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ORIGINAL RESEARCH

Omalizumab in Chronic Spontaneous Urticaria: A Real-World Study on Effectiveness, Safety and Predictors of Treatment Outcome

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Background: Although omalizumab has shown success in treating chronic spontaneous urticaria (CSU) patients unresponsive to antihistamines, the exact mechanism of action and predictive markers of response remain unclear.

Purpose: The aim of this study was to examine the correlation between baseline levels of biomarkers and clinical parameters with omalizumab response and response rate in patients with CSU.

Methods: This retrospective study included 82 adult CSU patients who received omalizumab 300mg every 4 weeks for 16 weeks between January 2022 and December 2023. Treatment response was assessed using UAS7 and DLQI scores at baseline and weeks 4, 8, 12, and 16. Responders were defined as patients achieving UAS7 < 7, with early and late responders categorized based on response within or after 4 weeks, respectively. Baseline clinical features and laboratory biomarkers were compared between responders and non-responders.

Results: The overall response rate was 71.95% (59/82), with 23 early responders and 36 late responders. Responders had significantly lower baseline UAS7 (median: 28 vs 35, $P < 0.01$), DLQI (median: 8 vs 15, $P < 0.001$), and IL-17 levels (median: 0.53 vs 1.26 pg/mL, $P < 0.001$) compared to non-responders. Baseline UAS7 > 31, DLQI > 9.5, and IL-17 > 0.775 pg/mL predicted non-response with sensitivities of 78.26%, 100%, and 78.26%, and specificities of 67.8%, 59.32%, and 72.88%, respectively. ASST positivity and comorbid allergic diseases were associated with early response ($P < 0.05$). Adverse events were reported in 6.09% of patients, including mild injection site reactions and transient urticaria exacerbation, not requiring treatment discontinuation.

Conclusion: This study suggests that omalizumab is an effective and safe treatment option for antihistamine-refractory CSU. Baseline UAS7, DLQI, ASST status, serum total IgE levels, and IL-17 may serve as potential predictors of omalizumab response. Notably, ASST positivity and comorbid allergic diseases were associated with an early response to treatment. These findings highlight the importance of considering individual patient characteristics when predicting the likelihood and timing of response to omalizumab in CSU.

Keywords: Chronic spontaneous urticaria, omalizumab, response, early responder, late responder

Introduction

Chronic spontaneous urticaria (CSU) is a debilitating skin disorder characterized by the recurrent appearance of wheals, angioedema, or both for more than six weeks, with no identifiable external trigger.[1] Standard-dose second-generation antihistamines have been established as the primary treatment for CSU. Nevertheless, in China, almost one-third of CSU patients exhibit resistance to second-generation antihistamines, even at four times the standard dosage, leading to suboptimal treatment outcomes.[2] The 2021 edition of theEAACI/GA2LEN/EuroGuiDerm/APAAACI guidelines[3] for urticaria recommend that CSU patients who have not achieved control with high-dose antihistamine treatment for 2 to 4 weeks should be considered for omalizumab therapy.

Omalizumab, a recombinant humanized anti-IgE monoclonal antibody, has exhibited efficacy in the management of CSU based on a wealth of data from clinical trials and real-world studies.[4] A comprehensive meta-analysis encompassing

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45 studies and 1158 patients revealed an average complete control rate of 72.2% following omalizumab therapy, underscoring its effectiveness in addressing CSU.[5] Nevertheless, it is crucial to acknowledge that a considerable subset of CSU patients (approximately one-third) do not attain favorable therapeutic responses to omalizumab treatment.[6] Consequently, elucidating the underlying pharmacodynamics governing the therapeutic efficacy of omalizumab holds promise for discerning optimal indications and duration of omalizumab therapy in the future.

Despite the established efficacy of omalizumab in CSU, approximately one-third of patients do not achieve a satisfactory response.[7] Identifying predictors of treatment response is crucial for optimizing patient selection and outcomes. Previous studies have investigated various clinical and laboratory parameters, such as baseline urticaria activity, disease duration, total IgE levels, and basophil counts, as potential predictors of omalizumab response.[8] However, the results have been inconsistent, and there is a lack of consensus on reliable predictive markers.[9] Recent literature has highlighted two main endotypes of CSU: type I autoallergic and type IIb autoimmune.[10] Autoimmune CSU, characterized by the presence of autoantibodies against IgE or FcεRI, has been associated with a more severe disease course, positive autologous serum skin test (ASST) results, and reduced response to antihistamines and omalizumab.[11] Investigating the relationship between these endotypes and treatment outcomes may help predict response to omalizumab and guide personalized management strategies. Insights from studies on predictors of treatment response in other allergic diseases, such as the efficacy of JAK inhibitors in atopic dermatitis, may also be relevant to CSU. For example, higher baseline disease severity, serum thymus and activation-regulated chemokine (TARC) levels, and early-stage improvements have been associated with better long-term outcomes in atopic dermatitis patients treated with JAK inhibitors.[12–14] Exploring similar predictive factors in CSU could help guide treatment decisions and improve patient care.This study aimed to evaluate the effectiveness and safety of omalizumab in a real-world setting and identify baseline clinical and laboratory factors associated with treatment response and response time in antihistamine-refractory CSU patients.

Methods

Study Design and Data Collection

This retrospective cohort study investigated the effectiveness of omalizumab treatment in patients with CSU at the Guangzhou Dermatology Hospital from January 2022 to December 2023. The study was conducted in accordance with the guidelines of the hospital's Ethics Committee, and all participants provided informed consent. Diagnosis of CSU and assessment of disease activity were based on the current international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for urticaria.[3] Data on demographic, clinical, and laboratory parameters were systematically collected for analysis. The eligibility criteria for patients with CSU were as follows: (1) Antihistamine resistance was defined as a lack of response to two to four times the standard dose of H1-antihistamines for a minimum of 30 days, (2) Age requirement of 12 years or older, (3) Completion of at least 16 weeks of omalizumab treatment during the course of their disease to ascertain treatment response, (4) UAS7 of equal to or greater than 16 at the start of omalizumab treatment. Patients exhibiting inducible urticaria, a positive personal history of cancer, prior treatment with long-term systemic corticosteroids (> 10 days), methotrexate, ciclosporin, cyclophosphamide, or other immunosuppressants, as well as those who had received intravenous immunoglobulins or undergone plasmapheresis within 30 days preceding the initiation of omalizumab treatment, were excluded. Short-term corticosteroid use for acute urticaria exacerbations was allowed.

Demographic information obtained from patient records encompassed gender, age, disease duration, as well as comorbid allergic conditions (including allergic rhinitis, asthma, atopic dermatitis, and eczema), alongside disease-specific parameters such as UAS7 (measured on a scale of 0–42) and Dermatology Life Quality Index (DLQI, measured on a scale of 0–30). Disease activity and quality of life were assessed using the Urticaria Activity Score over 7 days (UAS7), a validated tool for measuring wheals and pruritus severity,[15] and the Dermatology Life Quality Index (DLQI), a questionnaire evaluating the impact of skin diseases on patients' lives.[16] Furthermore, data pertaining to biochemical assessments encompassed serum total IgE levels, IgG anti-IgE antibody, IgG anti-FcεR I antibody, autologous serum skin test (ASST), C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), complement components (C3, C4), eosinophil and basophil counts, as well as levels of IgG thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), D-dimer, and cytokines (including Interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IFN-α,

IFN-γ, and TNF-α). Serum samples were collected at baseline, stored at −80°C, and later analyzed for levels of cytokines, IgG anti-IgE, and IgG anti-FcεRI antibodies based on their potential involvement in chronic urticaria pathogenesis.[17,18] Serum cytokine levels were measured using a multiplex bead-based immunoassay (Bio-Plex Pro Human Cytokine Assay, Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions. Serum levels of IgG anti-IgE and IgG anti-FcεRI antibodies were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai honey Chun Biotechnology Co. Ltd. Shanghai, China) according to the manufacturer's instructions.

Treatment Response

Each patient received a dose of 300 mg of omalizumab once every four weeks for a duration of 16 weeks. Disease activity and the therapeutic impact of omalizumab were assessed using the UAS7 and DLQI metrics at baseline, and at weeks 4, 8, 12, and 16. Subsequently, patients were categorized based on their response during the 16 weeks of treatment. Responders were identified as those patients with a UAS7 score of less than 7 points, while non-responders were characterized by a UAS7 score of 7 points or more.[19] "Early response" was defined as the resolution of CSU symptoms (UAS7 < 7) within 4 weeks from the initiation of omalizumab treatment, and "late response" as the resolution of CSU symptoms (UAS7 < 7) occurring after 4 weeks from the initiation of omalizumab treatment. All adverse events were meticulously documented following the initial administration of omalizumab treatment.

Statistical Analysis

Data analysis was performed using SPSS 26.0, while GraphPad Prism 6 was utilized to generate graphical representations. Descriptive statistics were employed to characterize normally distributed continuous variables, with results reported as mean ± standard deviation. Intergroup comparisons for these variables were conducted using independent sample *t*-tests. For non-normally distributed continuous variables, median and interquartile range values were presented, and two-group comparisons were carried out using the Mann–Whitney *U*-test or Wilcoxon signed-rank test, and multiple independent sample comparisons were appraised using the Kruskal–Wallis *H*-test. The variables (measured before omalizumab treatment) with a $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis to predict responders to omalizumab treatment at the 16-week follow-up. Receiver operating characteristic (ROC) analysis was utilized to assess the predictive accuracy of factors for panel data exhibiting statistically significant differences among groups. Predictive factors yielding an area under the ROC curve (AUC) exceeding 0.7 were deemed to possess a high level of accuracy. The Youden Index, computed as the sum of sensitivity and specificity minus one, was utilized to identify the optimal critical value for continuous variable indicators by maximizing its value. Sensitivity and specificity for predictive efficacy were calculated for categorical variables displaying statistically significant differences among groups. After applying the Bonferroni correction for multiple comparisons, only IL-17 remained significantly associated with treatment response (adjusted $P < 0.001$). Statistical significance was defined at a threshold of $P < 0.05$. There were no missing data for the variables included in the analyses.

Results

Patient Characteristics and Overall Treatment Response

A total of 82 CSU patients were included, with a mean age of 39.18 ± 14.84 years (range: 12–75 years) and a median disease duration of 18 months (IQR: 7.25–45, range: 2–388 months). Three patients (3.7%) were under 18 years old. The baseline median UAS7 and DLQI scores were 28 (IQR: 26–35) and 10 (IQR: 5.25–14.75), respectively. Detailed patient characteristics are summarized in Table 1. After 16 weeks of omalizumab treatment, 71.95% (59/82) of patients were classified as responders, with 23 early responders and 36 late responders. Both UAS7 and DLQI scores significantly decreased from baseline at weeks 4, 8, 12, and 16 ($P < 0.05$), with further improvements at week 16 compared to week 4 ($P < 0.05$) (Figure 1).

Table 1 Clinical Features and Laboratory Examination of CSU Patients Before the Treatment of Omalizumab

Variables	Total (n = 82)	Responders (n = 59)	Non-responders (n = 23)	Statistic	*P*
Age (years)	39.18 ± 14.84	38.08 ± 14.48	42.00 ± 15.70	t=1.07	0.286
Sex, n(%)				χ^2=0.91	0.340
Female	39 (47.56)	30 (50.85)	9 (39.13)		
Male	43 (52.44)	29 (49.15)	14 (60.87)		
Mean disease duration (months)	18.00 (7.25, 45.00)	18.00 (7.00, 42.50)	18.00 (8.00, 44.00)	Z=−0.13	0.893
History of allergy, n(%)				χ^2=0.60	0.439
Negative	63 (76.83)	44 (74.58)	19 (82.61)		
Positivity	19 (23.17)	15 (25.42)	4 (17.39)		
Baseline UAS7	28.00 (26.00, 35.00)	28.00 (21.00, 35.00)	35.00 (34.50, 42.00)	Z=−3.98	**<0.001**
Baseline DLQI	10.00 (5.25, 14.75)	8.00 (4.00, 12.50)	15.00 (12.00, 16.50)	Z=−4.82	**<0.001**
Total IgE (IU/mL)	158.40 (109.57, 245.25)	159.00 (116.00, 235.50)	150.00 (73.05, 335.70)	Z=−0.55	0.584
Total IgE level, n(%)				χ^2=8.65	**0.003**
≤100 IU/mL	18 (21.95)	8 (13.56)	10 (43.48)		
> 100 IU/mL	65 (78.05)	51 (86.44)	13 (56.52)		
ASST, n(%)				χ^2=8.13	**0.004**
Negative	52 (63.41)	43 (72.88)	9 (39.13)		
Positivity	30 (36.59)	16 (27.12)	14 (60.87)		
TPOAb (IU/mL)	3.86 (1.92, 6.17)	4.17 (2.39, 7.04)	3.65 (1.19, 5.45)	Z=−1.20	0.231
TGAb (IU/mL)	0.90 (0.90, 0.97)	0.90 (0.90, 0.90)	0.90 (0.90, 1.52)	Z=−2.38	**0.018**
Anti-IgE antibody (ug/mL)	9.65 (4.60, 15.30)	10.80 (5.15, 16.55)	7.00 (4.00, 13.10)	Z=−1.13	0.260
Anti-FcεR I antibody (ug/mL)	142.50 (74.80, 267.77)	171.10 (92.00, 278.50)	120.00 (61.55, 159.15)	Z=−1.59	0.111
C3 (μg/mL)	1.25 (1.11, 1.44)	1.23 (1.10, 1.42)	1.26 (1.13, 1.49)	Z=−0.75	0.451
C4 (μg/mL)	0.29 (0.22, 0.41)	0.27 (0.20, 0.39)	0.33 (0.28, 0.43)	Z=−2.24	**0.025**
Eosinophil count (×10^9/L)	0.11 (0.07, 0.18)	0.11 (0.07, 0.17)	0.11 (0.07, 0.22)	Z=−0.57	0.566
Basophils count (×10^9/L)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.02 (0.01, 0.02)	Z=−0.83	0.406
CRP (mg/L)	1.77 (0.05, 5.90)	1.76 (0.05, 5.85)	1.94 (0.25, 6.37)	Z=−0.30	0.766
ESR (mm/H)	7.00 (5.00, 12.00)	7.00 (5.00, 12.50)	6.00 (4.50, 10.50)	Z=−0.81	0.419
D-dimer (ng/mL)	0.39 (0.22, 0.70)	0.37 (0.23, 0.72)	0.44 (0.22, 0.69)	Z=−0.27	0.784
IL-1β (pg/mL)	1.42 (0.08, 8.74)	2.13 (0.16, 8.98)	0.45 (0.03, 5.67)	Z=−1.26	0.206
IL-2 (pg/mL)	0.77 (0.52, 1.28)	0.79 (0.59, 1.28)	0.68 (0.41, 1.25)	Z=−1.11	0.265
IL-4 (pg/mL)	0.26 (0.12, 0.37)	0.23 (0.12, 0.36)	0.29 (0.12, 0.51)	Z=−0.70	0.482
IL-5 (pg/mL)	0.90 (0.14, 2.13)	1.00 (0.20, 2.13)	0.54 (0.12, 2.09)	Z=−0.37	0.710
IL-6 (pg/mL)	0.87 (0.46, 1.68)	0.98 (0.47, 1.65)	0.78 (0.44, 1.64)	Z=−0.75	0.454
IL-8 (pg/mL)	2.67 (1.65, 4.61)	2.62 (1.65, 4.35)	2.73 (1.60, 5.31)	Z=−0.34	0.733
IL-10 (pg/mL)	0.77 (0.34, 1.14)	0.79 (0.34, 1.12)	0.65 (0.39, 1.12)	Z=−0.44	0.661
IL-12 (pg/mL)	0.65 (0.50, 1.23)	0.68 (0.55, 1.27)	0.50 (0.32, 0.82)	Z=−2.11	**0.035**
IL-17 (pg/mL)	0.65 (0.41, 1.26)	0.53 (0.35, 0.88)	1.26 (0.90, 1.94)	Z=−3.57	**<0.001**
IFN-α (pg/mL)	1.11 (0.50, 2.03)	1.26 (0.55, 1.99)	0.63 (0.35, 1.81)	Z=−1.16	0.248
IFN-γ (pg/mL)	0.45 (0.01, 3.96)	0.71 (0.01, 3.29)	0.01 (0.01, 5.20)	Z=−0.80	0.423
TNF-α (pg/mL)	0.10 (0.01, 1.33)	0.03 (0.01, 0.98)	0.60 (0.01, 2.64)	Z=−0.83	0.406

Notes: Data presented as mean ± standard deviation, number (%), or median (1st Quartile, 3st Quartile). The bold values are indicates $P < 0.05$.
Abbreviations: t, *t*-test; Z, Mann–Whitney test; χ^2, Chi-square test; UAS7, Urticaria Activity Score-7; DLQI, Dermatology Life Quality Index; ASST, autologous serum skin test; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; C, complement components; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody.

Comparison Between Responders and Non-Responders

Responders had significantly lower baseline UAS7 (median: 28 vs 35, P < 0.01), DLQI (median: 8 vs 15, P < 0.001), and IL-17 levels (median: 0.53 vs 1.26 pg/mL, P < 0.001) compared to non-responders (Table 2). In multivariate logistic regression analysis, baseline UAS7 > 31 (OR: 0.88, 95% CI: 0.78–0.99, P = 0.037), DLQI > 9.5 (OR: 0.82, 95% CI: 0.70–0.96, P = 0.016), and IL-17 >0.775 pg/mL (OR: 0.19, 95% CI: 0.05–0.79, P = 0.023) were independently associated with non-response (Table 3). ROC analysis revealed that these thresholds predicted non-response with sensitivities of

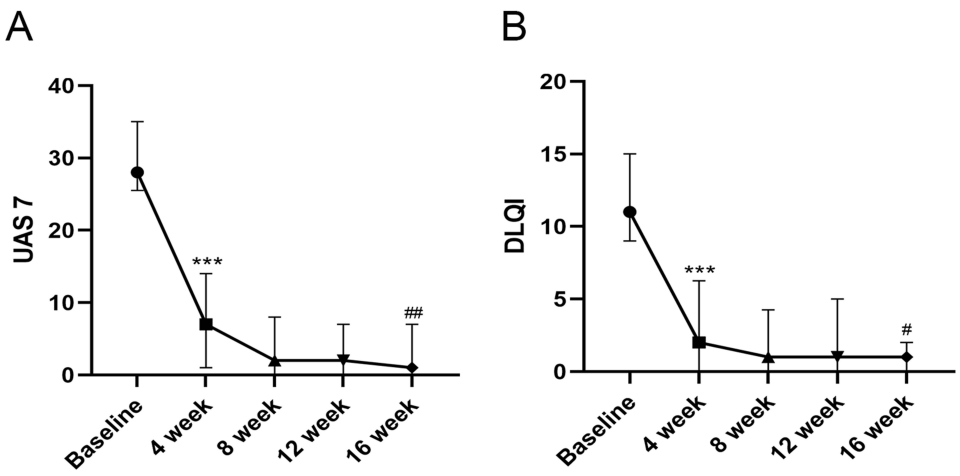

Figure 1 Change in median UAS7 (**A**) and DLQI (**B**) scores from baseline during the 16-week omalizumab treatment period. ***P< 0.001 compared with baseline; #P <0.05, ##P < 0.01 compared with week 4. UAS7: Urticaria Activity Score 7; DLQI: Dermatology Life Quality Index.

78.26%, 100%, and 78.26%, and specificities of 67.8%, 59.32%, and 72.88%, respectively (Figure 2). ASST positivity was more common among non-responders (60.87% vs 27.12%, P = 0.004). Patients with baseline total IgE > 100 IU/mL were more likely to respond to omalizumab (86.44% vs 56.52%, P = 0.003).

Comparison Between Early and Late Responders

Among responders, early responders had a higher prevalence of ASST positivity (56.52% vs 8.33%, P < 0.001) and history of allergic diseases (47.83% vs 11.11%, P = 0.002) compared to late responders (Table 4). In multivariate logistic regression, these factors were independently associated with early response (ASST positivity: OR: 0.09, 95% CI: 0.02–0.41, P = 0.002; allergic diseases: OR: 0.20, 95% CI: 0.05–0.89, P = 0.034). No significant differences were found in age, sex, disease duration, baseline UAS7, DLQI, or other biomarkers between the two groups (P > 0.05).

Safety

Adverse events were reported in 6.09% (5/82) of patients, including injection site reactions (2.44%, 2/82) and transient urticaria exacerbation (3.66%, 3/82). All adverse events were mild and did not require treatment discontinuation.

Table 2 Binary Logistic Regression Analysis in the Prediction of Responders to Omalizumab Before Treatment

Variables	Univariate analysis					Multivariate analyses				
	β	S.E	Z	*P*	OR (95% CI)	β	S.E	Z	*P*	OR (95% CI)
Baseline UAS7	−0.15	0.04	−3.68	**<0.001**	0.86 (0.79 ~ 0.93)	−0.13	0.06	−2.09	**0.037**	0.88 (0.78 ~ 0.99)
Baseline DLQI	−0.23	0.06	−3.78	**<0.001**	0.80 (0.71 ~ 0.90)	−0.20	0.08	−2.41	**0.016**	0.82 (0.70 ~ 0.96)
ASST Positivity	−1.43	0.52	−2.76	**0.006**	0.24 (0.09 ~ 0.66)	−1.69	0.86	−1.97	**0.049**	0.18 (0.03 ~ 0.99)
Total IgE level > 100 IU/mL	1.59	0.57	2.80	**0.005**	4.90 (1.61 ~ 14.90)	1.81	0.84	2.14	**0.032**	6.11 (1.17 ~ 31.97)
C4	−2.65	1.46	−1.82	0.069	0.07 (0.00 ~ 1.23)					
TGAb	0.00	0.01	0.43	0.668	1.00 (0.98 ~ 1.03)					
IL-12	0.27	0.45	0.60	0.547	1.31 (0.54 ~ 3.15)					
IL-17	−1.88	0.49	−3.80	**<0.001**	0.15 (0.06 ~ 0.40)	−1.64	0.72	−2.28	**0.023**	0.19 (0.05 ~ 0.79)

Note: The bold values are indicates *P* < 0.05.

Abbreviations: UAS7, Urticaria Activity Score-7; DLQI, Dermatology Life Quality Index; ASST, autologous serum skin test; C, complement components; TGAb, thyroglobulin antibody; OR, Odds Ratio; CI, Confidence Interval.

Table 3 Clinical Features and Laboratory Examination of the Omalizumab Responders

Variables	Total (n = 59)	Early responders (n = 23)	Late responders (n = 36)	Statistic	*P*
Age (years)	38.08 ± 14.48	39.26 ± 18.95	37.33 ± 10.97	t=0.44	0.661
Sex, n(%)				χ^2=2.07	0.150
Female	30 (50.85)	9 (39.13)	21 (58.33)		
Male	29 (49.15)	14 (60.87)	15 (41.67)		
Mean disease duration (months)	18.00 (7.00, 42.50)	13.00 (8.50, 33.00)	24.00 (7.00, 59.50)	Z=−1.20	0.231
History of allergy, n(%)				χ^2=9.98	**0.002**
Negative	44 (74.58)	12 (52.17)	32 (88.89)		
Positivity	15 (25.42)	11 (47.83)	4 (11.11)		
Baseline UAS7	28.00 (21.00, 35.00)	26.00 (20.00, 31.50)	28.00 (25.50, 35.00)	Z=−1.22	0.223
Baseline DLQI	8.00 (4.00, 12.50)	6.00 (4.00, 13.00)	9.00 (3.75, 10.50)	Z=−0.15	0.882
Total IgE (IU/mL)	159.00 (116.00, 235.50)	162.89 (110.45, 241.75)	158.20 (120.90, 231.75)	Z=−0.16	0.871
Total IgE level, n(%)				χ^2=1.16	0.281
≤100 IU/mL	8 (13.56)	5 (21.74)	3 (8.33)		
> 100 IU/mL	51 (86.44)	18 (78.26)	33 (91.67)		
ASST, n(%)				χ^2=16.49	**<0.001**
Negative	43 (72.88)	10 (43.48)	33 (91.67)		
Positivity	16 (27.12)	13 (56.52)	3 (8.33)		
TPOAb (IU/mL)	4.17 (2.39, 7.04)	3.26 (1.90, 7.82)	4.57 (2.48, 6.93)	Z=−0.40	0.686
TGAb (IU/mL)	0.90 (0.90, 0.90)	0.90 (0.90, 1.80)	0.90 (0.90, 0.90)	Z=−1.48	0.139
Anti-IgE antibody (ug/mL)	10.80 (5.15, 16.55)	10.41 (4.00, 14.90)	10.85 (6.30, 17.73)	Z=−0.83	0.406
Anti-FcεRI antibody (ug/mL)	171.10 (92.00, 278.50)	131.30 (65.90, 197.78)	208.10 (108.22, 324.27)	Z=−1.87	0.061
C3 (μg/mL)	1.23 (1.10, 1.42)	1.29 (1.13, 1.49)	1.21 (1.01, 1.35)	Z=−1.46	0.144
C4 (μg/mL)	0.27 (0.20, 0.39)	0.30 (0.21, 0.39)	0.24 (0.17, 0.38)	Z=−1.11	0.266
Eosinophil count ($\times10^9$/L)	0.11 (0.07, 0.17)	0.11 (0.07, 0.18)	0.11 (0.07, 0.16)	Z=−0.16	0.876
Basophils count ($\times10^9$/L)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	Z=−0.30	0.762
CRP (mg/L)	1.76 (0.05, 5.85)	2.16 (0.05, 5.58)	1.50 (0.05, 6.51)	Z=−0.09	0.931
ESR (mm/H)	7.00 (5.00, 12.50)	8.00 (5.00, 13.50)	7.00 (5.00, 12.25)	Z=−0.02	0.988
D-dimer (ng/mL)	0.37 (0.23, 0.72)	0.37 (0.19, 0.69)	0.39 (0.26, 0.71)	Z=−0.45	0.652
IL-1β (pg/mL)	2.13 (0.16, 8.98)	2.23 (0.47, 7.54)	1.78 (0.04, 9.12)	Z=−0.67	0.503
IL-2 (pg/mL)	0.79 (0.59, 1.28)	0.89 (0.63, 1.41)	0.77 (0.57, 1.07)	Z=−0.74	0.460
IL-4 (pg/mL)	0.23 (0.12, 0.36)	0.27 (0.15, 0.37)	0.21 (0.12, 0.35)	Z=−0.65	0.519
IL-5 (pg/mL)	1.00 (0.20, 2.13)	1.23 (0.44, 2.01)	0.74 (0.07, 2.22)	Z=−1.00	0.315
IL-6 (pg/mL)	0.98 (0.47, 1.65)	0.98 (0.49, 1.55)	0.90 (0.49, 1.75)	Z=−0.06	0.950
IL-8 (pg/mL)	2.62 (1.65, 4.35)	3.18 (1.69, 5.70)	2.45 (1.59, 3.68)	Z=−1.56	0.118
IL-10 (pg/mL)	0.79 (0.34, 1.12)	0.79 (0.47, 1.10)	0.74 (0.31, 1.17)	Z=−0.64	0.524
IL-12 (pg/mL)	0.68 (0.55, 1.27)	0.68 (0.53, 1.39)	0.67 (0.59, 1.11)	Z=−0.16	0.870
IL-17 (pg/mL)	0.53 (0.35, 0.88)	0.45 (0.34, 0.98)	0.60 (0.40, 0.85)	Z=−0.77	0.442
IFN-α (pg/mL)	1.26 (0.55, 1.99)	1.65 (0.57, 2.73)	1.25 (0.54, 1.84)	Z=−1.31	0.192
IFN-γ (pg/mL)	0.71 (0.01, 3.29)	1.03 (0.01, 4.37)	0.45 (0.01, 2.98)	Z=−0.62	0.535
TNF-α (pg/mL)	0.03 (0.01, 0.98)	0.11 (0.01, 3.12)	0.01 (0.01, 0.56)	Z=−1.26	0.208

Notes: Data presented as mean ± standard deviation, number (%), or median (1st Quartile, 3st Quartile). The bold values are indicates $P < 0.05$.
Abbreviations: t, *t*-test; Z, Mann–Whitney test; χ^2, Chi-square test; UAS7, Urticaria Activity Score-7; DLQI, Dermatology Life Quality Index; ASST, autologous serum skin test; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; C, complement components; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody.

Discussion

Omalizumab, a monoclonal anti-IgE antibody, presents a promising therapeutic option for patients with chronic spontaneous urticaria (CSU) that is refractory to antihistamine treatment, owing to its demonstrated efficacy and long-term safety profile. However, it is important to note that response to treatment may not always be complete or sufficient. Building upon prior research, our study observed a response rate of 71.9% (n=59/82) among patients with CSU at the end of the 16-week treatment period. Notably, our investigation revealed that patients receiving omalizumab exhibited a significant decrease in UAS7 and DLQI scores at the 16-week time point compared to the results obtained at week 4. These findings suggest that

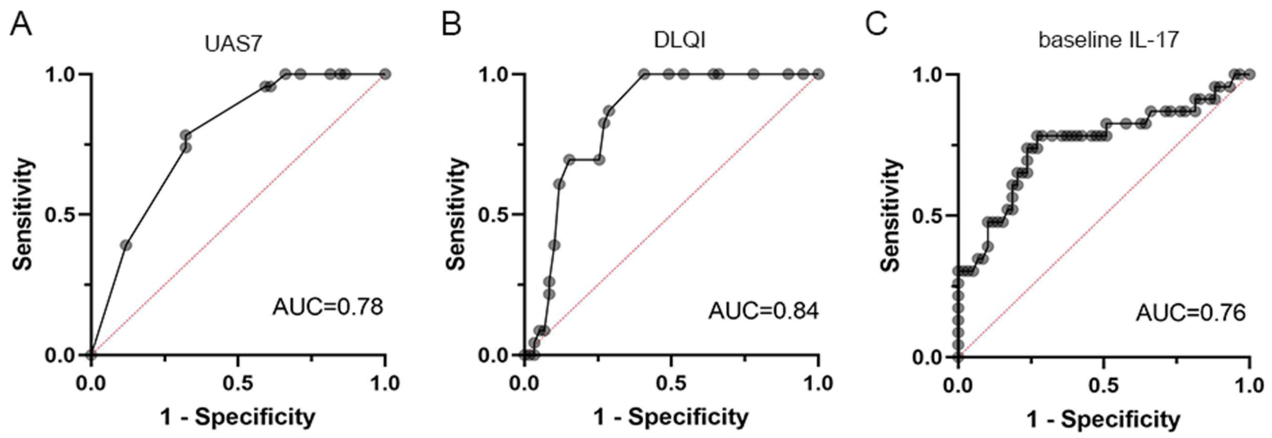

Figure 2 Receiver operating characteristic (ROC) curves for (**A**) baseline UAS7 (threshold: 31), (**B**) baseline DLQI (threshold: 9.5), and (**C**) baseline IL-17 (threshold: 0.775 pg/mL) in predicting non-response to omalizumab treatment.
Abbreviations: AUC, area under the curve; CI, confidence interval. UAS7, Urticaria Activity Score 7; DLQI, Dermatology Life Quality Index; IL, interleukin.

continuing omalizumab treatment for a duration of 16 weeks may lead to improved response rates in patients who initially demonstrated insufficient response.

Our findings of lower baseline disease severity and quality of life impairment predicting better omalizumab response in CSU are consistent with observations in atopic dermatitis, where lower baseline Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI) scores were associated with higher efficacy of JAK inhibitors.[12–14] This suggests that initiating treatment earlier in the disease course, when the inflammatory burden is lower, may lead to better outcomes across different allergic conditions.

The ASST presents with clinical ease in its performance, yet its specificity is somewhat diminished, owing to its potential to detect not only IgG antibodies against mast cell-bound IgE, but also other histamine-releasing factors, eliciting a positive ASST response.[20] Our present investigation unveiled that over a third of CSU patients tested positive for ASST. Significantly, the proportion of ASST-positive patients was markedly elevated among those exhibiting early treatment response compared to their late-responding counterparts.[21,22]

The exact mechanism underlying the early response to omalizumab in ASST-positive patients remains unclear. One possible explanation is that the presence of autoantibodies against mast cell-bound IgE or FcεRI may lead to a more severe and treatment-resistant form of CSU.[20] These autoantibodies can trigger mast cell degranulation and inflammatory mediator release, which may be effectively controlled by omalizumab's action of reducing free IgE levels in the early phase of treatment. Additionally, the autoimmune nature of the disease in ASST-positive patients may involve other pathogenic pathways beyond IgE-mediated signaling, thus requiring longer treatment durations to achieve complete symptom control.[23]

The association between ASST positivity, comorbid allergic diseases, and early omalizumab response in our study highlights the potential impact of autoimmune and atopic mechanisms on treatment efficacy. Similarly, in atopic dermatitis, the presence of autoantibodies and concomitant allergic comorbidities has been linked to suboptimal response

Table 4 Binary Logistic Regression Analysis in the Prediction of Early Response and Late Response to Omalizumab Before Treatment

Variables	Univariate analysis					Multivariate analyses				
	β	S.E	Z	*P*	OR (95% CI)	β	S.E	Z	*P*	OR (95% CI)
ASST Positivity	−2.66	0.74	−3.62	**<0.001**	0.07 (0.02 ~ 0.30)	−2.40	0.77	−3.13	**0.002**	0.09 (0.02 ~ 0.41)
History of allergy positivity	−1.99	0.67	−2.95	**0.003**	0.14 (0.04 ~ 0.51)	−1.61	0.76	−2.12	**0.034**	0.20 (0.05 ~ 0.89)

Note: The bold values are indicates $P < 0.05$.
Abbreviations: ASST, autologous serum skin test; OR, Odds Ratio; CI, Confidence Interval.

to JAK inhibitors.[13] These findings underscore the need for personalized treatment approaches that consider the individual patient's immunologic profile and comorbidities.

Numerous studies in the existing literature have established a strong correlation between the efficacy of omalizumab treatment and baseline serum total IgE levels.[24,25] However, our current study does not unequivocally substantiate a robust correlation between omalizumab response and baseline serum total IgE levels. Nevertheless, it is noteworthy that patients exhibiting a poor response to omalizumab demonstrated serum levels below 100 IU/mL, a trend also observed by Chuang et al.[26] Although the specific diagnostic threshold remains elusive, it is imperative to assess baseline serum total IgE levels in all chronic urticaria patients being considered for omalizumab administration, as this evaluation can provide predictive insights into treatment response. Notably, for patients unresponsive to alternative treatments, the proactive recommendation of omalizumab may be warranted, particularly in cases where baseline serum total IgE levels are elevated.

Our study elucidates that serum IL-17 levels were notably higher in non-responders to omalizumab compared to responders. This finding aligns with previous research by Atwa et al[18] who documented a substantial positive correlation between serum IL-17 and UAS7 levels. Taking these findings into consideration, it is postulated that IL-17, as a marker of pro-inflammatory cytokines, may serve as a potential prognostic indicator for resistance to omalizumab. A prospective clinical trial involving eight CSU patients, unresponsive to conventional therapies including antihistamines and omalizumab, demonstrated a substantial reduction in UAS7 scores by 55% and 82% after 30 and 60 days, respectively, following the transition to secukinumab.[27]

This study is subject to certain limitations. Primarily, it was conducted at a single center, had a retrospective design, and did not employ a randomized placebo-controlled methodology. One limitation of our study is the inclusion of patients resistant to 2 to 4 times the standard dose of antihistamines, which may introduce bias, as some patients not responding to a 2-fold dose may benefit from a 4-fold dose. Future prospective studies should ensure a standardized definition of antihistamine resistance before initiating omalizumab therapy. Another limitation is the inclusion of a small number of pediatric patients (3.7%), who may exhibit different treatment responses and cytokine profiles compared to adults. Future studies should analyze adult and pediatric populations separately to account for potential age-related differences. The exclusion of patients with prior use of immunosuppressive therapies may have resulted in a selection bias towards a treatment-naïve population. Future studies should include patients with diverse treatment histories to better reflect real-world clinical practice. Another limitation of our study is the definition of non-responders based on a 16-week treatment period. Some late responders may achieve symptom control after 6 months of omalizumab therapy.[28] Future studies with longer follow-up durations are needed to better characterize delayed treatment responses and refine the definition of non-responders. The higher proportion of male patients (52.44%) in our study, contrary to the typical female predominance in CSU, suggests a potential selection bias. This gender distribution may limit the generalizability of our findings and warrants further investigation in future studies with a more representative sample.

In conclusion, this retrospective study suggests that omalizumab is an effective and safe treatment option for antihistamine-refractory CSU. Baseline UAS7, DLQI, ASST status, serum total IgE levels, and IL-17 may serve as potential predictors of treatment response, while ASST positivity and comorbid allergic diseases may be associated with early response. However, given the study's retrospective design and relatively small sample size, further prospective studies with larger cohorts are needed to validate these findings and establish definitive predictive markers for omalizumab response in CSU.

Ethics Statement

The study protocol was approved by Ethical Committee of Guangzhou Dermatology Hospital. The patients in this manuscript have given written informed consent to publication of their case details. This study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors declare no conflicts of interest in this work.

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