

BRIEF REPORT

Remission of chronic spontaneous urticaria following omalizumab with gradually extended dosing intervals: Real-life data

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ABSTRACT

Omalizumab is a well-established treatment option in chronic spontaneous urticaria unresponsive to antihistamines at standard or higher doses. However, characteristics of the remission and relapse following the withdrawal of omalizumab remain largely unknown. We aimed to define the characteristics of remission in CSU following omalizumab with gradually lengthened dosing intervals in this retrospective study of 102 patients who were treated with at least 3 doses of omalizumab between 2013 and 2020. Of 102 patients, 70 (68.6%) showed a CR to omalizumab at standard doses. Omalizumab could be discontinued in 47 of 70 patients using gradually lengthened dosing intervals. Following a mean follow-up duration of 12.2 months, 25 (58.1%) patients were still in remission while 18 (41.9%) had relapse (Follow-up data were not available in 4 patients). The relapses were unresponsive to antihistamines in 14 patients (77.7%), however, re-treatment with omalizumab led to complete control of symptoms. The patients younger than 40 were more likely to relapse. Despite the need for comparison with fixed-dosing intervals in larger, prospective studies, the results of this study imply that omalizumab with gradually extended dosing

intervals might provide a long duration of remission in CSU.

Key words: chronic spontaneous urticarial, omalizumab, recurrence, remission.

LEARNING POINTS

- A higher rate of relapse was demonstrated in patients younger than 40 years, hence a closer follow-up plan might be prudent in this group of patients.
- Following gradually extended dosing intervals and discontinuation of omalizumab, 58.1% of the patients maintained remission at 14.9 months
- The relapses following omalizumab treatment are often unresponsive to antihistamines, however, can be managed with omalizumab re-treatment in the majority of the patients.

INTRODUCTION

The safety and effectiveness of omalizumab in chronic spontaneous urticaria (CSU) have been repeatedly demonstrated in clinical trials and real-life studies.¹ In patients with complete response to omalizumab, treatment can be discontinued either directly or following a gradually extended dosing interval up to 8 weeks.² However, little is known about the characteristics and predictors of remission and relapses following the withdrawal of omalizumab in CSU in real life. This study aimed to investigate the remission/relapse rates and influencing characteristics following omalizumab treatment with gradually extended dose intervals.

REPORT

A retrospective chart review of patients with CSU who had received omalizumab between 2013 and 2020 was

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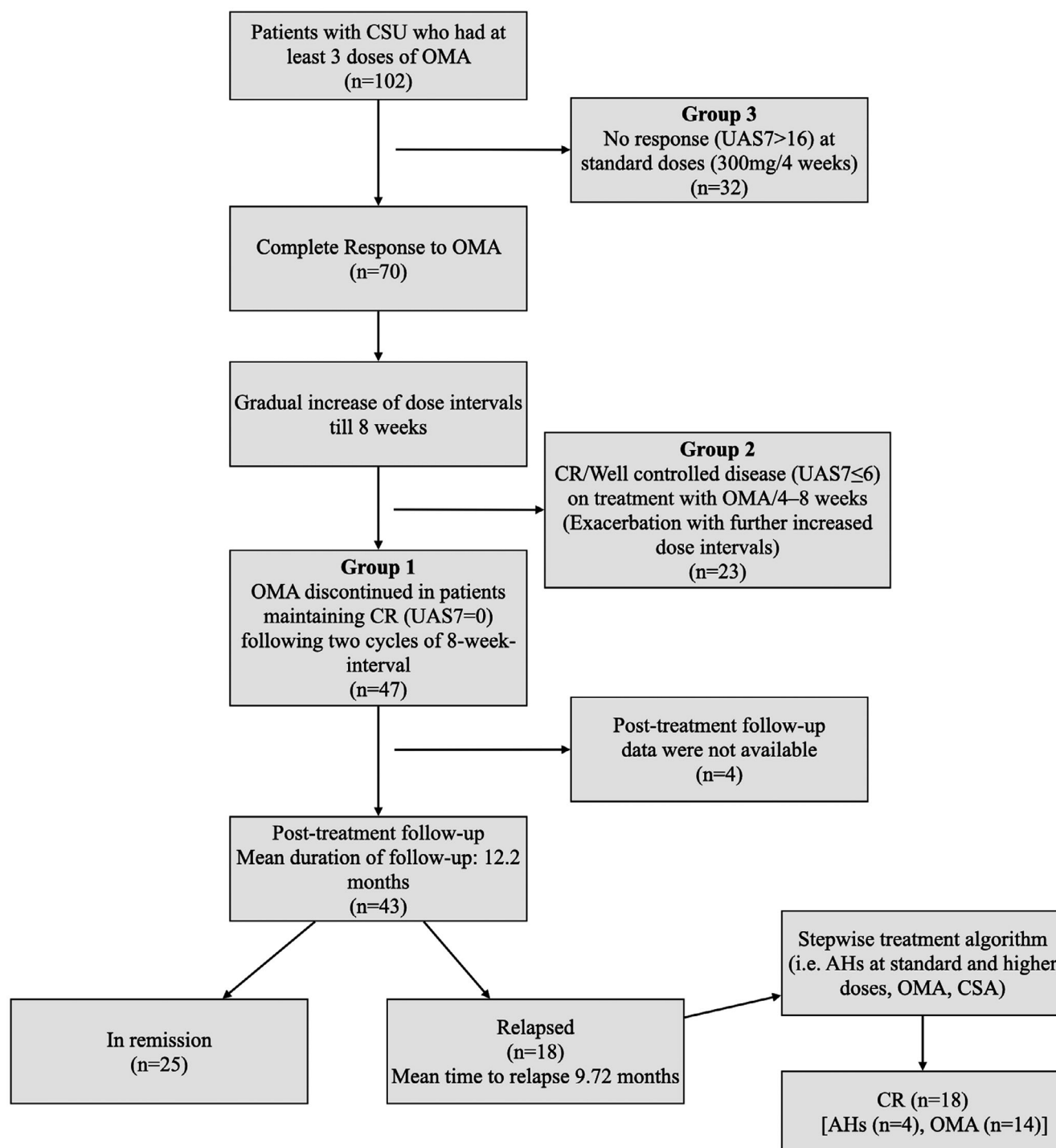


Figure 1 Flow chart of the study. (AH: Antihistamine, CR: Complete response, CSA: ciclosporin, CSU: Chronic spontaneous urticaria, OMA: Omalizumab, UAS7: urticaria activity score over 7 days).

performed. The study protocol was reviewed and approved by the institutional review board (07.02.2020-09.2020.227).

In our referral centre, the dosing intervals are gradually increased by one week after each treatment, unless the patient experiences any relapse during the previous interval, in all patients showing complete response (CR) after

three doses of omalizumab. In patients who experience no exacerbation of disease during two consecutive 8-week intervals, the treatment is withdrawn, as previously proposed.¹ In patients experiencing relapse before eight weeks, the treatment is continued with the maximum dosing interval allowing the maintenance of CR (UAS7 = 0). In

Table 1 The baseline and post-treatment follow-up characteristics of the study group

Characteristics	Baseline (<i>n</i> = 102)			Post-treatment follow-up (<i>n</i> = 45)	
	Group 1 (<i>n</i> = 47) <i>n</i> (%) or mean $\pm$ SD (range)	Group 2 (<i>n</i> = 25)	Group 3 (<i>n</i> = 32)	Remission (<i>n</i> = 25)	Relapse (<i>n</i> = 18)
Age	45.87 $\pm$ 15.40 (16–70)	42.57 $\pm$ 15.61 (20–74)	36.91 $\pm$ 11.64 (17–67)	48.28 $\pm$ 11.48 (25–65)	38.22 $\pm$ 12.46 (16–62)
Gender					
Female	51 (72.1)	15 (65.2)	20 (62.5)	16 (64)	15 (83.3)
Male	12 (27.9)	8 (34.8)	12 (37.5)	9 (36)	3 (16.7)
Personal history of atopy	4 (8.5)	3 (13)	4 (12.5)	3 (12)	1 (5.6)
Duration of disease (months)	32.85 $\pm$ 50.56 (2–360)	51.74 $\pm$ 63.81 (2–240)	46.75 $\pm$ 70.89 (2–240)	26.96 $\pm$ 50.15 (2–240)	37.76 $\pm$ 55.27 (3–240)
Baseline serum total IgE	187.24 $\pm$ 386.58 (6.8–2284)	166.87 $\pm$ 203.3 (7–736)	275.52 $\pm$ 381.98 (0–1446)	109.25 $\pm$ 97.41 (6.8–333)	262.77 $\pm$ 557.3 (12.5–2284)
Baseline D Dimer	0.91 $\pm$ 0.79 (0.14–3.24)	0.66 $\pm$ 0.81 (0.09–3.29)	0.84 $\pm$ 1.41 (0.17–6.6)	0.76 $\pm$ 0.56 (0.19–1.81)	1.01 $\pm$ 0.96 (0.14–3.24)
Baseline CRP	6.39 $\pm$ 5.73 (0.57–22.7)	13.03 $\pm$ 29.55 (0.23–113)	7.2 $\pm$ 18.84 (0.16–88)	6.9 $\pm$ 5.44 (1–15.4)	5.85 $\pm$ 6.41 (0.57–22.7)
Baseline ESR	15.61 $\pm$ 8 (4–34)	22.95 $\pm$ 15.08 (5–60)	17.65 $\pm$ 11.38 (2–47)	15.25 $\pm$ 8.13 (4–33)	14.6 $\pm$ 7.01 (5–28)
Baseline UAS7	26.35 $\pm$ 8.26 (14–42)	25.83 $\pm$ 6.94 (15–41)	27.42 $\pm$ 9.57 (10–42)	28.05 $\pm$ 9.32 (14–42)	22.82 $\pm$ 4.95 (18–35)
Baseline UCT	6.52 $\pm$ 2.53 (0–12)	6.33 $\pm$ 2.37 (2–10)	5.17 $\pm$ 2.88 (1–12)	6.32 $\pm$ 2.92 (0–12)	7 $\pm$ 2 (4–10)
Number of omalizumab treatments until discontinuation				9.86 $\pm$ 3.85 (5–20)	9.85 $\pm$ 6.67 (3–30)
Duration of post-treatment follow-up (months)				12.16 $\pm$ 5.19 (3–22)	12.22 $\pm$ 4.46 (6–24)
Time until relapse (months)				N/A	9.72 $\pm$ 8 (3–24)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation; UAS7, urticaria activity score over 7 days; UCT, urticaria control test.

patients without CR at week 8, the treatment is continued for 6 months. If there is still no CR/well-controlled disease (UAS7 $\leq$ 6), omalizumab up dosing (450/600 mg) or treatment switch to ciclosporin (CSA) is made. The flow chart of the study and patient groups is shown in Fig. 1. The primary objective of the study was to define the characteristics of remission and relapse (UAS7 $>$ 16 at any time point during follow-up) following omalizumab treatment. The secondary objectives were to compare the demographic (age and gender), clinical [duration of disease, smoking status, presence of atopy/autoimmune disease/chronic inducible urticaria/angioedema, previous treatments, baseline UAS7,⁵ urticaria control test (UCT)⁴ scores] and laboratory [baseline total IgE, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and D-Dimer levels] characteristics between these groups.

A total of 102 patients, meeting the above-mentioned response and treatment status criteria, were included in the study [Group 1: 47 (Patients maintaining CR following two-cycles of 8-week interval and discontinued omalizumab), Group 2: 23 (Patients with CR/Well-controlled disease on treatment with omalizumab), Group 3: 32 (Patients with no response to omalizumab at standard doses)]. The comparison of baseline demographic, clinical and laboratory characteristics revealed no significant differences between the three groups. The remission and relapse data were analysed in 45 of the 47 patients in group 1 in whom the post-omalizumab follow-up data were available (Table 1). Following a mean duration of 12.2 months, 25 patients (58.1%) were still in remission. Eighteen patients (41.9%) having a relapse were treated

accordingly with the stepwise treatment algorithm (i.e. AHs at standard and higher doses, OMA, CSA). While antihistamines led to complete response in 4 (22.3%) patients, a re-treatment with omalizumab was required to obtain CR in the remaining 14 (77.7%) patients.

The baseline characteristics and duration of post-treatment follow-up were similar between the patients with recurrent and non-recurrent CSU, except that the patients experiencing relapse were significantly younger (38.22 vs 48.28, $P < 0.05$). A Kaplan–Meier survival analysis indicated that the rate of remission for 24 patients aged >40 years was 64.3% and for the 19 patients aged ≤ 40 years was 24.2%. The log rank test showed a statistically significant difference between the remission rates of two groups ($P = 0.017$). The mean remission times for patients aged >40 and ≤ 40 years were 14.9 and 11.9 months, respectively (Fig. 2).

DISCUSSION

The present study demonstrates that in patients who discontinued omalizumab with gradually extending dosing intervals following a complete response, 58.1% maintained the remission at 14.9 months. An earlier study with fixed-dosing intervals has reported lower remission rates (39–39.8%) compared to the present data.⁵ Another study, using a similar tapering schedule to ours, has reported a remission rate of 58% which is comparable to our findings.⁶ Similarly, in a small series in which the dosing intervals were prolonged depending on the symptoms, the mean optimal dosing interval was 47 days.⁷ Taken

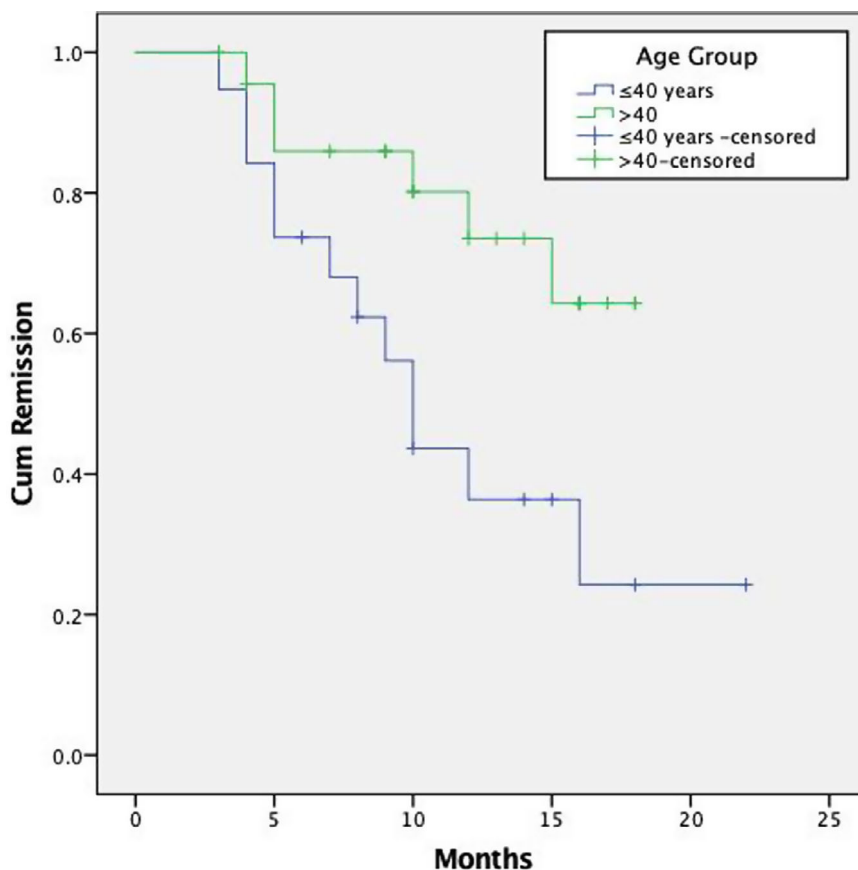


Figure 2 Kaplan–Meier survival analysis of patients aged >40 years vs aged ≤40 years. (The Log Rank test: $P = 0.017$).

together, despite the need for validation in larger prospective studies, these results might indicate that discontinuation of omalizumab following a gradually extended dosing interval might be of benefit for better disease control during treatment and longer maintenance of remission. The comparison of fixed and gradually extended dosing intervals in terms of cost-effectiveness might be of interest for future research.

Previous studies have shown an increased risk of relapse/faster symptom return in patients with a longer duration of CSU, a higher UAS7 score at the baseline or slow response to omalizumab.^{5,8} In contrast to earlier research demonstrating no negative effect of younger age on the prognosis of CSU,⁹ the relapse rates in the present study were significantly higher in younger (≤40 years) patients. Although this finding needs to be tested in prospective studies, a closer follow-up plan for younger patients after withdrawal of omalizumab might be considered. The current study also supports the existing data¹ by showing that re-treatment with omalizumab is effective and required in most of the patients for the adequate control of the relapses.

Although this study failed to show any differences in demographic and disease characteristics of the groups, it would be of interest to investigate the predictors of response and successful discontinuation of

omalizumab in patients with complete response for future studies.

This study is limited by the relatively small sample size and its retrospective design. Also, the heterogeneous and shorter duration of the follow-up period in some of the patients might have understated the relapse rates. Despite these limitations, the current study demonstrates a high remission rate following omalizumab with the use of gradually extended dosing intervals, higher relapse rates in patients younger than 40 years and high effectiveness of re-treatment with omalizumab in case of relapse. These results warrant future, prospective studies investigating the effect of different dosing interval or treatment withdrawal approaches on the duration of remission and relapse rates.

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