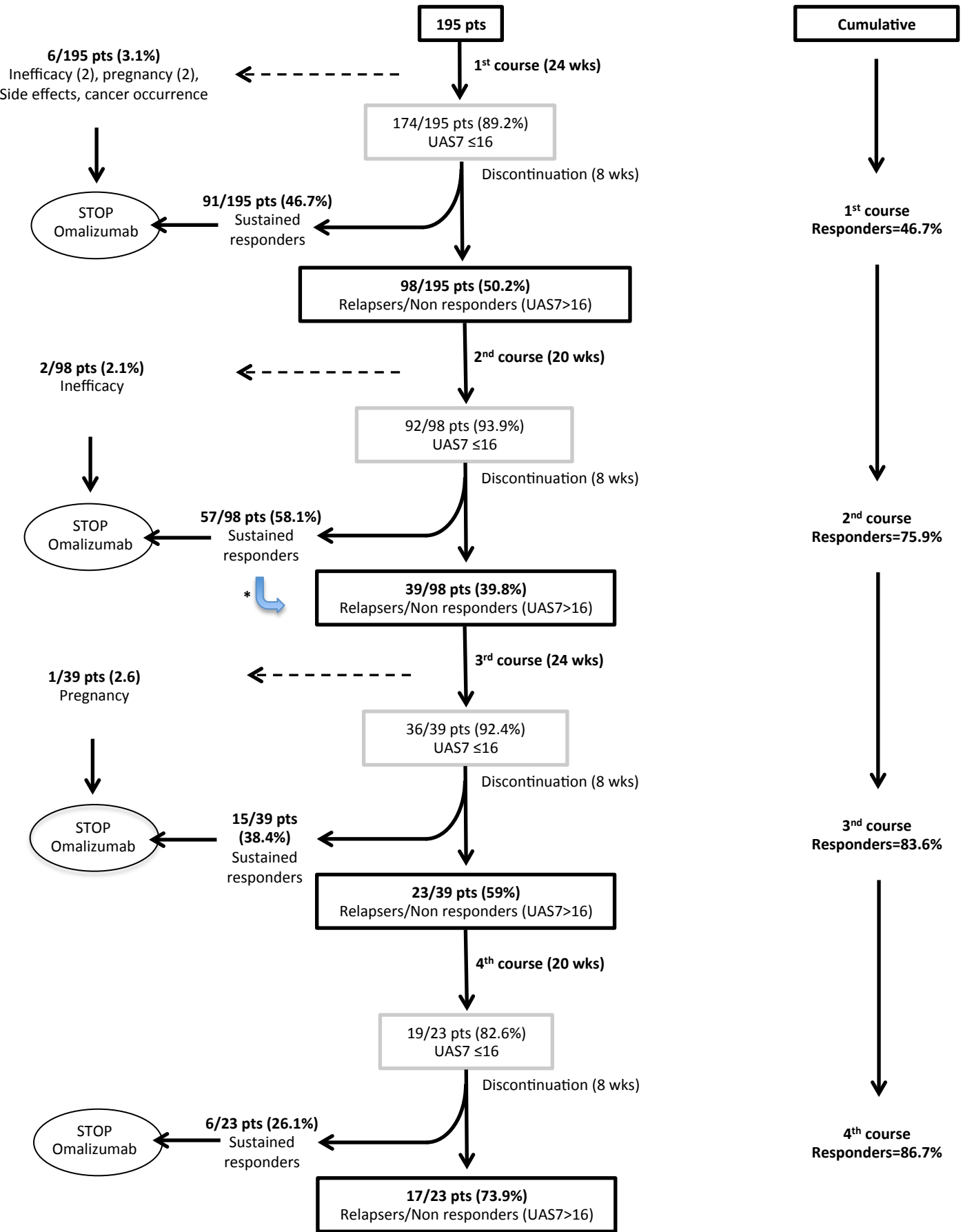
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.



SUPPLEMENTS

References

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