Clinical Communications

Age and fast initial response predict omalizumab retreatment in chronic urticaria

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Clinical Implications

We found that omalizumab can be discontinued to reveal disease remission and avoid drug exposure in patients with chronic urticaria. Higher age and fast initial response predict the need for retreatment and can be used to counsel patients in clinical practice.

Omalizumab, a monoclonal anti-IgE antibody, is an effective and safe add-on treatment in patients with chronic spontaneous urticaria (CSU) with insufficient response to a 4-fold dose of second-generation antihistamines.[1] In daily practice, omalizumab treatment protocols differ between centers and countries with regard to dose escalation, prolongation of dosing intervals, and stopping criteria. Little is known about the treatment-free intervals after discontinuation of omalizumab when the disease is well controlled and the determinants that predict the need to restart treatment.

The objectives of our study were (1) to analyze the treatment-free period after discontinuation of omalizumab and identify predictors for retreatment and (2) to compare treatment effectiveness and treatment intervals between the first and second treatment episode.

Data concerning patient and treatment characteristics of all patients with chronic urticaria (CU; including all subtypes: CSU, angioedema, and chronic inducible urticaria) on omalizumab treatment (February 2012 to May 2021) in 2 Dutch university centers (University Medical Center Utrecht [UMCU] and Erasmus Medical Center [EMC] Rotterdam) were collected. According to the International and Dutch guidelines,[1,2] all patients showed insufficient response to high-dose antihistamines and were initially treated with omalizumab 300 mg every 4 weeks. After 3 (EMC Rotterdam) and 6 (UMCU) administrations, respectively, treatment intervals in patients with well-controlled disease (Urticaria Activity Score [UAS7] $\leq$6 or Urticaria Control Test [UCT] $\geq$12) were gradually increased within 1 week. Treatment was discontinued in symptom-free patients with an 8-week treatment interval or in patients with insufficient response or side effects.[3] Patients with relapse of symptoms could restart omalizumab with the steady-state interval of the first treatment period, which was subsequently gradually prolonged. The steady-state interval was defined as the longest well-controlled (UCT $\geq$12 or UAS $\leq$6) treatment interval achieved on at least 2 consecutive administrations.[3,4]

To eliminate potential bias due to a too short treatment period, patients with a follow-up period of $\leq$14.5 months after the initial start of omalizumab were excluded. Patients with a follow-up period of $\leq$6 months after the start of the second treatment period were excluded from comparative analyses of effectiveness and steady-state interval between treatment episodes.

We identified 633 patients with CU who had received omalizumab treatment. A total of 142 patients were excluded (treatment $\leq$14.5 months) and 492 patients (mean age 41 years; 71% female) were included. At data lock, 204 patients (41.5%) were continuously treated. A total of 288 patients (58.5%) discontinued omalizumab after the first treatment period, of whom 116 (40.3%) restarted omalizumab treatment with a median treatment-free period of 4.4 months (minimum-maximum: 1.8-54.5 months).

Patient and treatment characteristics were comparable between the 2 centers and other daily practice populations (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).[5] The treatment-free period after discontinuation of the first treatment period was analyzed by survival analysis. The 1-, 2-, 4-, and 7-year treatment-free survival rates were 66%, 58%, 54%, and 52%, respectively (Figure 1). By Cox regression multivariate analysis, higher age and fast initial treatment response (UAS7 $\leq$6 or UCT $\geq$12 within 1 month of treatment) were identified as predictors for a shorter treatment-free period (Figure 2). Of patients who restarted, total percentages of patients who achieved complete, good, partial, or poor response did not differ significantly between the 2 treatment episodes (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The majority of patients (88.1%) achieved equal or better effectiveness in the second treatment episode. Of patients with a good or complete response in the first treatment period, 90.1% again achieved a good or complete response. Of patients with an initial partial or poor response (n = 16), 44 % (n = 7) achieved a good or complete response in the second treatment period. Only 8 patients (7.9%) achieved a worse response during the second treatment episode (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The mean steady-state treatment interval in the second treatment period was significantly longer (8.1 weeks) compared with the first period (7 weeks; $P = .002$). A total of 88.2% of patients (n = 82) showed an equal or longer steady-state interval in the second treatment period compared with the first.

In this study, we display the omalizumab-free survival rates after 1 to 7 years and show that only few patients need to restart omalizumab after a 1-year treatment-free period. A recent study by Di Bona et al[6] (n=137) also demonstrated long-term remission after discontinuation of omalizumab treatment in approximately 50% of patients with a follow-up period of up to 4 years. In this study, age above 60 years, high wheal score, and longer treatment duration were independent predictors for disease relapse after omalizumab treatment discontinuation.

We also found higher age as an independent predictor for omalizumab retreatment, which might be explained by immunosenescence mechanisms, needing further investigation. In addition, we identified fast treatment response as an independent predictor for

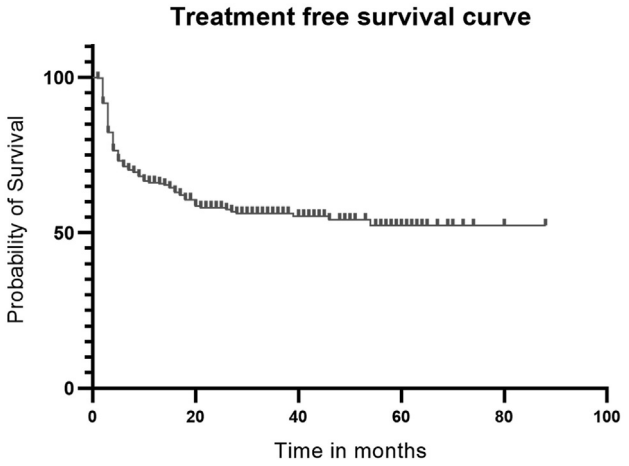
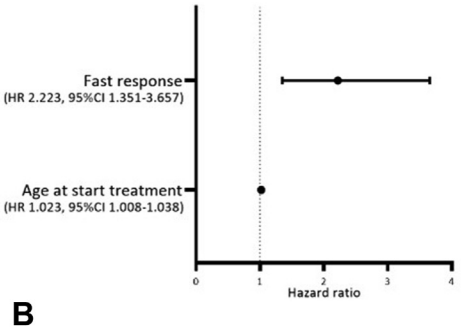


FIGURE 1. Treatment-free survival after discontinuation of the first omalizumab treatment period. Kaplan-Meier curve representing treatment-free period survival, analyzing the time between the last administration of the first treatment period and the first administration of the second treatment period.

Characteristic	P-value	Hazard ratio (95% CI)
Female sex	0.511	0.873 (0.583-1.308)
Disease duration > 2 years prior to OMA	**0.073**	**1.409 (0.969-2.049)**
Age at start treatment (scale, higher)	**0.004**	**1.016 (1.005-1.027)**
Autoimmune disease	0.512	0.854 (0.532-1.370)
Mean UAS7 at baseline (scale, higher)	**0.122**	**1.019 (0.995-1.043)**
Fast response	**<0.001**	**2.188 (1.432-3.344)**
Spontaneous wheals as main diagnosis	0.737	0.911 (0.529-1.569)
Angioedema as main diagnosis	**0.040**	**1.831 (1.027-3.265)**
CindU as main diagnosis	**0.095**	**0.303 (0.075-1.228)**
Time-on-OMA	0.640	0.996 (0.981-1.012)

A



B

FIGURE 2. Predictors of time to restart after discontinuation of the first omalizumab (OMA) treatment period. (**A**) Characteristics that were deemed relevant were analyzed in a univariate Cox regression analysis. Candidate predictors with a *P* value of $\leq$.2 (marked in bold) were used in the multivariate Cox regression analysis with backward selection. (**B**) Determinants with a *P* value of $<$.05 were considered statistically significant and were identified as independent predictors of time to restart . *CI*, Confidence interval; *CindU*, chronic inducible urticaria; *UAS7*, Urticaria Activity Score.

omalizumab retreatment. Patients with a fast response, according to our treatment algorithm, will quickly initiate interval prolongation with subsequent early discontinuation, potentially leaving less time for "true" disease remission and therefore have a higher chance of relapse. This theory might be supported by the finding that within patients who discontinued omalizumab due to well-controlled disease, the treatment duration was shorter in patients who restarted (median 12 months) than in patients who did not restart omalizumab (median 14 months) (strong trend; $P = .053$). Our findings suggest that some delay in discontinuation in patients with a fast response might be reasonable.

Our data also show that omalizumab is equally or more effective in a second treatment period compared with the first period in the majority of patients with equal or longer dosing intervals, on population and individual level. A few small studies have compared the effectiveness of the first and second omalizumab treatment episodes and showed comparable percentages of patients with a good or complete response.[5]

In conclusion, these data provide important real-world practice information demonstrating that omalizumab can be effectively discontinued to reveal disease remission and avoid unnecessary drug exposure. In addition, we found higher age and a fast initial treatment response to be important determinants for the need to restart omalizumab treatment. These findings are of great value for patient counseling when discontinuing omalizumab in clinical practice.

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TABLE E1. Characteristics and disease activity of patients with CU

Characteristic	Total (N = 492)	CT* (N = 204)	Stop-NR† (N = 172)	Restart-E1‡ (N = 116)	Restart-E2§ (N = 116)	*P* value S-NR/restart-E1
Female, n (%)	355 (72.2)	148 (72.5)	124 (71.6)	83 (73.3)	n.a.	.920
Age at start treatment (y) (mean ± SD)	42.1 ± 15.7	42.3 ± 14.7	39.6 ± 15.9	45.5 ± 16.4	n.a.	.003**
CU duration (y), n (%)					n.a.	.044**
<1	70 (14.2)	23 (11.3)	29 (16.9)	18 (15.5)		
1-2	88 (17.9)	37 (18.1)	36 (20.9)	15 (12.9)		
2-5	98 (19.9)	45 (22.1)	29 (16.9)	24 (20.7)		
>5	146 (29.7)	64 (31.4)	44 (25.6)	37 (31.9)		
Subtype CU, n (%)					n.a.	.029**
CSU-wheals	416 (84.6)	166 (81.4)	149 (86.6)	101 (87.1)		
CSU-AE	40 (8.1)	17 (8.3)	10 (5.8)	13 (11.2)		
CindU	36 (7.3)	31 (10.3)	13 (7.6)	2 (1.7)		
UAS7						
T-Baseline‖	27 (0-42); M¶: 167	27 (0-42); M: 74	25 (0-42); M: 54	29.6 (0-42); M: 39	23.6 (0-42); M: 68	.040**
UCT						
T-Baseline‖	4 (0-16); M: 138	4 (0-16); M: 48	4 (0-16); M: 56	5 (0-16); M: 34	4 (0-16); M: 59	.663
Treatment response#, n (%)						
Complete				56 (55.4)	49 (48.5)	n.a.
Good				28 (27.7)	31 (30.7)	n.a.
Partial				7 (6.9)	11 (10.9)	n.a.
Poor				9 (8.6)	7 (6.9)	n.a.
Missing				1 (1.0)	3 (3.0)	n.a.

CindU, Chronic inducible urticaria; *CSU-AE*, chronic spontaneous urticaria angioedema; *CU*, chronic urticaria; *n.a.*, not applicable; *SD*, standard deviation; *UAS7*, Urticaria Activity Score; *UCT*, urticaria control test.
*CT: continuous treatment of omalizumab.
†Stop-NR: patients stopped omalizumab and did not restart.
‡Restart-E1: first episode of omalizumab treatment for restart patients.
§Restart-E1: second episode of omalizumab treatment for restart patients.
‖T-baseline: start of omalizumab.
¶M: number of missing values.
#Comparison of response between the first and second treatment period on group level (Wilcoxon signed-rank test) (*P* value = .331).
**Significant difference between S-NR and restart-E1 ($P < .05$).

TABLE E2. Response in the first and second omalizumab treatment episode

	Second treatment episode				
First treatment episode	Complete	Good	Partial	Poor	Total
Complete	36	15	2	1	56
Good	9	13	3	2	28
Partial	2	2	3	0	7
Poor	2	1	2	4	9
Total	49	31	11	7	

Patients with restart omalizumab and follow-up of >6 months after the start of the second treatment period are analyzed (n = 100).
Complete response = Urticaria Activity Score [UAS7] 0 at end; good response = 0 < UAS7 ≤ 6 at end; partial response = UAS7 reduction ≥10; and poor response = UAS7 reduction <10.
Comparison of response between the first and second treatment period on patient level: κ: 0.295.