

## Clinical Communications

### High-dose omalizumab use in patients with chronic spontaneous urticaria

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#### Clinical Implications

- Updosing omalizumab shows a clinical benefit in 61% of the patients with insufficient response to the standard dose of omalizumab.

#### TO THE EDITOR:

Omalizumab, a monoclonal anti-IgE antibody, is an effective and safe treatment option in patients with chronic spontaneous urticaria who respond poorly to 4-fold standard-dose antihistamines.<sup>1</sup> The recommended dose of omalizumab is 300 mg every 4 weeks.<sup>1</sup> In our center, patients with insufficient response to 300 mg omalizumab are administered with an increased dose. However, the effectiveness thereof is insufficiently investigated. The objective of this retrospective daily practice cohort study was to assess the effectiveness and safety of the referred-to treatment strategy.

Data of all patients diagnosed with chronic urticaria and treated with omalizumab in our department (February 2012–October 2018) were collected. According to the drug label and International and Dutch guidelines,<sup>1,2</sup> all patients were initially treated with omalizumab 300 mg every 4 weeks. On the basis of our local protocol, to patients with insufficient response (weekly Urticaria Activity Score [UAS7] > 16, Urticaria Control Test [UCT] score < 11, and/or moderate to severe angioedema) after 5 injections, updosing is offered. Subsequently, the omalizumab dose was increased to 450 mg or 600 mg every 4 weeks. If treatment response was still insufficient after 3 doses of 600 mg omalizumab, treatment interval could be shortened to 2 weeks. Omalizumab was discontinued in cases in which 2 consecutive doses of 600 mg at 2-week interval yielded insufficient response.

Treatment response was assessed using urticaria disease activity scores, UAS7 and UCT,<sup>3</sup> before the first administration (baseline-T0), before updosing omalizumab (baseline-HD), and at the end of high-dose (HD) treatment (T-end-HD). Response was defined as improvement in disease activity by a minimal important difference of 10 UAS7 points or, if UAS7 was not available, 3 UCT points.<sup>4,5</sup> Complete response was defined as UAS7 = 0 or UCT score = 16. Treatment response and side effects were compared before and after updosing omalizumab.

This study was approved by the Medical Ethic Review committee (METC-Utrecht no. 18-557).

A total of 166 patients (mean age, 42 years; 73% females) were treated with omalizumab. A total of 122 patients (73%) received a standard dose (300 mg) and 44 patients (27%) a higher dose of 450 mg (n = 11) or 600 mg (n = 33). In 9 patients, treatment interval was additionally shortened to 3 or 2 weeks during HD treatment, resulting in an effective dose higher

than 600 mg every 4 weeks. Patient and treatment characteristics did not differ significantly between patients treated with standard-dose and HD omalizumab (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). All patients confirmed compliance to antihistamines 4 times a day at start and during HD treatment.

Higher doses of omalizumab were introduced after a mean of 8.3 administrations of standard dose (interquartile range [IQR], 5–9). UAS7 scores showed a significant improvement on comparing UAS7 before dose increase (median, 20.0; IQR, 10.5–26.0) to end of HD treatment (median, 4.3; IQR, 0–14.0) ( $P < .0001$ ) (Figure 1).

Treatment response after updosing compared with standard dose based on UAS7 scores could be calculated for 41 of the 44 patients (Table I). Three patients with missing UAS7 and UCT score were classified as nonresponders, on the basis of information from their individual records. Sixty-one percent (n = 27) of the patients showed an improved treatment response after updosing, of which 32% (n = 14) showed a complete and 30% (n = 13) a partial response, whereas 17 patients did not improve upon updosing. Seven patients who became complete responders on HD were nonresponders on standard dose, 5 complete responders were partial responders on standard dose, and in 2 cases of complete response, exact data regarding treatment response on standard dose were missing. Analysis, including multiple testing correction, of all available baseline variables showed no significant predictors of response to HD omalizumab. In 9 patients

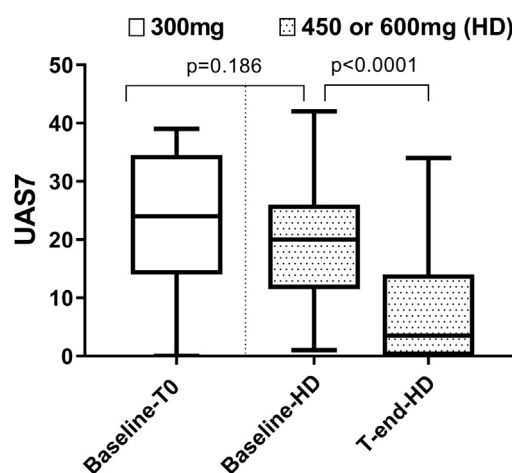


**FIGURE 1.** Urticaria activity in patients with HD treatment. Urticaria activity based on UAS7 scores of patients receiving HD treatment (n = 44) is presented. White box-plot: Baseline-T0: before start of omalizumab 300 mg; median UAS7 = 24 (IQR, 14.0–34.50); dotted box-plot: Baseline-HD: before start of HD omalizumab (450 or 600 mg); median UAS7 = 20 (IQR, 11.25–26.0); T-end-HD: at the ends of HD treatment; median UAS7 = 3.3 (IQR, 0.0–14.0). If symptom scores were missing, data of a maximum of 4 weeks away were used. Missing UAS7 scores at baseline, baseline-HD, and T-end-HD, respectively: n = 15, n = 7, n = 6.

**TABLE I.** Treatment response to standard-dose and HD treatment

| Treatment response based on UAS7 and UCT score* | Standard dose       | HD                 |
|-------------------------------------------------|---------------------|--------------------|
| Complete responders                             | 0 (0)               | 14 (32)            |
| Partial responders                              | 13 (30)             | 13 (30)            |
| Nonresponders                                   | 23 (52)             | 14 (32)            |
| Missings                                        | 8 <sup>†</sup> (18) | 3 <sup>‡</sup> (7) |

Values are n (%).

Clinical response in patients treated with HD omalizumab (n = 44) is presented.

Response to standard dose (300 mg) was determined by comparing UAS7 between baseline-T0 and baseline-HD (before updosing).

Response to HD is determined by comparing UAS7 between baseline-HD and T-end-HD. Complete response: UAS7 = 0; partial response: minimum reduction of 10 UAS7 points; nonresponse: no UAS7 reduction or <10 UAS7 points.

If UAS7 was missing, response was calculated using UCT score; complete response: UCT score = 16; partial response: minimum raise of 3 UCT points; nonresponse: no UCT score raise or <3 UCT points.

\*The UCT score was used to determine treatment response for 10 patients for standard-dose treatment and for 4 patients for HD treatment.

<sup>†</sup>Patient records of 8 patients with missing data were studied, but no valid estimation of response could be made.

<sup>‡</sup>Three patients without clinical activity scores showed no treatment response according to their patient record and were defined as nonresponders.

with interval frequency shortening during HD (600 mg) omalizumab treatment, no additional clinical improvement was observed. The HD nonresponder group (n = 17) received a median of 3 doses (IQR, 1-12.5) of HD omalizumab before stopping treatment.

Although HD omalizumab treatment up to 600 mg/2 wk, based on body weight and total IgE, is a regularly applied approach in patients with asthma,<sup>6</sup> this therapeutic approach is rarely applied in chronic urticaria.

A small number of recent studies with lower patient numbers, describing the strategy of omalizumab updosing in patients with chronic spontaneous urticaria, showed a comparable percentage (23%) of patients using higher doses<sup>7,8</sup> as observed in our study and also described the effect of updosing omalizumab, with complete or partial responses ranging from 45% to 83%.<sup>7-9</sup> These were, however, analyzed by comparing disease activity before starting omalizumab treatment and at the end of HD treatment, which was comparable to 72% in our population. Importantly, we analyzed the additional effect of updosing by comparing the effect of standard dose to HD and observed relevant improvement in 61% of patients, which had not been depicted before. Additional updosing of omalizumab by interval shortening did not show clinically relevant improvement. However, higher patient numbers are needed to validate this initial finding.

The most frequently reported side effects during HD treatment were headache, fever-like sensations, and tiredness, which were not increased compared with standard treatment.

Likewise, higher doses of omalizumab are well tolerated in patients with asthma.<sup>6</sup>

In conclusion, updosing omalizumab led to an additional clinical improvement in 61% of the patients without reporting additional side effects. Further studies are needed to determine the best strategy for updosing omalizumab in patients who do not respond to the standard treatment of chronic spontaneous urticaria.

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Conflicts of interest: A. C. Knulst is a member of Advisory Board for Novartis and has received health care innovation grant from Novartis to his institution. H. Röckmann is a member of National Advisory Board for Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 29, 2019; revised September 17, 2019; accepted for publication October 13, 2019.

Available online ■■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.10.018>

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## ONLINE REPOSITORY

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

| Characteristic                                  | Total (N = 166) | Standard dose (n = 122) | HD (n = 44)     |
|-------------------------------------------------|-----------------|-------------------------|-----------------|
| Sex: female, n (%)                              | 121 (73)        | 88 (72)                 | 33 (75)         |
| Age (y), mean $\pm$ SD*                         | 41.6 $\pm$ 14.9 | 42.1 $\pm$ 15.6         | 40.3 $\pm$ 12.8 |
| Disease duration (y), median (IQR 25-75)†       | 2.27 (1-5)      | 2.20 (1-5)              | 2.33 (1-6)      |
| Main diagnosis, n (%)                           |                 |                         |                 |
| CSU-wheals                                      | 129 (78)        | 96 (79)                 | 33 (75)         |
| CSU-AE                                          | 25 (15)         | 17 (14)                 | 8 (18)          |
| CindU                                           | 12 (7)          | 9 (7)                   | 3 (7)           |
| Comorbidity, n (%)‡                             |                 |                         |                 |
| CSU-wheals                                      | 24 (14)         | 16 (13)                 | 8 (18)          |
| CSU-AE                                          | 83 (50)         | 61 (50)                 | 22 (50)         |
| CindU                                           | 39 (23)         | 30 (25)                 | 9 (20)          |
| Immunosuppressive while start omalizumab, n (%) | 76 (46)         | 50 (41)                 | 26 (59)         |
| Prednisone                                      | 47 (28)         | 33 (27)                 | 14 (32)§        |
| Baseline median disease activity score  , ¶     |                 |                         |                 |
| UAS7                                            | 26 (17-34)      | 26 (17-34)              | 24 (13-33.75)   |
| UCT                                             | 5 (3-7)         | 5 (3-7)                 | 4.5 (2-7)       |
| AAS                                             | 26.5 (9.25-45)  | 32 (14-51)              | 7 (1-37.75)     |
| T-end#, ** median activity score                |                 |                         |                 |
| UAS7                                            | 1 (0-5)         | 0 (0-4)                 | 2.5 (0-16.25)   |
| UCT                                             | 13.5 (9-16)     | 15 (11-16)              | 11 (7-16.00)    |
| AAS                                             | 0 (0-1)         | 0 (0-0)                 | 2 (0-9.5)       |

Because of rounding, percentages may not add up to 100%.

AAS, Angioedema Activity Score; AE, angioedema; CindU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria.

\*At start of treatment.

†Disease duration in years before start of omalizumab treatment.

‡Comorbidity subordinate to main diagnosis.

§Eight of the 14 patients who used prednisolone when omalizumab treatment was initiated also used prednisolone during HD omalizumab treatment varying between a single dose, short course, or longer low-dose course with a tapering schedule.

||Score before first administration of omalizumab, median (IQR 25-75).

¶Data available for, respectively, 107, 136, and 16 patients.

#At the end of data collection (data lock) or end of treatment (T-end), median (IQR 25-75).

\*\*Data available for, respectively, 147, 154, and 80 patients.