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Early Omalizumab Response Is Associated with Relapse after Withdrawal in Adolescents with Chronic Spontaneous Urticaria

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ABSTRACT

Data on relapse after omalizumab discontinuation in adolescents with chronic spontaneous urticaria (CSU) remain limited. We evaluated whether month-3 response and baseline biomarkers are associated with relapse among adolescents who discontinue omalizumab after a complete response.

This single-center retrospective cohort study included patients aged 12 to 18 years with antihistamine-refractory CSU treated with omalizumab 300 mg every 4 weeks between June 2023 and June 2025. Urticaria Activity Score over 7 days (UAS7) and Urticaria Control Test scores were recorded at treatment initiation, month 3 and month 9. Relapse was defined as a UAS7 greater than 6 after withdrawal.

Of 38 adolescents, 35 (92.1%) achieved complete response at month 9 and discontinued omalizumab; 13 of these (37.1%; 95% confidence interval [CI], 21.5-55.1) relapsed at a median of 5.0 months. Relapse frequency rose across worsening month-3 categories: 0 of 8 complete responders (0%; 95% CI, 0.0-36.9), 3 of 13 with controlled disease (23.1%; 95% CI, 5.0-53.8) and 10 of 14 with uncontrolled disease (71.4%; 95% CI, 41.9-91.6). In exploratory analyses, month-3 UAS7 discriminated relapse (area under the curve, 0.83; 95% CI, 0.69-0.97), as did lower baseline total immunoglobulin E (0.78; 95% CI, 0.62-0.95). Higher baseline total immunoglobulin E and eosinophil counts accompanied complete response at month 3.

These were unadjusted associations from a small cohort, estimated only among adolescents who discontinued after complete response; the cutoffs derived here were not validated and should not be applied clinically.

Keywords: Adolescent; Chronic urticaria; Immunoglobulin E; Omalizumab; Recurrence; Withholding treatment

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a mast cell-driven inflammatory disorder characterized by recurrent

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wheals, angioedema, or both for more than six weeks without an identifiable external trigger.[1] Less well characterized in children and adolescents than in adults, its burden is substantial: persistent pruritus, unpredictable activity and recurrent angioedema may impair sleep, school attendance, psychosocial functioning and quality of life.[2,3]

Guidelines recommend a stepwise approach beginning with a standard-dose second-generation H1-antihistamine, followed by dose escalation when control is inadequate.[1] Omalizumab, a humanized anti-immunoglobulin E (IgE) monoclonal antibody, is recommended as add-on therapy for CSU uncontrolled despite appropriately dosed antihistamines,[4,5] with efficacy and safety established in pivotal trials of patients aged 12 years and older.[6,7] Considerable heterogeneity nonetheless remains in treatment duration, response definitions, discontinuation strategies and post-treatment follow-up.[7-10]

A central unresolved issue is identifying patients likely to maintain control after withdrawal: relapse is reported in adult and pediatric cohorts, yet the factors associated with sustained remission remain incompletely defined.[11,12] Baseline total IgE, eosinophil count, pretreatment disease activity, disease duration and time to response have been evaluated as correlates of responsiveness and relapse.[12-16] These associations are derived mainly from adults, and pediatric studies have largely addressed overall effectiveness rather than the relationship between early residual disease activity and relapse after discontinuation.

This study aimed to identify factors associated with relapse after omalizumab discontinuation in adolescents with antihistamine-refractory CSU. Secondary objectives were to characterize disease-activity trajectories, to quantify the frequency and timing of relapse, and to explore baseline correlates of an early complete response.

MATERIALS AND METHODS

Study Design, Ethical Approval and Population

This single-center retrospective cohort study was conducted at the pediatric allergy outpatient clinic of a tertiary referral hospital and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations. It followed the Declaration of Helsinki and was approved by the Harran University Clinical Research Ethics Committee (approval number HRÜ/24.08.23); informed consent was waived because of the retrospective, non-interventional design, and all data were anonymized.

Records of patients aged 12-18 years with physician-diagnosed CSU who remained symptomatic despite second-generation H1-antihistamines and received omalizumab as part of routine care between June 2023 and June 2025 were screened; CSU was diagnosed according to the international guideline.[1] Eligibility and exclusion criteria are detailed in Supplementary Methods; of 46 records screened, 8 were excluded. Participant flow is shown in Figure 1.

Analytical Populations

Two analytical populations followed from the design. The treatment-response cohort comprised all 38 patients who completed the 9-month course and was used to characterize the disease activity trajectories, the distribution of month-3 responses, safety and baseline correlates of an early complete response. The post-discontinuation relapse cohort comprised the 35 who achieved a complete response at month 9 and in whom omalizumab was withdrawn; only these contributed to the relapse analysis; the 3 without a complete response had continued treatment and had never been at risk. That analysis is therefore conditioned on a complete response at month 9, and its associations apply to adolescents who discontinue omalizumab after such a response, not to all adolescents who initiate omalizumab.

Treatment Protocol, Assessment Schedule and Discontinuation

All patients received omalizumab (Xolair; Novartis Pharma AG, Basel, Switzerland), 300 mg subcutaneously every 4 weeks, given as two 150 mg injections, without adjustment for body weight or baseline total IgE.[17] The planned course was 9 months.

In Türkiye, omalizumab for CSU is dispensed under a national reimbursement framework requiring documented reassessment at fixed intervals: an initial 3-month authorization, renewed for a further 6 months only where a response is demonstrated (Supplementary Methods). Formal assessment using the Urticaria Activity Score over 7 days (UAS7)[18] and Urticaria Control Test (UCT)[19] therefore took place at treatment initiation, month 3, and month 9; because this schedule was externally imposed, the analysis time points could not have been chosen after inspecting the data. Between

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assessments patients attended every 4 weeks for administration, when disease status was documented as the presence or absence of wheals, angioedema, and pruritus without formal scoring.

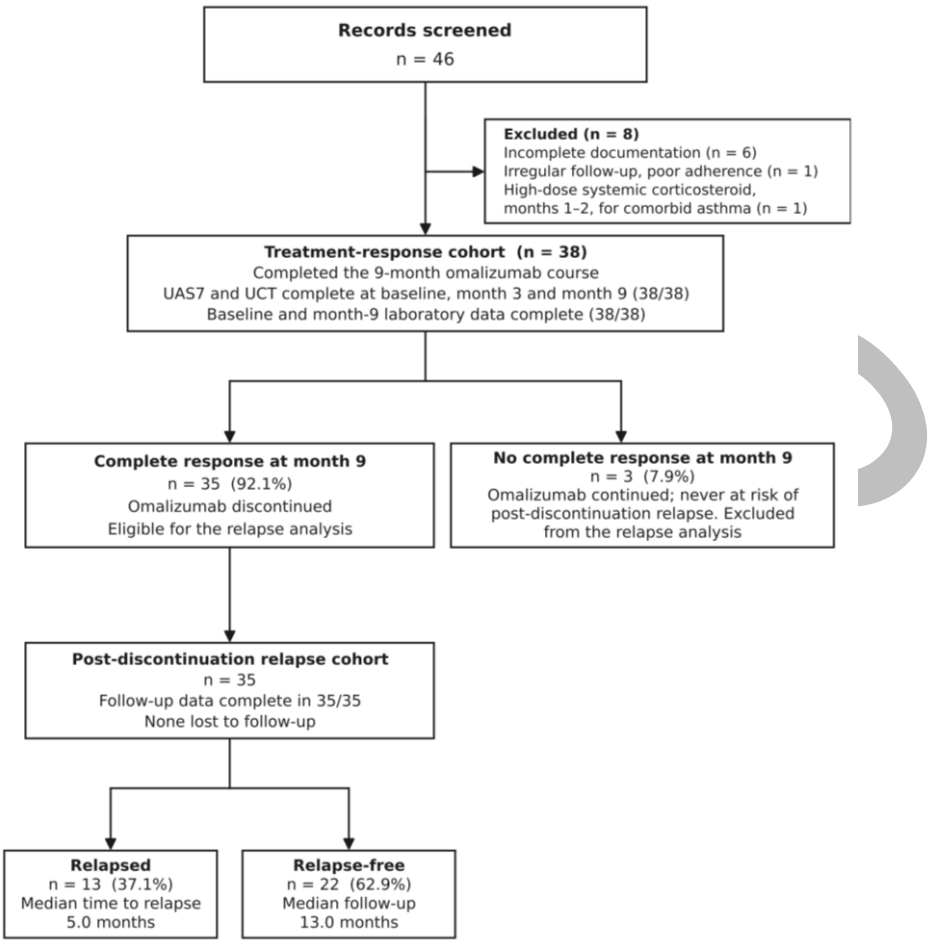

Figure 1. Participant flow through the study. Flow of participants in this single-center retrospective cohort study of adolescents aged 12 to 18 years with antihistamine-refractory chronic spontaneous urticaria treated with omalizumab, 300 mg every 4 weeks for 9 months. The diagram shows the records screened, the reasons for exclusion, the treatment-response cohort used for analyses of treatment response and baseline biomarkers, the post-discontinuation relapse cohort used for the primary relapse analysis, and the number of patients who relapsed. Data were complete for all participants at every assessment point, and no patient was lost to follow-up. UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

Omalizumab was discontinued at month 9 in patients with a complete response (UAS7=0) at the month-9 assessment and in whom no wheals, angioedema or pruritus had been documented at any intervening monthly visit. Patients not meeting both conditions continued treatment and were excluded from the relapse analysis.

Baseline total IgE, eosinophil count and hematological parameters were obtained immediately before the first injection and are therefore treatment-naive. Total IgE and eosinophil count were repeated at month 9, approximately 4 weeks after the last dose and immediately before the next dose would have been due, and therefore represent trough values. Screening for systemic autoimmune disease (antinuclear, anti-thyroid peroxidase and anti-thyroglobulin antibodies, celiac serology) was an exclusion assessment with no diagnostic value for type IIb CSU. Concomitant therapy is reported in Table 1.

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Table 1. Baseline demographic, clinical and laboratory characteristics of the study population. Characteristics recorded before the first omalizumab injection in the 38 adolescents aged 12 to 18 years with antihistamine-refractory chronic spontaneous urticaria who completed a 9-month course of omalizumab, 300 mg every 4 weeks in this single-center retrospective cohort study (the treatment-response cohort). The table describes the population in which the relationship between early treatment response, baseline biomarkers, and relapse after omalizumab withdrawal was subsequently examined.

Characteristic	Value*
Demographic and clinical characteristics	
Age, years, mean ± SD	14.97 ± 1.75
Sex, female / male, n (%)	23 (60.5) / 15 (39.5)
Disease duration, months, median (IQR)	16.0 (11.0–22.8)
Concomitant atopy, n (%)	6 (15.8)
Disease activity and control at treatment initiation	
UAS7, median (IQR)	22.0 (18.0–26.0)
UCT, median (IQR)	6.0 (4.0–8.0)
Concomitant urticaria-directed therapy during omalizumab treatment	
Omalizumab monotherapy, n (%)	33 (86.8)
H1-antihistamine alone, n (%)	4 (10.5)
H1-antihistamine plus montelukast, n (%)	1 (2.6)
Baseline laboratory and diagnostic findings	
Total IgE, IU/mL, median (IQR)	240.5 (126–355)
Eosinophil count, cells/µL, median (IQR)	123 (46–298)
Neutrophil-to-lymphocyte ratio, median (IQR)	2.07 (1.55–3.03)
Positive screening for concomitant systemic autoimmune disease†, n/N (%)	0/38 (0.0)

IgE – immunoglobulin E; IQR – interquartile range; n – number of patients; SD – standard deviation; UAS7 – Urticaria Activity Score over 7 days; UCT – Urticaria Control Test.

* Data are presented as n (%), mean ± SD, or median (IQR), as appropriate. All baseline laboratory samples were obtained immediately before the first omalizumab injection and are therefore treatment-naive. No observation was missing for any variable in this table.

† Screening comprised antinuclear antibody, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody and celiac serology, and was performed to exclude concomitant systemic autoimmune disease, which was an exclusion criterion. Autologous serum skin testing was reviewed when available as part of routine care. This panel has no diagnostic value for type IIb autoimmune chronic spontaneous urticaria, and a negative result does not exclude that endotype.

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Post-discontinuation Follow-up and Outcome Definitions

After the final injection, patients were reviewed monthly for 3 months, every 2 months between months 3 and 6, and every 3 months thereafter, and were advised to attend without an appointment if symptoms recurred; UAS7 was recorded at every scheduled and unscheduled visit. Antihistamines were stopped together with omalizumab in all patients, so the cohort was followed off all urticaria-directed therapy and no antihistamine up-dosing preceded the events analyzed here.

The primary outcome was relapse, defined as a documented UAS7 greater than 6,[16,20] irrespective of any treatment given in response to it. Time was measured from the final injection to the first documented relapse; patients without relapse were right-censored at their last documented relapse-free contact, and censoring was assumed to be non-informative. All 13 relapsing patients were restarted on omalizumab, but only the first event was analyzed. Early response was classified by the month-3 UAS7 as complete response (0), controlled disease (1-6), or uncontrolled disease (greater than 6).[16,20,21]

Statistical Analysis

Analyses used Jamovi 2.7 (The Jamovi Project, Sydney, Australia) and GraphPad Prism 9.5.1 (GraphPad Software, Boston, MA, USA); figures were finalized in Adobe Illustrator 2025 (Adobe Inc., San Jose, CA, USA). Nonparametric methods were used throughout and all tests were two-sided. No observation was missing for any variable at any assessment point in either cohort (Supplementary Table S5).

The primary analysis was the association between month-3 UAS7 category and relapse, tested using the Cochran-Armitage trend test in the relapse cohort; this is the only analysis on which the principal conclusion rests. Secondary descriptive analyses comprised the treatment trajectories and safety. All univariable comparisons and logistic regression models, all receiver operating characteristic (ROC) analyses and threshold derivations, and the baseline biomarker comparison by month-3 complete response were exploratory. False discovery rate (FDR) adjustment was applied only to the last of these; other *p* values are unadjusted and carry less weight.

No variable selection was performed: every recorded demographic, clinical and laboratory variable was entered into the univariable comparisons (Supplementary Table S2) and into univariable logistic regression (Supplementary Table S3), irrespective of the result, and none was added or removed after inspecting the data. Multivariable adjustment was precluded by the number of events, so all estimates are unadjusted. Exact (Clopper-Pearson) 95% confidence intervals (CI) were calculated for all proportions, and Kaplan-Meier estimates are reported with log-log 95% CI. Thresholds were identified in the same cohort in which they were evaluated, so the areas under the curve are apparent, in-sample values, optimistically biased and uncorrected (Supplementary Methods).

RESULTS

Treatment Response

The treatment-response cohort comprised 38 patients (mean age, 14.97±1.75 years; 23 female [60.5%]). Median disease duration was 16.0 months (interquartile range [IQR], 11.0-22.8) and 6 patients (15.8%) had concomitant atopy. Median baseline UAS7 was 22.0 (IQR, 18.0-26.0), UCT 6.0 (IQR, 4.0-8.0), total IgE 240.5 IU/mL (IQR, 126-355) and eosinophil count 123 cells/µL (IQR, 46-298); autoimmune screening was negative in all patients (Table 1).

Disease activity fell during treatment: median UAS7 was 22.0 at baseline, 6.0 (IQR, 3.0-8.0) at month 3 and 0.0 at month 9, with a parallel rise in UCT from 6.0 to 11.0 and 14.0 (Friedman $p<0.001$ for both; all pairwise comparisons significant), and the proportion with well-controlled disease rose from 18.4% to 47.4% and 84.2% (Cochran Q $p<0.001$) (Figure 2). At month 3 the distribution was complete response in 8 (21.1%), controlled disease in 13 (34.2%) and uncontrolled disease in 17 (44.7%). At month 9, 35 patients (92.1%; 95% CI, 78.6-98.3) discontinued after a complete response, and 3 (7.9%) continued (Supplementary Table S1). Adverse events occurred in 4 (10.5%; 95% CI, 2.9-24.8), all mild and self-limiting.

Month-3 UAS7 was higher in the 3 patients who did not reach a complete response at month 9 than in the 35 who did (median 9.0 [IQR, 8.5-11.5] versus 6.0 [IQR, 3.0-8.0]; $p=0.029$). By category, however, the relationship with eventual remission was weak: all 8 month-3 complete responders and all 13 with controlled disease reached a complete response at month 9, as did 14 of 17 (82.4%) with uncontrolled disease. Month-3 UAS7 therefore identified only a small minority who would fail to remit, and conditioning on complete response excluded only 3 of 38 patients (7.9%).

Relapse after Discontinuation

Among the 35 patients of the relapse cohort, 13 (37.1%; 95% CI, 21.5-55.1) relapsed at a median of 5.0 months (IQR, 3.0-6.0; range, 2-8); the 22 who did not had a median relapse-free follow-up of 13.0 months (IQR, 9.5-17.8; range, 7-33). Relapse frequency varied by month-3 response: none of the 8 complete responders relapsed (0%; exact 95% CI, 0.0-36.9), versus 3 of 13 with controlled disease (23.1%; 95% CI, 5.0-53.8) and 10 of 14 with uncontrolled disease (71.4%; 95% CI, 41.9-91.6); the trend was significant (Cochran-Armitage $p=0.0004$; Table 2). The upper bound of 36.9% shows that these data remain compatible with a substantial relapse risk even in the absence of residual month-3 disease activity.

Relapse-free survival differed across the three categories (log-rank $p=0.0008$; Figure 3). At 6 and 12 months it was 100% in the complete-response category (no events; CI not estimable), 84.6% (95% CI, 51.2-95.9) and 76.9% (95% CI, 44.2-91.9) in the controlled category, 42.9% (95% CI, 17.7-66.0) and 28.6% (95% CI, 8.8-52.4) in the uncontrolled category, and 71.4% (95% CI, 53.4-83.5) and 62.6% (95% CI, 44.4-76.3) overall; numbers at risk are displayed beneath the x-axis of Figure 3. Total observation time differed across categories (medians 13.0, 12.0 and 5.5 months; Kruskal-Wallis $p=0.016$) because observation ended at relapse, but among patients who did not relapse, for whom observation time represents censoring, follow-up was closely comparable (medians 13.0, 12.5 and 14.0 months; $p=0.837$).

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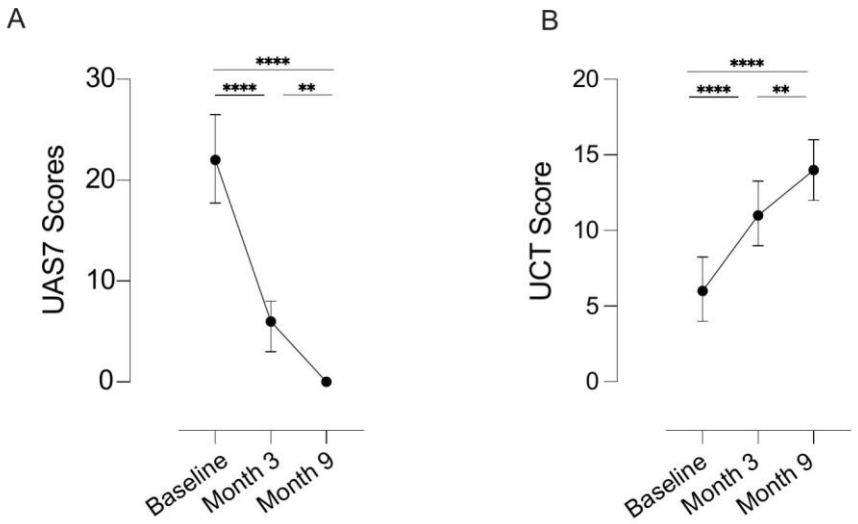

Figure 2. Changes in disease activity and disease control during 9 months of omalizumab treatment in adolescents with chronic spontaneous urticaria. (A) Urticaria Activity Score over 7 days (UAS7) and (B) Urticaria Control Test (UCT) scores at treatment initiation, month 3, and month 9 in the treatment-response cohort of 38 adolescents. This figure shows the magnitude and timing of the improvement in disease activity and disease control achieved during a fixed 9-month course of omalizumab. Data are shown as median with interquartile range. Time points are months of omalizumab treatment, with month 0 corresponding to treatment initiation. Overall change across time points was evaluated by the Friedman test and post hoc pairwise comparisons by Dunn's multiple comparisons test. Statistical significance is shown as two asterisks for *p* less than 0.01 and four asterisks for *p* less than 0.0001. UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

Table 2. Relapse after omalizumab discontinuation according to the depth of response at month 3. Frequency of relapse, defined as a documented Urticaria Activity Score over 7 days (UAS7) greater than 6 after withdrawal, in the 35 adolescents of the post-discontinuation relapse cohort — that is, those in whom omalizumab was discontinued at month 9 after a documented complete response. Patients are grouped by their UAS7-based response category at month 3, measured while still on treatment. This table shows whether residual disease activity at month 3 is related to the probability of losing disease control after treatment is stopped, and displays the statistical uncertainty around each proportion given the small number of patients per group.

Month-3 response category	Relapse, n/N (%)	Exact 95% CI	No relapse, n/N (%)
Complete response, UAS7 = 0	0/8 (0.0)	0.0–36.9	8/8 (100.0)
Controlled disease, UAS7 = 1–6	3/13 (23.1)	5.0–53.8	10/13 (76.9)
Uncontrolled disease, UAS7 > 6	10/14 (71.4)	41.9–91.6	4/14 (28.6)
Overall	**13/35 (37.1)**	**21.5–55.1**	**22/35 (62.9)**

CI – confidence interval; df – degrees of freedom; UAS7 – Urticaria Activity Score over 7 days.

Exact (Clopper–Pearson) 95% confidence intervals were calculated for all relapse proportions. The trend in relapse proportions across the ordered month-3 response categories was evaluated using the Cochran-Armitage trend test (χ^2 = 12.3, df = 1, p=0.0004). No confidence interval is estimable for the complete-response category by survival methods because no events occurred; the exact binomial interval given here (0.0–36.9%) indicates that these data remain compatible with a relapse risk of up to approximately 37% in that group.

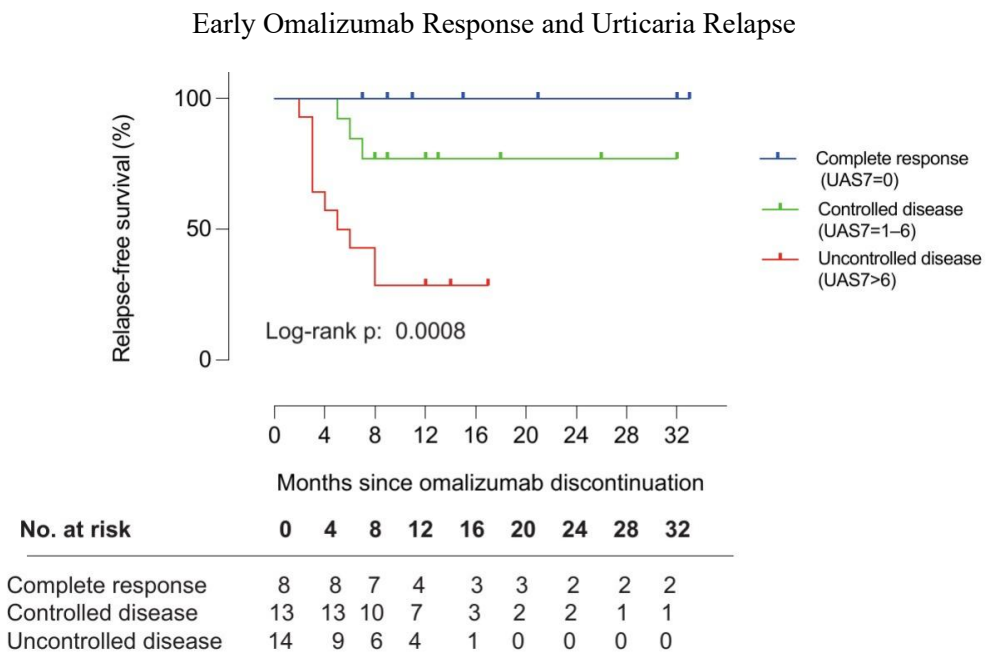

Figure 3. Relapse-free survival after omalizumab discontinuation according to depth of response at month 3. Kaplan-Meier curves for the 35 adolescents with chronic spontaneous urticaria in whom omalizumab was discontinued after a documented complete response at month 9. This figure shows whether residual disease activity at month 3, measured during treatment, is related to how long disease control is maintained after treatment is withdrawn. Patients were classified by their UAS7-based response at month 3 as complete response (UAS7=0), controlled disease (UAS7=1-6), or uncontrolled disease (UAS7 greater than 6). Time was measured from the last omalizumab injection to the first documented relapse, defined as a UAS7 greater than 6. Patients without relapse were right-censored at their last relapse-free follow-up visit; tick marks indicate censored observations. The numbers at risk are shown below the x-axis. Survival curves were compared using the Mantel-Cox log-rank test (chi-squared=14.19, df=2, *p*=0.0008). No confidence interval is estimable in the complete-response group because no events occurred. df, degrees of freedom; UAS7, Urticaria Activity Score over 7 days.

Biomarkers

Relapsing patients had higher month-3 UAS7 (median 8.0 [IQR, 7.0-10.0] versus 4.0 [IQR, 0.0-6.0]; *p*=0.001) and lower baseline total IgE (150.0 [IQR, 88.0-186.0] versus 345.0 IU/mL [IQR, 224.8-623.5]; *p*=0.006); no other variable differed significantly (Supplementary Table S2). Total IgE rose during treatment in 36 of 38 patients (cohort median 240.5 to 502.5 IU/mL; Wilcoxon $p<0.001$), the expected pharmacodynamic effect of anti-IgE therapy. Within the relapse cohort, month-9 total IgE was lower in relapsing patients (210.0 versus 708.5 IU/mL; *p*=0.002) and the rise from baseline was correspondingly smaller (median increase 49.0 versus 259.5 IU/mL; *p*=0.039). Because month-9 samples were drawn while drug was still present, these findings reflect the same phenomenon—the extent of the total-IgE response—and neither is an independent pretreatment biomarker.

In univariable logistic regression of all recorded variables (Supplementary Table S3), only three were associated with relapse: each 1-point increase in month-3 UAS7 raised the odds (odds ratio [OR], 1.62; 95% CI, 1.15-2.28; *p*=0.005), whereas each 100 IU/mL increase in baseline total IgE (OR, 0.65; 95% CI, 0.43-0.99; *p*=0.046) and in month-9 total IgE (OR, 0.74; 95% CI, 0.57-0.94; *p*=0.016) lowered them. The CI for month-3 UAS7 derives from 13 events and its point estimate is not a stable quantity.

Patients achieving complete response at month 3 had higher baseline total IgE (683 [IQR, 320-786] versus 183 IU/mL [IQR, 95-340]; *p*=0.007; FDR-adjusted *q*=0.014) and higher eosinophil counts (359 [IQR, 283-419] versus 82 cells/μL [IQR, 23-184]; *p*=0.004; *q*=0.013) (Supplementary Figure S1A, B).

Exploratory Discrimination

Month-3 UAS7 discriminated relapse (area under the curve [AUC], 0.83; 95% CI, 0.69-0.97), as did baseline total IgE (0.78; 95% CI, 0.62-0.95) (Figure 4); baseline total IgE and eosinophil count discriminated month-3 complete response (AUC, 0.82 [95% CI, 0.66-0.97] and 0.84 [95% CI, 0.68-1.00], respectively)

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(Supplementary Figure S1C). Candidate Youden-index thresholds, the patients on either side of each threshold and exact CIs for sensitivity and specificity are given in Supplementary Table S4. Between 7 and 25 patients contributed to each estimate: the sensitivity of a baseline total IgE above 597 IU/mL for month-3 complete response has a 95% CI of 24.5% to 91.5%. These thresholds describe this cohort and are not decision rules.

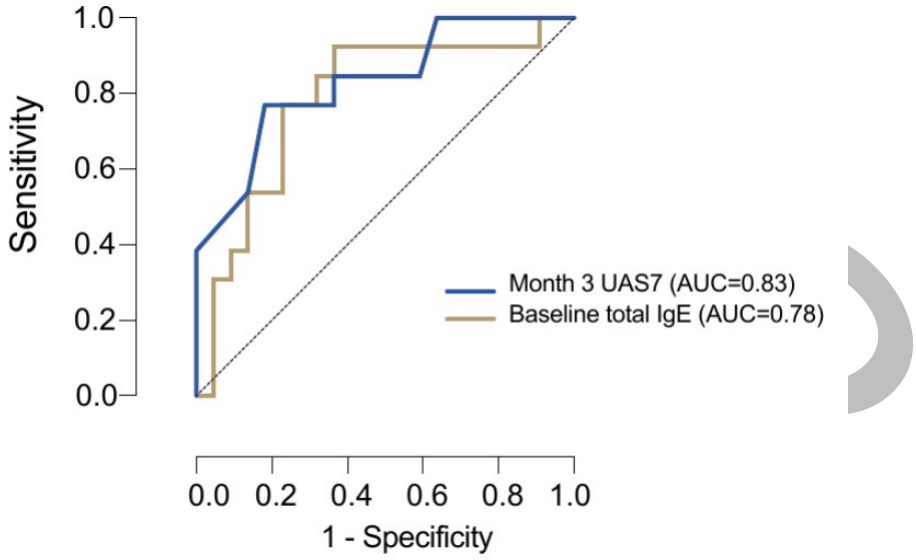

Figure 4. Exploratory receiver operating characteristic analyses for relapse after omalizumab discontinuation. Receiver operating characteristic (ROC) curves constructed in the post-discontinuation relapse cohort of 35 adolescents to evaluate how well month-3 UAS7 and baseline total IgE separate patients who subsequently relapsed from those who did not. This figure quantifies, within this cohort, the degree of separation underlying the relapse associations reported in the text. Month-3 UAS7 had an area under the ROC curve (AUC) of 0.83 (95% CI, 0.69-0.97; $p = 0.0013$) and baseline total IgE an AUC of 0.78 (95% CI, 0.62-0.95; $p = 0.0057$). The diagonal reference line indicates no discriminatory ability. Candidate thresholds were derived using the Youden index within this same cohort and were not validated externally; the AUCs therefore describe apparent, in-sample discrimination and are optimistically biased. Abbreviations: AUC, area under the curve; CI, confidence interval; IgE, immunoglobulin E; ROC, receiver operating characteristic; UAS7, Urticaria Activity Score over 7 days.

DISCUSSION

In this retrospective cohort of adolescents with antihistamine-refractory CSU, a fixed 9-month omalizumab course achieved a high rate of disease control (92.1% complete response), consistent with recent pediatric cohorts and a systematic review.[7,22,23] The key finding concerned relapse: no adolescent with a complete response at month 3 relapsed, whereas relapse occurred in about one-quarter of those with controlled disease and nearly three-quarters of those with persistent month-3 activity. This is among the first studies in an exclusively adolescent CSU population to relate early disease-control depth to relapse after discontinuation.

Residual activity at month 3 was a poor marker of whether an adolescent would eventually remit, since the great majority did so regardless, but a comparatively strong marker of whether that remission would survive withdrawal. The signal is therefore not one of treatment response but of the durability of a response already achieved, the quantity a clinician faces at discontinuation.[24]

Our relapse frequency and timing are consistent with the only other cohort dedicated to adolescents: Caka et al followed 59 adolescents and reported relapse in 47.4% at a median of 6.0 months,[11] against our 37.1% at 5.0 months. The difference should not be over-read, since our 95% CI (21.5-55.1) contains their figure; both indicate that roughly four in ten adolescents lose control within the first half-year after withdrawal. They identified delayed initiation and longer pretreatment

duration as correlates, whereas disease duration did not differ in our cohort (p=0.572); the markers are complementary rather than competing.[12,25,26]

The discontinuation strategy is a further determinant that our design could not isolate. All patients received a uniform 9-month course and were withdrawn abruptly with antihistamines stopped simultaneously, a more complete withdrawal than many centers use, which sets an upper bound on the relapse risk attributable to stopping treatment. In a 52-week adult study, discontinuation after prior optimization was followed by relapse in 32.8% at a median of 3.0 months, which the authors contrasted with higher figures after abrupt withdrawal.[26,27]

Our biomarker observations are compatible with, but do not establish, the endotype framework in which type I disease has been associated with higher total IgE and a rapid anti-IgE response and type IIb autoimmune disease with low IgE, eosinopenia and a poorer response.[14,15,28] We did not perform the defining assays. The uniformly negative autoimmune screening is not evidence that type IIb disease was absent: that panel excludes concomitant systemic autoimmune disease but is not diagnostic for type IIb CSU, and basophil activation and anti-FcεRIα (high-affinity IgE receptor) assays were unavailable.

The association between lower baseline total IgE and relapse should be presented as novel rather than confirmatory. Baseline total IgE has been studied extensively as a predictor of response to omalizumab, where higher values are reproducibly associated with a favorable outcome,[13,14] but far less often as a predictor of relapse; a recent narrative review of routinely available relapse predictors does not identify it as an established marker.[28] A single small cohort reporting a previously unexamined association based on 13 unadjusted events is precisely the circumstance requiring replication. By contrast, the higher month-9 total IgE among relapse-free patients is pharmacodynamic, because total IgE assays detect omalizumab-bound as well as free IgE.[13]

The thresholds reported here carry no clinical authority: each was selected to maximize the Youden index within the same small cohort in which it was evaluated, and they are reported only so that future cohorts have concrete values to test. The same applies to the central finding: only 8 adolescents achieved a complete response at month 3, and the absence of relapse among them is compatible with a true risk of up to 37%. These data cannot support a response-guided discontinuation strategy and we make no such recommendation.

Several limitations apply, and are expanded in the Supplementary Methods. This single-center retrospective study had a small sample and only 13 relapse events, precluding multivariable adjustment; all associations are unadjusted and hypothesis-generating, and the discriminatory analyses are additionally vulnerable to in-sample optimism. Because omalizumab was withdrawn only in patients reaching a complete response at month 9, the relapse analysis was conditioned on that response, which may bias the estimates and restricts their applicability. Formal scoring was performed at three points determined by the reimbursement schedule rather than chosen for research, so a transient unrecorded flare between months 3 and 9 cannot be excluded; any such bias would tend to inflate the observed relapse rate rather than create the association we report. Month-9 laboratory values cannot be interpreted independently of treatment, and because pediatric CSU frequently remits spontaneously, roughly 44% within 1 year,[29] some relapse-free outcomes may reflect natural resolution.

These findings should be validated in larger, prospective, multicenter pediatric cohorts with external threshold validation, formal endotyping, and trials comparing response-guided with fixed-duration discontinuation, an approach that will become more relevant as dupilumab and remibrutinib enter the antihistamine-refractory CSU landscape.[1]

In adolescents with antihistamine-refractory CSU, omalizumab was highly effective, but relapse after discontinuation was common. Among those who achieved a complete response and discontinued omalizumab, the depth of response at month 3 and lower baseline total IgE were associated with relapse. These are unadjusted associations from a small single-center cohort and require prospective validation before they can inform decisions about treatment duration.

STATEMENT OF ETHICS

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Harran University Clinical Research Ethics Committee (approval number HRÜ/24.08.23). The requirement for informed consent was waived owing to the retrospective, non-interventional design, and all data

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were anonymized before analysis. As a retrospective, non-interventional cohort study, prospective clinical-trial registration was not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

The statistical analyses of this study were performed by the authors using Jamovi 2.7 and GraphPad Prism 9.5.1, as described in the Methods. During preparation of the original manuscript, ChatGPT (OpenAI) was used for English-language editing, and an artificial intelligence image-generation tool was used to design the graphical abstract, and the same type of tool was used to redraw it for this revision. During revision, a large language model (Claude, Anthropic) was used as an assistive computational and editorial tool: to compute the additional statistics requested by the reviewers, to cross-check the values reported in the manuscript, tables and supplementary material against the source dataset, and to assist with drafting the revised text. Figures 2-4 were produced by the authors. Figure 1 is a schematic participant flow diagram drawn programmatically (Matplotlib) from the counts reported in the text; no image-generation model was used for any figure in the manuscript. All outputs were reviewed by the authors. No artificial intelligence tool participated in study design, patient care, or data collection, and all scientific interpretations and final decisions were made by the authors, who take full responsibility for the manuscript.

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