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DURATION OF CHRONIC SPONTANEOUS URTICARIA REMISSION AFTER OMALIZUMAB DISCONTINUATION: A LONG-TERM OBSERVATIONAL STUDY.

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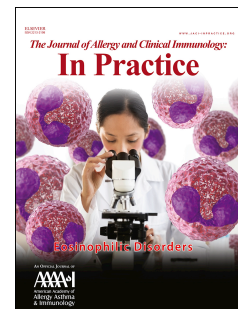
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TITLE: DURATION OF CHRONIC SPONTANEOUS URTICARIA REMISSION AFTER
OMALIZUMAB DISCONTINUATION: A LONG-TERM OBSERVATIONAL STUDY.

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CONFLICTS OF INTEREST

The Authors declare that they have no conflicts of interest.

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28 CLINICAL IMPLICATIONS

29

30 A single course or two consecutive omalizumab courses are associated with long-term CSU
31 remission (≥ 4 years) in about 50% of patients. Planned discontinuation of omalizumab may lead
32 to considerable cost savings and avoid unnecessary drug exposure for patients.

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Omalizumab is highly effective in controlling symptoms in patients with antihistamine-refractory chronic spontaneous urticaria (CSU).¹ However, symptoms can relapse after treatment discontinuation. Daily practice (real-life) data on long-term duration of CSU remission after omalizumab discontinuation are scarce.²

According to the Italian drug regulatory Agency (AIFA), omalizumab can be administered for 24 weeks (300 mg every 4 weeks) in patients with urticaria activity score (UAS) and UAS in the last 7 days (UAS7) >3 and >16 , respectively. Then, after a 8-week discontinuation period, necessary to evaluate a possible relapse, a second 20-week course can be prescribed (Figure E1).³ This strategy, based on a planned omalizumab discontinuation, permits identification of patients who actually need to continue the therapy.

Using this treatment strategy,³ we recently showed that about half of the patients achieved a reasonable symptom control (UAS7 <16) after the first omalizumab course, whereas the other half underwent a second treatment course.⁴ Approximately the same percentage of patients achieved symptom control after the second course.⁴

Here we expand the previous findings, providing data on the duration of CSU remission (post-treatment UAS7 ≤ 6) after omalizumab discontinuation, over an observation period up to 4 years. This retrospective study was conducted according to Good Clinical Practice and in observance of the Declaration of Helsinki and was approved by the local Ethical Committees. Patients were asked for their informed oral consent.

The method of survival analysis (Kaplan-Meier estimator) was used to analyse data on duration of CSU remission. The event was considered the symptom relapse (UAS7 >6) after 1 or 2 consecutive omalizumab courses. Multivariate analysis was based on the Cox proportional-hazards model. Statistical analyses were conducted using R 4.0.2.⁵

In July 2020, patients with CSU from 3 Italian University hospitals (Bari, Foggia, Parma) who had undergone omalizumab treatment were retrospectively evaluated by a structured telephone interview and asked to report their itch intensity and wheal count, completing a UAS7 form.

The study population included 137 adult patients (mean age at baseline 46.5 ± 18.8 years; 66.4% females) with anti-histamine refractory CSU (median duration 12 months; Table E1), who had been successfully treated with either one or two consecutive omalizumab courses, from 2016 to 2019.

Sixty-eight patients did not experience relapse ($UAS7 \leq 6$) at the time of data lock (July 2020) and were considered asymptomatic/paucisymptomatic. The probability of maintaining the clinical response after omalizumab discontinuation was approximately 50% after 1 year and remained relatively stable for up to 4 years (Figure 1).

As shown in Figure 2, the probability of maintaining the treatment response was lower among patients ≥ 60 years, with symptom duration prior to start omalizumab ≥ 22 months, baseline $UAS7$ score < 30 , baseline wheal score ≥ 9 , baseline pruritus score < 15 , and in patients receiving 2 consecutive omalizumab courses. IgE levels (< 45 kU/L) and positive autologous serum skin test were not significantly associated with a higher risk of relapse.

Factors independently associated with significantly elevated hazard ratios for symptom recurrence were: age ≥ 60 years (aHR, 2.02; 95%CI, 1.16-3.52; $P < 0.05$), wheal score ≥ 9 (aHR, 3.90; 95%CI, 1.94-7.83; $P < 0.001$), 2 omalizumab courses (aHR, 2.48; 95%CI, 1.49-4.14; $P < 0.001$). Basal $UAS7 \geq 30$ was associated with a lower hazard ratio for recurrence (aHR, 0.36; 95%CI, 0.20-0.65; $P < 0.001$).

Despite the widespread omalizumab use for CSU in clinical practice, few studies on the duration of symptom remission after treatment discontinuation have been published.²

Our data show that, after a single omalizumab course or 2 consecutive courses, the chance of maintaining symptom remission is approximately 50%, over a long time period (up to 4 years).

The protocol used in Italy is different from protocols used in other Countries, which include tapering attempts, decreasing dosage, prolonging dose intervals and individualized discontinuations.⁶ These strategies stem from the resistance of patients to discontinuing omalizumab abruptly owing to fear of disease recurrence.

Our data showed a 50% chance of recurrence over a long-time period. Furthermore, we and other groups have previously shown that re-treatment with omalizumab, after discontinuation, results in rapid urticaria remission in most patients.^{4,7} Taken together this evidence suggests that planned omalizumab discontinuation can be a safe and (cost-)effective strategy and avoid unnecessary drug exposure in approximately 50% of patients.

Whether and to what extent omalizumab is capable of leading to remission of urticaria or whether it is simply capable of relieving symptoms of a otherwise spontaneously regressing disease is still debated. Benralizumab was recently shown to be effective in CSU, with a benefit lasting after treatment discontinuation.⁸ This prolonged effect may be explained by a modification of the biologic pathways promoting persistent cutaneous inflammation associated with CSU, suggesting that immune-modifying agents, such as benralizumab and omalizumab, may actually play a mechanistic role. A better understanding of patients' endotypes might help to inform more targeted approaches.

High wheal score (≥ 9) was associated with a higher risk of relapse. This is in contrast with the UAS7 effect, since a lower baseline UAS7 score was associated with a higher risk of relapse (as well as a lower pruritus score). This means that pruritus score and wheal score (the two components of UAS7) display opposite directions in predicting the outcome. However, a discrepancy between pruritus score and wheal score in UAS7 is not infrequent. It has been suggested that this may be connected to the location of wheals, which may affect their reporting by the patients.⁹

This consideration may explain why the UAS itch severity sub-scale was found to be more often statistically significantly correlated with both EuroQol-5D and the disease-specific Chronic Urticaria Quality of Life scale than the hives sub-scale.⁹

In conclusion, this study shows that the probability of CSU remission after 1 or 2 omalizumab courses is about 50% over an observation period up to 4 years. We identified different subgroups with variable probabilities and patterns of relapse. However, further studies are needed to select

reliable biomarkers able to predict long-term CSU outcomes in patients who responded to omalizumab. Until then, treatment interruption might be a useful strategy to assess potential remission. That may lead to considerable cost savings and avoid unnecessary drug exposure for patients.

AUTHOR CONTRIBUTION

DDB and LM developed the concept of this study and wrote the protocol. EN, ER, EM, MCN and MA collected the data for the study. MB did the statistical analysis. The first draft of the manuscript was written by DDB and thoroughly revised by MFC and LM.

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FIGURE LEGENDS

Figure 1. Symptom-free overall survival up to 4 years in 137 CSU adult patients after**stopping omalizumab treatment.** The overall symptom-free survival before symptom relapse

was estimated by standard Kaplan-Meier estimator of the survival function. The time to event

(symptom recurrence with $UAS > 6$) was calculated as the number of months from the end of

omalizumab course (4 weeks after the last injection, assuming a drug effects lasting 4 weeks) to

relapse (occurrence of the event). For subjects treated with 2 consecutive omalizumab courses

the event was considered as the symptom relapse after the second omalizumab course. The +

sign indicates right-censored patients (patients who did not experience the event of interest up to

the observation time-point, that was July 2020). These patients remained asymptomatic or

paucisymptomatic ($UAS_7 \leq 6$) for the entire duration of the study (up to July 2020) and were

considered “survivors”.

Figure 2. Symptom free-survival in CSU subgroups of patients after stopping omalizumab.

The symptom-free survival before symptom relapse was estimated by standard Kaplan-Meier

estimator of the survival function. Data were arranged according to age (A), disease (symptom)

duration (B), baseline UAS_7 (C), baseline wheal score (D), baseline pruritus score (E), number

of omalizumab courses (F). The + sign indicates censored data. For the only binary independent

variable (number of omalizumab courses), univariate analysis was conducted comparing the

survival curves of the two subgroups by means of log-rank test. Continuous variables were

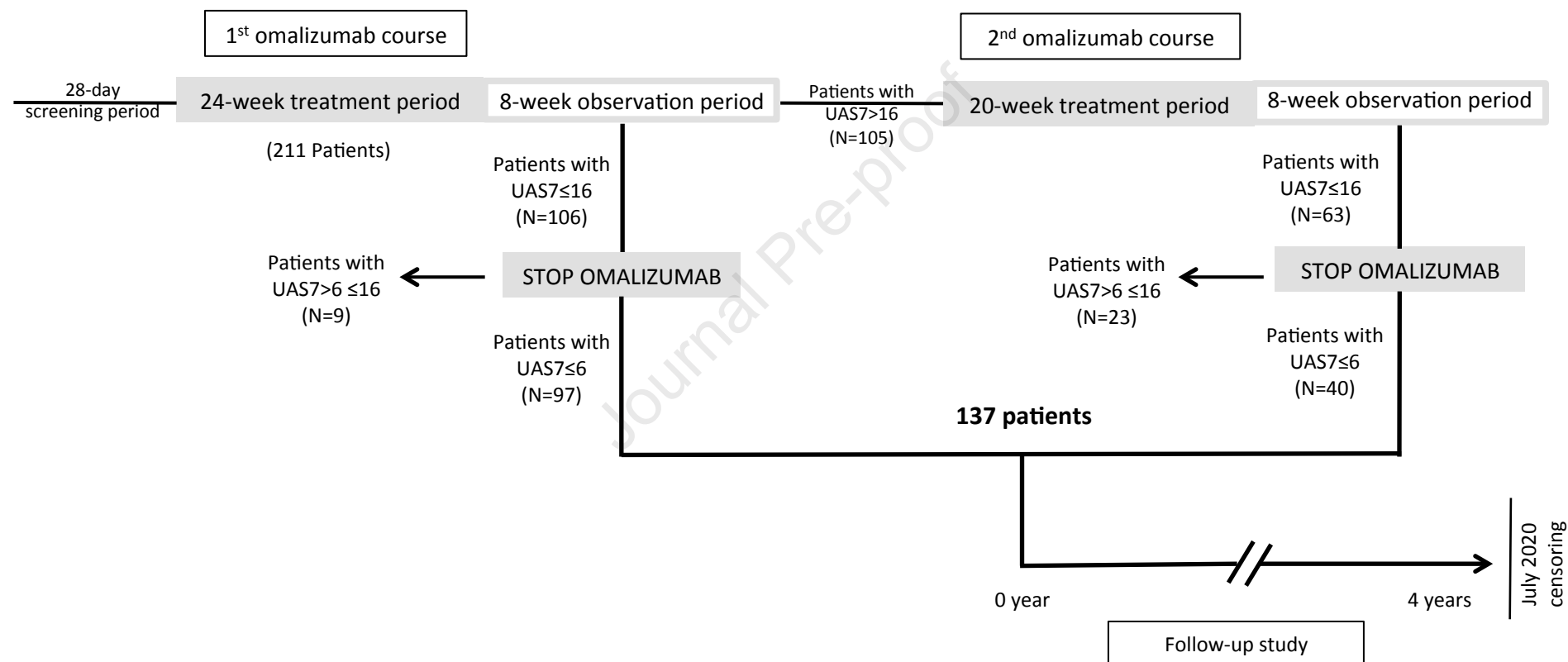
dichotomized determining the optimal cut point that minimized the p-value of the log-rank

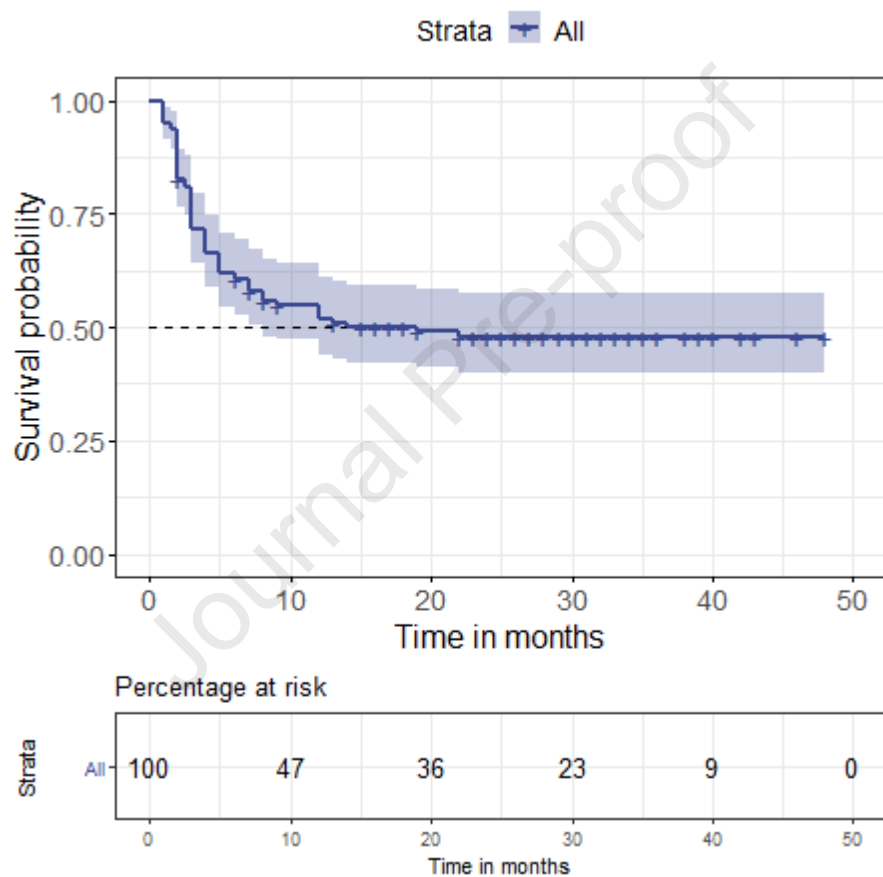
statistics between the two subgroups, suitably adjusted for multiple testing.

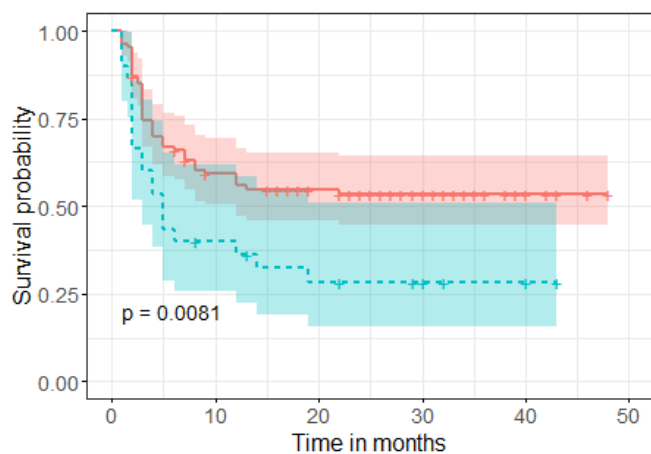
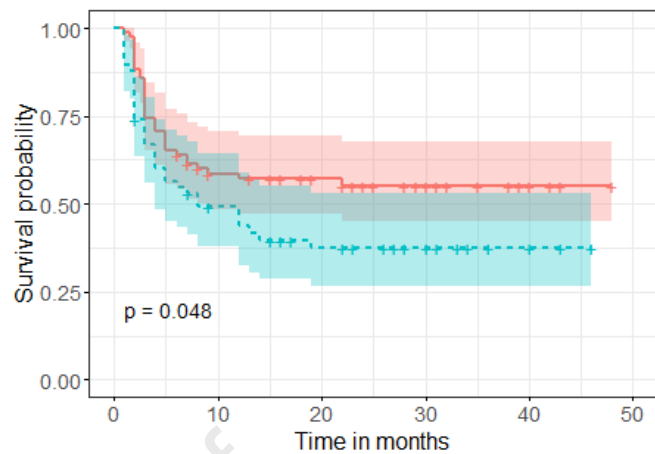
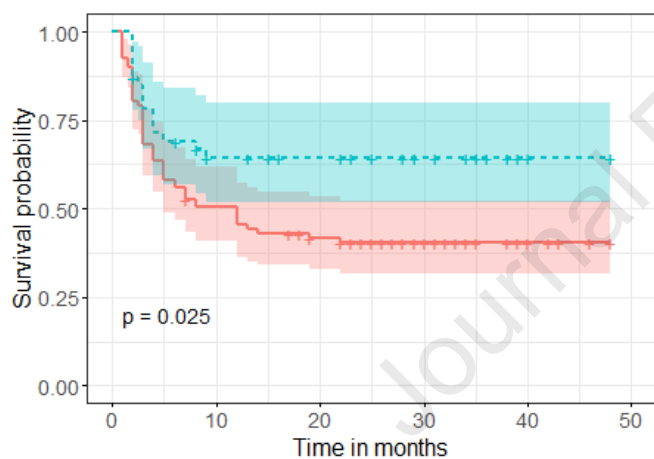
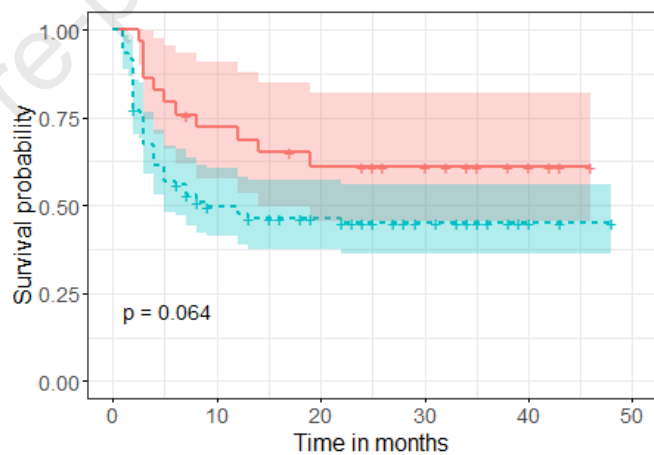
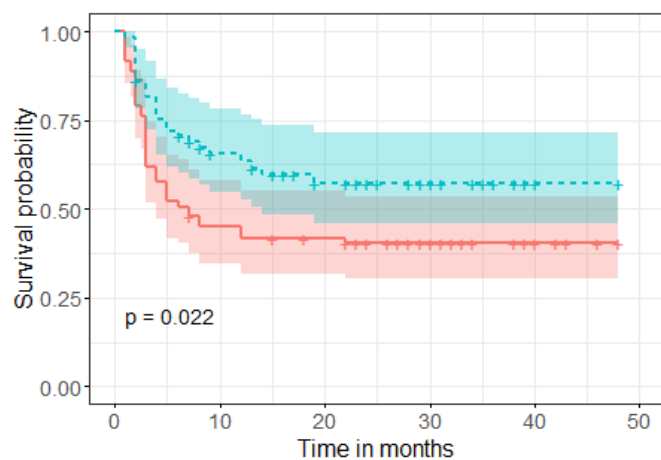
Table E1. Baseline characteristics of patients included in the study.

Baseline characteristics	Patients N=137
Age, years	
Mean $\pm$ SD	46.5 $\pm$ 15.8
Sex, n (%)	
Female	91 (66.4)
Duration of CSU, months	
Median (IQR)	12 (6–36)
History of angioedema, n (%)	52 (37.9)
History of CSU medications, n (%)	
H1 antihistamines at regular dosage	137 (100)
H1 antihistamines at high dosage	81 (59.1)
Systemic steroids	67/103 (65) [§]
Total IgE levels, kU/L	
Median (IQR)	150 (51–154)
Positive ASST, n (%)	14/39 (35.9) [§]
Positive thyroid autoantibody test, n (%)	16/109 (14.7) [§]
UAS7*, Mean $\pm$ SD	26.8 $\pm$ 7.15
- Wheal score	12 $\pm$ 4.6
- Pruritus score	14 $\pm$ 4

SD, standard deviation; CSU, chronic spontaneous urticaria; IQR, interquartile range; ASST, autologous serum skin test; UAS7, 7-day urticaria activity score. [§]Percentages were calculated considering 137 patients as the denominator, unless differently specified (systemic steroids; positive ASST; positive thyroid autoantibody tests). *Based on data collected from patient's daily diary in the week before first treatment.





Age — <60 — ≥60Symptom duration — <22 — ≥22Baseline UAS7 — <30 — ≥30Wheal score — <9 — ≥9Pruritus score — <15 — ≥15Number of administered cycles — 1 — 2