

Clinical Communications

Effectiveness and tolerability of personalized omalizumab treatment in patients with chronic inducible urticaria

Thomas P. Buters, MD^{a,b},

Willemijn A.C. van der Velden, BSc^a,

Ismahaan Abdisalaam, MD^{a,b}, Maurits S. van Maaren, MD^c,
and Martijn B.A. van Doorn, MD, PhD^{a,b}

Clinical Implications

- Our results indicate that updosing of omalizumab is well-tolerated and can improve the clinical benefit in chronic inducible urticaria patients with a suboptimal response to omalizumab at the standard dosing regimen.

In chronic inducible urticaria (CIndU), clinical symptoms can be elicited by specific triggers.¹ The pathogenesis of CIndU is not fully understood, but mast cells releasing various inflammatory mediators have a key role.² Omalizumab is currently licensed only for the treatment of chronic asthma and chronic spontaneous urticaria (CSU). Consequently, published evidence of omalizumab in CIndU is limited to small case series and randomized controlled trials evaluating the standard dosing regimen (300 mg/4 wk).³ For CSU, there is increasing evidence that updosing of omalizumab is effective in patients who are unresponsive to the standard dose.^{4,5} At our center, antihistamine refractory CSU and CIndU patients with high disease activity are treated with omalizumab using a personalized

treatment approach that includes updosing.⁶ The aim of this retrospective study was to evaluate the effectiveness and tolerability of this personalized treatment approach in various CIndU subtypes.

Patients included in this report were provided with a diagnosis of CIndU; they were aged greater than 18 years and were given omalizumab as add-on treatment to oral antihistamines. Patients with CIndU and comorbid CSU were included unless the CSU-related symptoms were predominant. To measure the effectiveness of omalizumab treatment, we used the Urticaria Control Test (UCT), a validated patient-reported outcome measure for both CSU and CIndU.⁷ The UCT questionnaire is composed of four questions about the control of urticaria; every answer is given a score from zero to four. Therefore, the outcome of the questionnaire can vary from zero to 16, in which zero indicates no control and 16, complete control. The UCT scores were divided into four categories of no control (UCT 0-4), partial control (UCT 5-11), good control (UCT 12-15), and complete control (UCT 16). Data were collected for up to 1 year after the start of omalizumab treatment. Patients received three administrations of the standard dose of 300 mg omalizumab with a 4-week interval. After 12 weeks, based on the UCT score and in communication with the patient, it was decided whether the dose or dosing interval should be adjusted.

A total of 44 CIndU patients were included. The CIndU subtypes included delayed pressure (13 patients), cholinergic (12 patients), symptomatic dermographism (eight patients), cold (six patients), heat (four patients), and aquagenic urticaria (one patient). Before omalizumab, 31 patients had no disease control and 13 had partial control. Four weeks after the first three standard doses (T = 12 weeks), six patients achieved complete control (14%), 16 had good control (36%), 14 had partial

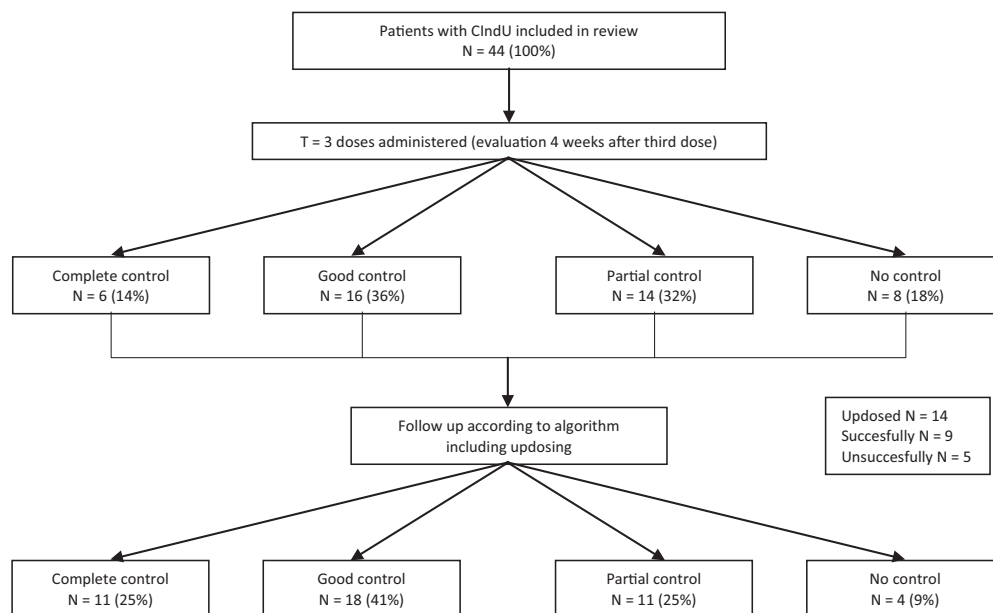


FIGURE 1. Flowchart of patients with chronic inducible urticaria (CIndU) treated with omalizumab according to the personalized treatment approach.

TABLE 1. Overview of clinical response per subtype after three standard administrations of 300 mg omalizumab per 4 wk (T = 12 wk) and response after dose escalation during personalized follow-up phase, which could include up dosing up to 450 mg/4 wk or 600 mg/4 wk

Subtype	Patients, n	Response after three standard administrations					Response after personalized follow-up				
		No control	Partial control	Good control	Complete control	No control	Partial control	Good control	Complete control	Including up dosing	Up dosing successful*
Delayed-pressure	13	0	5	4	4	0	3	5	5	2/13	0
Cholinergic	12	2	4	5	1	0	4	7	1	5/12	4
Symptomatic dermatographism	8	2	3	2	1	2†	2	1	3	4/8	2
Cold	6	2	1	3	0	1‡	2	2	1	1/6	1
Heat	4	2	0	2	0	1§	0	2	1	1/4	1
Aquagenic	1	0	1	0	0	0	0	1	0	1/1	1
Total	44	8	14	16	6	4	11	18	11	14	9

*Successful up dosing was defined as an improvement of at least one Urticaria Control Test category.

†One patient was lost to follow-up after three standard doses; one remained in the follow-up phase.

‡Still in the follow-up phase.

§Patient was lost to follow-up after three standard doses.

control (32%), and eight had no control of urticaria (18%) (Figure 1). Subsequently, all patients continued omalizumab treatment according to the personalized treatment algorithm. Not all patients who were eligible for up dosing chose to do so; 14 of 38 patients who had not reached complete control were up dosed (37%) (Table 1). After dose escalation, 11 patients achieved complete control (25%), 18 had good control (41%), 11 had partial control (25%), and four had no control of urticaria (9%). Of the 14 patients who were up dosed, nine showed significant benefit, meaning that the UCT score improved by at least one category. Of the four patients who still had no response, two were lost to follow-up after the three standard doses and two remained in the process of being up dosed. Nine patients were able to extend the omalizumab interval successfully up to 6 or 7 weeks; four of those nine patients were able to discontinue omalizumab treatment after reaching an 8-week interval. However, three of those patients experienced a relapse within 12 weeks after discontinuation. In all three patients, omalizumab was restarted and the symptoms quickly responded to retreatment.

Of the CIndU subtypes investigated, delayed-pressure urticaria (DPU) was the most prevalent (in 13 of 44 patients) and showed the best response (Table 1). After the first three administrations, four DPU patients reached complete control, four achieved good control, five patients had partial control, and no patients experienced no control. After personalized follow-up, 10 of the 13 DPU patients had completely or well-controlled disease.

Adverse effects after the start of omalizumab treatment were reported by 32 of 44 patients. All were minor; fatigue, headache, arthralgia, and weight gain were most frequently reported. Among the 14 patients who were up dosed, only three experienced new adverse effects (headache). Up dosing did not result in aggravation of preexisting adverse effects. Nevertheless, anticipated adverse effects had a role in shared decision-making regarding whether to up dose. Some patients thought that a partial or major response achieved with the standard dosing regimen was already such a major improvement that they were reluctant to up dose with the possibility of aggravation of adverse effects (notably weight gain). Although it is questionable whether weight gain is truly attributable to omalizumab treatment,⁸ and this was explained to patients, some chose to remain on the current dose. Based on our results, there does not appear to be a clear dose-dependent relationship regarding the occurrence or aggravation of adverse effects.

The strength of this study is that patients were treated in a real-life setting; nevertheless, the study design had some limitations. The outcome measure used in this study (UCT) is a subjective outcome measure, the data were collected retrospectively, and therefore no control group was included. However, we believe that these findings are valuable and could serve as a starting point for randomized controlled trials evaluating personalized dosing regimens of anti-IgE monoclonal antibodies compared with the standard regimen in CIndU patients.

The results of our retrospective analysis strengthen the conclusion of Maurer et al,³ who conducted a systematic review on the treatment effect of omalizumab in various CIndU subtypes and concluded that a growing body of evidence encourages the use of omalizumab in CIndU patients who are unresponsive to antihistamine therapy. Even more so, we provide

evidence that updosing of omalizumab can be beneficial for CIndU patients who are unresponsive to the standard dose. Furthermore, our results may support physicians who want to apply for omalizumab reimbursement for patients with therapy-resistant CIndU.

^aDepartment of Dermatology, Urticaria Center of Reference and Excellence, Erasmus Medical Center, Rotterdam, the Netherlands

^bCentre for Human Drug Research, Leiden, the Netherlands

^cDepartment of Allergology, Urticaria Center of Reference and Excellence, Erasmus Medical Center, Rotterdam, the Netherlands

Conflicts of interest: Dr van Doorn reports personal fees from Leopharma, grants and personal fees from Novartis, personal fees from Abbvie, personal fees from BMS, personal fees from Celgene, personal fees from Lilly, personal fees from MSD, personal fees from Pfizer, personal fees from Sanofi-Genzyme, and personal fees from Janssen Cilag, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Martijn B. A. van Doorn, MD, PhD, Department of Dermatology, Erasmus Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. E-mail: m.b.a.vandoorn@erasmusmc.nl.

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