# Effective omalizumab interval prolongation in the treatment of chronic urticaria

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***Clinical Implications***

- A total of 82% of patients with chronic spontaneous urticaria undergoing omalizumab treatment extended the interval between administrations while maintaining adequate disease control.

Omalizumab, a monoclonal anti-IgE antibody, is an effective and safe add-on treatment option in patients with chronic spontaneous urticaria who respond poorly to 4-fold standard dose antihistamines.[1] The recommended treatment dose of omalizumab is 300 mg every 4 weeks. In daily practice, interval shortening is used to intensify treatment in less responsive cases, whereas interval prolongation is aimed at discontinuing treatment.[2,3]

A few studies with small patient numbers (varying between 7 and 20) investigated the possibility of increasing omalizumab treatment intervals in patients with active chronic urticaria (CU).[4-7] However, no data are available from a large CU population. The objective of our study was to investigate the maximum treatment interval while maintaining well-controlled disease status in patients with active CU.

Data (February 2012 to October 2019) concerning patient and treatment characteristics of all patients with CU on omalizumab treatment in our department were collected. According to the summary of product characteristics, International, and Dutch guidelines,[1,8] all patients were initially treated with omalizumab 300 mg every 4 weeks. After 6 administrations, treatment intervals in patients with well-controlled disease (Urticaria Activity Score over 7 Days (UAS7) $\leq 6$ or Urticaria Control Test (UCT) $\geq 12$) were gradually increased by 1 week. Treatment was discontinued in patients with well-controlled disease at an 8-week treatment interval. Based on a shared decision between the patient and physician, continuous treatment with intervals longer than 8 weeks was possible.

When symptoms reoccurred during an extended treatment interval, the interval was shortened to the last symptom-free interval.

To identify the individual maximum omalizumab interval, we determined each patient's steady-state interval. This is defined as the longest well-controlled (UCT $\geq 12$ or UAS7 $\leq 6$) treatment interval that a patient achieved on at least 2 consecutive administrations. This interval was allowed to be interrupted once by a longer unsuccessful interval (ie, recurring symptoms) if the patient subsequently returned to a symptom-free steady-state interval. To eliminate possible bias due to a short treatment period, patients with a follow-up period (including treatment period) of 16 months or shorter were excluded from analyses. This timeframe was chosen to allow patients to finish the minimal treatment period of 12.5 months and a follow-up period of 2 times 8 weeks (steady state).

A total of 238 patients (mean age 41 years; 71% female) were screened. Of them, 106 patients were under treatment for less than 16 months and were thus excluded. Of the remaining 132 patients: (1) 38 patients (29%) discontinued omalizumab due to well-controlled disease without the need to restart treatment (WCD-stop group); (2) 26 patients (20%) initially discontinued omalizumab due to well-controlled disease, but later restarted treatment (RS group); (3) 58 patients (44%) had well-controlled disease under continuous treatment (CT group); and (4) 10 patients (8%) discontinued omalizumab due to poor response to treatment (PR group). For the RS group, treatment episodes were differentiated into first treatment episode, before discontinuing omalizumab (RS1), and second treatment episode, after restarting omalizumab (RS2).

Patient characteristics are presented in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) and were comparable with other daily practice populations.[9] Percentages of patients reaching a specific steady-state treatment interval are presented in Table I. Of the total population analyzed, 73% of patients were able to extend the treatment interval to a steady-state interval of 6 weeks or longer, whereas 57% of patients were able to extend the interval to a steady-state interval of 8 weeks or longer. Only 18% of the patients with response to treatment were unable to extend the interval beyond 4 weeks.

Patients with early clinical response to omalizumab (UAS7 $\leq 6$ or UCT $\geq 12$ within 1 month of treatment) were more likely to extend the interval to a steady-state interval of 6 weeks (or longer) and 8 weeks (or longer) as compared with patients with a delayed response (87% vs 70%, $P = .021$, and 71% vs 51%, $P = .034$, respectively).

To specifically investigate the effect of interval prolongation in patients with underlying active, but well-controlled disease due to omalizumab treatment, we focused on patients who restarted omalizumab and patients on continuous treatment (RS2 and CT group). Patients who successfully discontinued treatment (WCD-stop and RS1 group) are more likely to be in complete remission and may therefore bias effective treatment intervals. The median steady-state interval of patients with active disease was 7 weeks (interquartile range [IQR], 5-8), and analyzing the 2 subgroups RS2 and CT separately, the intervals were 8 weeks (IQR, 7-10) and 6 weeks (IQR, 5-7) ($P < .001$), respectively. A total of 25% of patients with an active disease were not able to extend the interval between administrations beyond 4 weeks. In the group of patients with active disease, 60% and 25% of patients reached a steady-state interval of 6 and 8 weeks or longer, respectively. Steady-state intervals were not associated with specific CU phenotypes (CU phenotypes depicted in Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Successful implementation of tapering (by increasing treatment interval) and discontinuing omalizumab treatment in

**TABLE I.** Percentage of patients who reached a specific (or longer) steady-state interval

| | Total study population | Active disease | RS2 | CT |
|---|---|---|---|---|
| | n = 132 | n = 84 | n = 26 | n = 58 |
| 3 wk or more | 121 (92%) | 76 (91%) | 19 (73%) | 57 (98%) |
| 4 wk or more | 119 (90%) | 74 (88%) | 19 (73%) | 55 (95%) |
| 5 wk or more | 108 (82%) | 63 (75%) | 19 (73%) | 44 (76%) |
| 6 wk or more | 96 (73%) | 50 (60%) | 18 (69%) | 32 (55%) |
| 7 wk or more | 87 (66%) | 38 (45%) | 15 (58%) | 23 (40%) |
| 8 wk or more | 75 (57%) | 21 (25%) | 10 (39%) | 11 (19%) |
| 9 wk or more | * | 10 (12%) | 6 (23%) | 4 (7%) |
| 10 wk or more | * | 9 (11%) | 5 (19%) | 4 (7%) |
| 11 wk or more | * | 5 (6%) | 3 (12%) | 2 (3%) |
| 12 wk or more | * | 3 (4%) | 2 (8%) | 1 (2%) |
| Not determined | 1 (1%) | 8 (10%) | 7 (27%)† | 1 (2%)‡ |

*CT*, Continuous treatment; *PR*, treatment stopped due to poor response; *RS2*, good response restart (second treatment episode).
Total study population: WCD-stop, RS, CT, and PR.
Active disease: RS2 and CT.
*After reaching an interval of 8 weeks, treatment was discontinued for the WCD-stop and RS1 group; hence no values are displayed after 8 weeks.
†Because of a short treatment duration in the second treatment episode.
‡Because of inconclusive activity scores.

patients with CU has recently been shown by several studies.[3,6,7,10,11] However, detailed data on varying omalizumab treatment intervals in patients with active CU are limited. Two previous smaller studies found that treatment intervals could be extended to at least 6 weeks in, respectively, 80% (n = 20)[6] and 43% (n = 7)[4,5] of patients with active CSU. Uysal et al[6] also showed that 30% of patients could be treated with an 8-week interval, which is comparable with our data (25%).

This is the first study with an in-depth analysis of omalizumab treatment intervals in a large population with active CU. A total of 75% of the patients with active disease successfully extended treatment intervals between omalizumab administration beyond 4 weeks: 60% to 6 weeks or more and 25% to 8 weeks or more. Our data support the possibility of extending the recommended treatment interval of 4 weeks while maintaining adequate disease control. Patients with an early response to treatment or with a second treatment episode (after stopping treatment due to well-controlled disease) have a higher chance to successfully extend the treatment interval. Therefore, interval extension needs to be individually managed. The reduced number of drug administrations and hospital visits may subsequently lead to substantial reduction in costs and increased quality of life.

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## ONLINE REPOSITORY

**TABLE E1.** Demographic and clinical characteristics of patients with CU

| | Total study population | WCD-stop | RS1 | CT | PR |
|---|---|---|---|---|---|
| **Demographic** | **n = 132** | **n = 38** | **n = 26** | **n = 58** | **n = 10** |
| Female | 95 (72%) | 31 (82%) | 16 (62%) | 43 (74%) | 5 (50%) |
| Age at start treatment* | 40.0 (15.3) | 40.0 (15.3) | 45.2 (16.3) | 42.1 (12.4) | 36.2 (18.3) |
| Disease duration† | 3.0 (1.2-7) | 2.50 (1-7) | 3.00 (1-8) | 3.20 (2-7) | 1.88 (1-6) |
| Follow-up duration‡ | n.a. | 14 (4-21)§ | 23 (15-30) | n.a. | 31 (22-43) |
| CU phenotype | | | | | |
| CSU-Wheals only | 25 (19%) | 9 (24%) | 5 (19%) | 8 (14%) | 3 (30%) |
| CSU-Angioedema only | 9 (7%) | 0 (0%) | 3 (12%) | 5 (9%) | 1 (10%) |
| CSU-Wheals and angioedema | 47 (36%) | 13 (34%) | 8 (31%) | 22 (38%) | 4 (40%) |
| CSU and CindU | 49 (37%) | 15 (39%) | 10 (38%) | 23 (40%) | 1 (10%) |
| CindU only | 2 (2%) | 1 (3%) | 0 (0%) | 0 (0%) | 1 (10%) |
| Immunosuppressive while start omalizumab | 57 (43%) | 13 (34%) | 15 (58%) | 23 (40%) | 6 (60%) |
| Prednisone | 41 (31%) | 9 (24%) | 12 (46%) | 18 (31%) | 2 (20%) |
| Ciclosporin | 12 (9%) | 3 (8%) | 2 (8%) | 5 (9%) | 2 (20%) |
| Methotrexate | 4 (3%) | 1 (3%) | 1 (4%) | 0 (0%) | 2 (20%) |
| Clinical effect omalizumab | | | | | |
| Complete response | 69 (52%) | 27 (71%) | 18 (69%) | 24 (41%) | 0 (0%) |
| Partial response | 35 (27%) | 8 (21%) | 4 (15%) | 23 (40%) | 0 (0%) |
| Nonresponse | 13 (10%) | 0 (0%) | 0 (0%) | 3 (5%) | 10 (100%) |
| Missing | 15 (11%) | 3 (8%) | 4 (15%) | 8 (14%) | 0 (0%) |
| Baseline score‖,¶ | | | | | |
| UAS7 | 28 (17-35) | 26 (9-34) | 28 (13-33) | 30 (23-36) | 21 (12-35) |
| UCT | 5 (3-8) | 4 (2-9) | 6 (5-8) | 4 (2-7) | 5 (4-8) |
| AAS | 27 (0-55) | 20 (0-54) | 0 (0-0) | 38 (11-61) | 25 (25-25) |
| T-end score#,** | | | | | |
| UAS7 | 0 (0-3) | 0 (0-0) | 0 (0-0) | 1 (0-5) | 33 (26-38) |
| UCT | 16 (12-16) | 16 (16-16) | 16 (15-16) | 13 (9-16) | 5 (2-9) |
| AAS | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-8) | 31 (31-31) |

*AAS*, Angioedema Activity Score; *CindU*, chronic inducible urticaria; *CSU*, chronic spontaneous urticaria; *CT*, continuous treatment; *CU*, chronic urticaria; *GR-RS1*, good response restart (first treatment episode); *GR-RS2*, good response restart (second treatment episode); *GR-stop*, good response stop (no restart); *IQR*, interquartile range; n.a., not applicable; *PR*, treatment stopped due to poor response; *SD*, standard deviation; *UAS7*, Urticaria Activity Score over 7 Days; *UCT*, Urticaria Control Test.

Total study population = GR-stop, GR-RS1, CT, PR, and ST.

Complete response was reached when UAS7 score = 0 or UCT = 16. Partial response was defined as improvement of disease activity by a minimal important difference of 10 UAS7 points or, if UAS7 was not available, 3 UCT points.[E1,E2]

*Mean (±SD) in years.

†Disease duration in years before the start of omalizumab, median (IQR, 25-75).

‡Median number (IQR) of months between last dose of omalizumab and data lock.

§Four patients had a post-treatment follow-up period shorter than 12 weeks.

‖Before the start of omalizumab treatment, median (IQR, 25-75).

¶Data available for respectively 90, 109, and 15 patients; in WCD-stop for 29, 35, and 4 patients; in RS1 for 13, 19, and 1 patients; in CT for 41, 47, and 9 patients; in PR for 7, 8, and 1 patients.

#At the time of the final analysis or end of treatment, median (IQR, 25-75).

**Data available for respectively 119, 125, and 69 patients; in GR-stop for 37, 37, and 19 patients; in GR-RS1 for 22, 26, and 14 patients; in CT for 53, 53, and 35 patients; in PR for 7, 9, and 1 patients.

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