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Drug persistence of omalizumab, cyclosporine, and hydroxychloroquine in antihistamine-refractory chronic spontaneous urticaria: A biomarker-stratified real-world study

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Abstract

Background: Real-world comparative data on alternatives to omalizumab for antihistamine-refractory chronic spontaneous urticaria (CSU) are limited, particularly in resource-constrained Asia-Pacific settings.

Objective: To compare drug survival among patients treated with omalizumab, cyclosporine, or hydroxychloroquine and evaluate associations between biomarkers and treatment persistence.

Methods: This retrospective single-center cohort of 409 patients (omalizumab n = 97, cyclosporine n = 85, hydroxychloroquine n = 227) analyzed drug survival using Kaplan-Meier analysis and Cox regression. Patients were stratified by total IgE and autoimmune biomarkers (antinuclear antibodies [ANA], thyroid autoantibodies).

Results: Omalizumab showed significantly longer drug survival than hydroxychloroquine (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.50–0.85), while cyclosporine did not retain significance after multivariable adjustment. After stratification by potential biomarkers, omalizumab demonstrated significantly longer drug survival than hydroxychloroquine in patients with elevated total IgE (HR 0.48, 95%CI 0.32–0.72), negative ANA (HR 0.63, 95%CI 0.45–0.88), or negative IgG thyroid autoantibodies (HR 0.58, 95%CI 0.37–0.93). In patients with normal total IgE levels, no significant differences in drug survival were observed among the three treatments (p = 0.795). Hydroxychloroquine showed drug survival comparable to cyclosporine irrespective of ANA status and among patients with IgG thyroid autoantibodies.

Conclusions: While omalizumab demonstrated longer overall drug survival, our findings suggest that in patients with normal total IgE or positive autoimmune biomarkers, hydroxychloroquine and cyclosporine may offer comparable drug persistence. These observations warrant prospective validation and suggest the potential value of biomarker-informed treatment approaches in resource-limited Asia-Pacific settings.

Key words: autoimmune markers, biomarkers, chronic spontaneous urticaria, cyclosporine, drug survival, hydroxychloroquine, omalizumab, total IgE, treatment persistence

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Introduction

The pathogenesis of chronic spontaneous urticaria (CSU) is fundamentally driven by mast cell and basophil activation, which subsequently releases histamine and pro-inflammatory mediators. These mechanisms are primarily categorized into Type I (autoallergic, IgE-mediated) and Type IIb (autoimmune, IgG-targeting FcεRI) endotypes.[3,8,13,18,31] This mechanistic diversity has spurred novel therapies, including next-generation biologics and intracellular signaling blockers like Bruton's tyrosine kinase (BTK) inhibitors.[24,33] While omalizumab effectively neutralizes IgE,[23] conventional immunomodulators like cyclosporine and hydroxychloroquine theoretically address the broader cellular and autoimmune pathways defining Type IIb CSU.[12,34]

Despite these novel targeted medications, the substantial real-world burden of CSU and the high costs of biologics severely restrict accessibility in resource-constrained regions like the Asia-Pacific.[22,27] Consequently, affordable oral immunomodulators remain frequently utilized.[6] Although hydroxychloroquine is an off-label therapy and not recognized as a standard second-line treatment in international guidelines, its well-established safety profile, low cost, and broad immunomodulatory properties make it a pragmatic alternative in resource-poor settings.[4,26] Given its real-world use as a cost-accessible alternative in our institution, particularly for patients with autoimmune features, we included hydroxychloroquine as a comparator in this study. A critical knowledge gap exists regarding their comparative real-world drug survival against omalizumab. Evaluating whether readily available biomarkers—such as total IgE and autoimmune markers—can predict treatment persistence is crucial for optimizing cost-effective, personalized care.[1,9]

In retrospective cohorts, standardized objective efficacy outcomes like the Urticaria Activity Score (UAS7) are often inconsistently documented. Therefore, this study utilizes "drug survival" as a pragmatic primary endpoint. We acknowledge that drug survival does not strictly equate to clinical efficacy; rather, it reflects a real-world composite of effectiveness, tolerability, patient preference, and financial constraints. By comparing the biomarker-stratified drug survival of these agents, we aim to identify biomarker-associated patterns in treatment persistence that may inform personalized, economically sustainable CSU management.

Materials and methods

Study population

This retrospective cohort study was conducted at a tertiary medical center in Taiwan and identified 17,294 CSU patients between January 1, 2013, and May 31, 2024. Their medical records were reviewed. The inclusion criteria included: (1) aged 18 years or older; (2) diagnosed with CSU (symptoms persisting for at least 6 weeks); and (3) receiving second-line therapy, including omalizumab, cyclosporine, or hydroxychloroquine, after failed second-generation H1-antihistamine treatment. Because objective scores (e.g., UAS7) were not routinely recorded in daily practice, first-line treatment failure was defined as the inability to achieve adequate disease control despite optimized H1-antihistamine therapy (a single or combination of second-generation H1-antihistamines at 2-4 times the standard dose for a minimum of 2 weeks), resulting from either poor efficacy (persistent symptoms) or intolerance (development of side effects that precluded dose maintenance), which ultimately prompted the physician to escalate to second-line therapy.

Patients were excluded if they had (1) concomitant autoimmune diseases, including systemic lupus erythematosus, Sjogren's syndrome, inflammatory myositis, pemphigus, rheumatoid arthritis, systemic sclerosis, mixed connective tissue disease, vasculitis, pemphigoid, Behcet's disease, and inflammatory bowel disease; and (2) combined use of omalizumab, cyclosporine, and hydroxychloroquine as second-line therapy. The final analysis included 409 patients: 97 in the omalizumab group, 85 in the cyclosporine group, and 227 in the hydroxychloroquine group (**Figure 1**). We employed an 'index-drug' approach, where each patient was counted only once based on their initial second-line therapy. To maintain group independence, patients switching medications were censored at the point of discontinuation. While the enrollment window spanned 10 years, individual drug survival was calculated from the index date to the last follow-up; patients with shorter treatment histories were treated as right-censored data. Because these medications are not reimbursed by Taiwan's National Health Insurance, treatment selection was determined through physician-patient shared decision-making, heavily factoring in out-of-pocket costs and long-term tolerability. For medications such as cyclosporine, a low-dose strategy was prioritized to achieve the minimal effective dose required for symptom control while minimizing potential adverse effects;

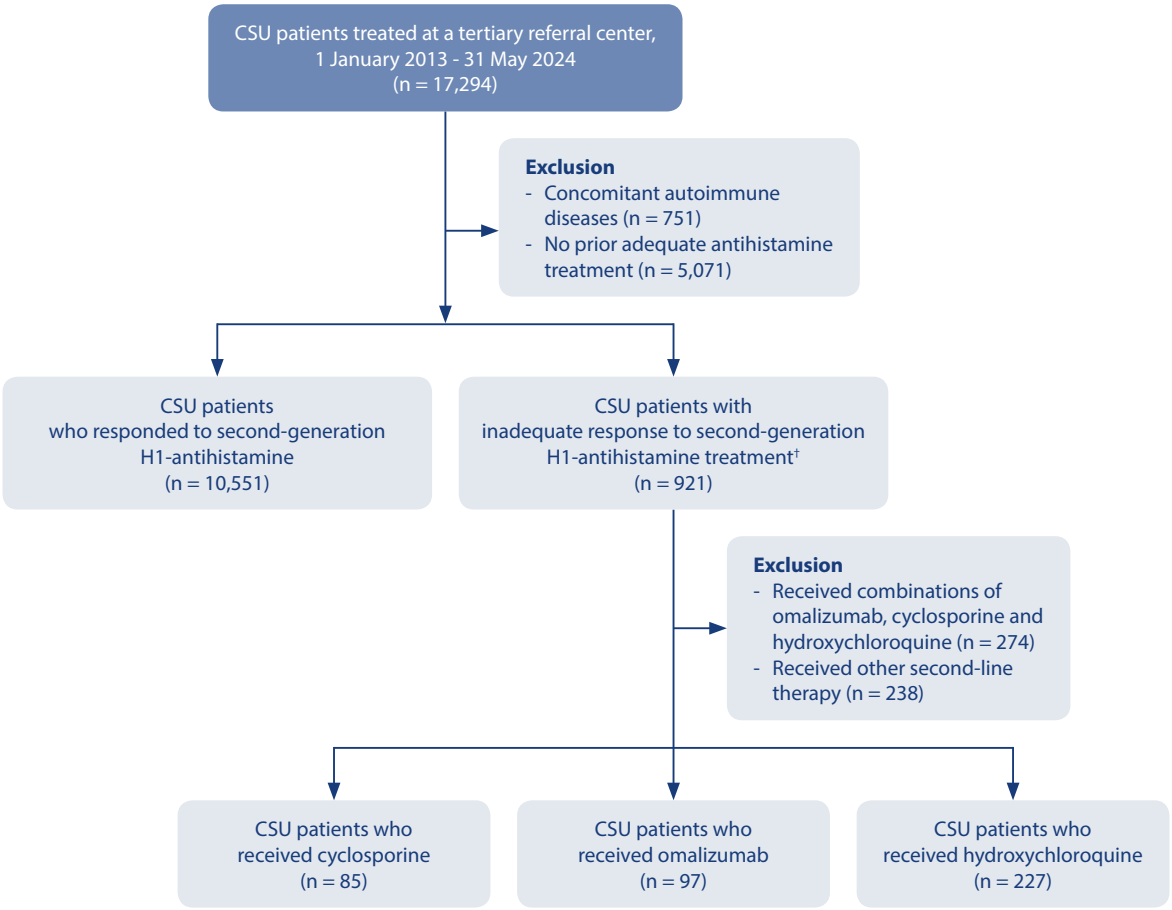

Figure 1. Patient enrollment flowchart.
†Defined as the inability to achieve adequate disease control despite a single or combination of second-generation H1-antihistamines at 2–4 times the standard dose for a minimum of 2 weeks, due to either poor efficacy (persistent symptoms) or intolerance (side effects precluding dose maintenance).
Abbreviations: CSU, chronic spontaneous urticaria

the specific dosing distributions are detailed in the Results section. The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital (approval number: CE24387C), and informed consent was waived due to the retrospective study design.

Data collection

Demographic data, clinical characteristics, laboratory results, and treatment details were extracted from the medical records. The first date of use of the patient's initially prescribed second-line therapy (omalizumab, cyclosporine, or hydroxychloroquine) was defined as the index date. Clinical characteristics included the presence of angioedema and prior systemic corticosteroid use for urticarial control. Laboratory parameters within 1 year before the index date were collected. Serum total IgE level was determined by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). The cut-off value for total IgE level was 114 kU/L. Biomarkers for autoimmunity included antinuclear antibody (ANA), IgG anti-thyroglobulin (ATG) antibody, and IgG anti-thyroid peroxidase (ATPO) antibody. ANA was determined with indirect immunofluorescence using a HEp-2 cell line (Medical & Biological Laboratories, Nagoya, Japan) and considered positive at titer ≥ 1:80.[2] Thyroid autoantibodies were determined by chemiluminescent immunoassay (Abbott, Chicago, IL). Positivity was defined according to the reference ranges: ATG antibody > 4.11 IU/mL, and ATPO antibody > 5.61 IU/mL.

Outcome measures

Primary outcome was drug survival, defined as the time from index date to drug discontinuation for any reason. This composite endpoint reflects real-world treatment persistence, integrating clinical response, tolerability, and accessibility. Patients continuing treatment until the end of the study period (December 31, 2024) or lost to follow-up were censored at their last outpatient visit. We compared the drug survival between omalizumab and cyclosporine users versus hydroxychloroquine users. In addition, reasons for discontinuation were recorded.

Stratification analysis

Pre-defined stratification analyses were conducted based on ANA positivity, positivity for thyroid autoantibodies (ATG or ATPO), and elevation of total IgE level.

Statistical analysis

Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. As the distributions for age, disease duration, total IgE levels, and creatinine significantly deviated from normality ($p < 0.05$), they were presented as the median with interquartile range (IQR) and compared using the Kruskal-Wallis test. Categorical variables were presented as counts with percentages and compared using the Chi-Square test or Fisher's exact test as appropriate. Drug survival was analyzed using the Kaplan-Meier method, and differences between treatment groups were assessed using the log-rank test. Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs) for drug discontinuation. Univariate Cox regression was performed for all baseline variables to screen for potential confounders. Because no background clinical or laboratory covariates reached statistical significance ($p < 0.05$) in the univariable Cox regression, they were excluded from the final multivariable models except for age and sex. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided p-value < 0.05 was considered statistically significant.

To address potential bias, analyses were anchored at treatment initiation to preclude immortal-time bias, and confounding by indication was addressed through Cox proportional hazards models adjusted for age and sex, as no other baseline covariates reached statistical significance in univariable Cox regression. Missing baseline covariates were handled with complete-case analysis, and percentages in descriptive tables exclude missing values unless otherwise specified; outcome times were not imputed. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations; the complete checklist is supplied.

Results

Demographics of selected patients

Patient characteristics are summarized in **Table 1**. The proportion of female patients was the highest in the hydroxychloroquine group (77.5%), compared to the omalizumab (67.0%) and cyclosporine (57.6%) groups ($p = 0.002$). The median disease duration was longer in the omalizumab group (33.6 weeks) compared to the cyclosporine (26.1 weeks) and hydroxychloroquine (13.2 weeks) groups ($p = 0.002$). Prior systemic corticosteroid use was most frequent in the cyclosporine group (57.6%), followed by the omalizumab group (40.2%) and the hydroxychloroquine group (30.0%) ($p < 0.001$). Treatment was discontinued in 74.2% of patients in the omalizumab group, 76.5% in the cyclosporine group, and 87.7% in the hydroxychloroquine group after a median follow-up of 45 months, 21 months, and 19 months, respectively. Reasons for drug discontinuation varied between groups (**Table 2**). Financial constraint was documented as a discontinuation reason in 29.2% of the omalizumab group, compared to 0% in the cyclosporine and hydroxychloroquine groups.

Regarding laboratory parameters, significant differences were observed in the total IgE level ($p = 0.019$), with the omalizumab group showing the highest level. The proportion of patients with elevated IgE was 57.3% (51/89) in the omalizumab group, 48.3% (28/58) in the cyclosporine group, and 45.2% (89/197) in the hydroxychloroquine group. ANA positivity rate was the lowest in the omalizumab group (23.9%), compared to the cyclosporine (42.6%) and hydroxychloroquine (33.6%) groups ($p = 0.044$). The ATG antibody positivity rate was higher in the hydroxychloroquine (33.0%) and omalizumab (24.1%) groups compared to the cyclosporine group (10.9%) ($p = 0.004$).

Table 1. Clinical and Demographic Characteristics of CSU Patients Treated with Omalizumab, Cyclosporine, and Hydroxychloroquine.

	Omalizumab users (n = 97)	Cyclosporine users (n = 85)	HCQ users (n = 227)	*p*-Value
Age, median (IQR) (years)	42.3 (33.4, 50.1)	47.6 (33.2, 57.4)	42.6 (33.1, 53.1)	0.252
Female sex, n (%)	65 (67.0)	49 (57.6)	176 (77.5)	0.002*
Disease duration, median (IQR) (weeks)[a]	33.6 (13.4, 104.3)	26.1 (8.6, 104.3)	13.2 (5.2, 52.3)	0.002*
Angioedema, n (%)	25 (25.8)	11 (12.9)	41 (18.1)	0.079
Prior systemic corticosteroids, n (%)	39 (40.2)	49 (57.6)	68 (30.0)	< 0.001*
Drug dosage				
Initial dose, median (IQR)	300.0 (150.0, 300.0) mg every 4 weeks	1.0 (0.8, 1.6) mg/kg/day	200.0 (200.0, 400.0) mg/day	
Maximum dose, median (IQR)	300.0 (150.0, 300.0) mg every 4 weeks	1.4 (0.8, 1.9) mg/kg/day	200.0 (200.0, 400.0) mg/day	
Drug discontinuation, n (%)	72 (74.2)	65 (76.5)	199 (87.7)	0.005*

Table 1. (Continued)

	Omalizumab users (n = 97)	Cyclosporine users (n = 85)	HCQ users (n = 227)	*p*-Value
Laboratory Parameters				
Creatinine, median (IQR) (mg/dL)[b]	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.7 (0.6, 0.9)	0.001*
Total IgE level, median (IQR) (kU/L)[c]	172.0 (68.3, 352.5)	96.2 (27.7, 361.5)	88.8 (36.8, 205.0)	0.019*
Markers for autoimmunity				
ANA[d]				0.044*
Negative, n (%)	67 (76.1)	39 (57.4)	144 (66.4)	
Positive, n (%)	21 (23.9)	29 (42.6)	73 (33.6)	
ATG antibody[e]				0.004*
Negative, n (%)	60 (75.9)	49 (89.1)	130 (67.0)	
Positive, n (%)	19 (24.1)	6 (10.9)	64 (33.0)	
ATPO antibody[f]				0.135
Negative, n (%)	57 (72.2)	48 (82.8)	136 (69.4)	
Positive, n (%)	22 (27.8)	10 (17.2)	60 (30.6)	

*$P < 0.05$ denotes statistical significance.
[a]Disease duration was not documented in 13 patients in the omalizumab group, 34 patients in the cyclosporine group, and 55 patients in the hydroxychloroquine group.
[b]Creatinine was not determined in 2 patients in the omalizumab group, 7 patients in the cyclosporine group, and 13 patients in the hydroxychloroquine group.
[c]Total IgE level was not determined in 8 patients in the omalizumab group, 27 patients in the cyclosporine group, and 30 patients in the hydroxychloroquine group.
[d]ANA antibody was not determined in 9 patients in the omalizumab group, 17 patients in the cyclosporine group, and 10 patients in the hydroxychloroquine group.
[e]ATG antibody was not determined in 18 patients in the omalizumab group, 30 patients in the cyclosporine group, and 33 patients in the hydroxychloroquine group.
[f]ATPO antibody was not determined in 18 patients in the omalizumab group, 27 patients in the cyclosporine group, and 31 patients in the hydroxychloroquine group.
Abbreviations: ANA, Anti-Nuclear antibody; ATG, Anti-Thyroglobulin; ATPO, Anti-Thyroid Peroxidase antibody; CSU, chronic spontaneous urticaria; HCQ, hydroxychloroquine; IQR, interquartile range

Table 2. Reasons for Drug Discontinuation.

	Omalizumab users (n = 97)	Cyclosporine users (n = 85)	Hydroxychloroquine users (n = 227)
Inefficacy, n (%)	12 (16.7)	2 (3.1)	4 (2.0)
Side effect, n (%)	1 (1.4)	5 (7.7)	5 (2.5)
Economic reason, n (%)	21 (29.2)	0 (0.0)	0 (0.0)
Unknown reason, n (%)	34 (47.2)	56 (86.2)	190 (95.5)
Remission, n (%)	4 (5.6)	2 (3.1)	0 (0.0)

Analysis of factors associated with drug survival

To compare the overall drug survival, Kaplan-Meier analysis demonstrated significant differences between the three treatment groups. Omalizumab showed a longer drug survival compared to cyclosporine and hydroxychloroquine users ($p = 0.005$) (**Figure 2A**). The median drug survival was 7.6 months for omalizumab, 7.2 months for cyclosporine, and 4.6 months for hydroxychloroquine. Furthermore, the univariable Cox regression demonstrated that both omalizumab (HR 0.68; 95%CI 0.52-0.89, $p = 0.005$) and cyclosporine (HR 0.69; 95%CI 0.52-0.92, $p = 0.011$) were significantly associated with a lower risk of drug discontinuation compared to hydroxychloroquine. In the multivariable Cox regression with adjustment for age and sex, only the omalizumab group retained statistical significance (HR 0.65; 95%CI 0.50-0.85, $p = 0.002$), while cyclosporine did not (HR 0.85; 95%CI 0.64-1.13, $p = 0.265$) (**Table S1**).

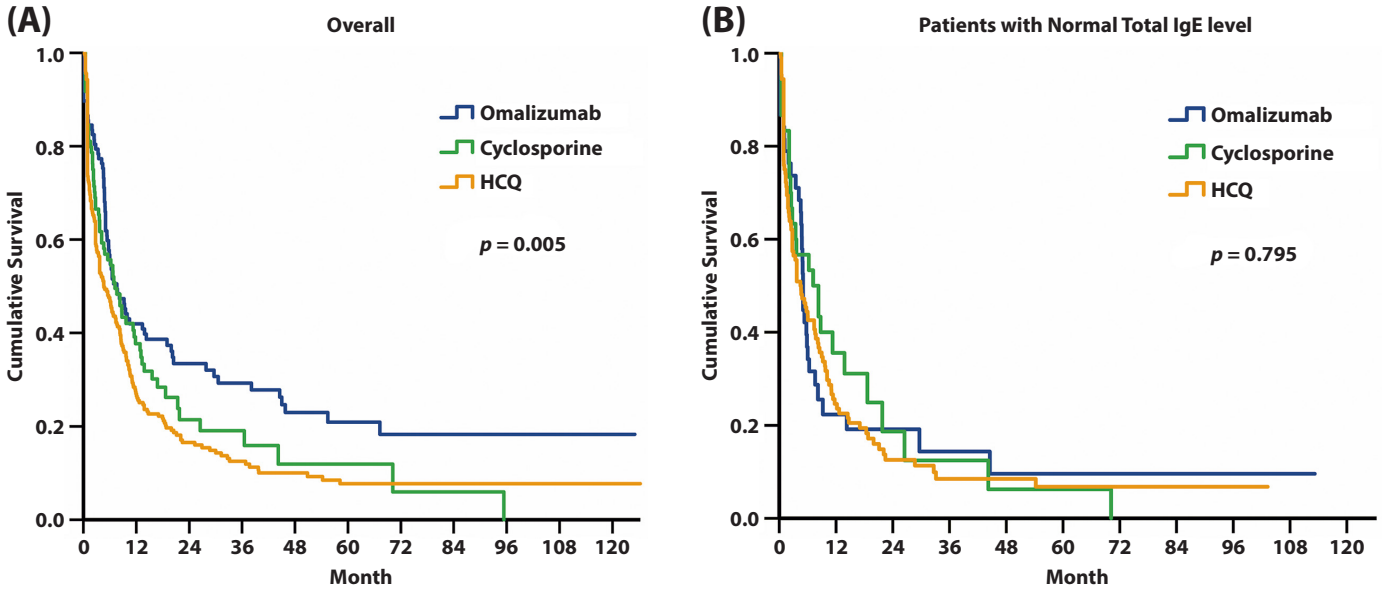

Figure 2. Kaplan-Meier Curves for Drug Survival. (A) Overall, (B) Patients with normal total IgE level.
[§]Total IgE level was not determined in 8 patients in the omalizumab group, 27 patients in the cyclosporine group, and 30 patients in the hydroxychloroquine group.
Abbreviations: HCQ, hydroxychloroquine

Stratified analyses by Kaplan-Meier survival curve

In patients stratified by ANA positivity (**Figure S1A, B**), significant differences in drug survival were observed in ANA-negative patients (p = 0.018), but not in ANA-positive patients (p = 0.244). In ANA-negative patients, the median drug survival was 6.9 months for omalizumab, 4.6 months for cyclosporine, and 4.4 months for hydroxychloroquine. When patients were stratified by positivity for thyroid autoantibodies (**Figure S1C, D**), no significant differences in drug survival were observed in either antibody-positive or antibody-negative patients. When stratified by total IgE level, omalizumab demonstrated a significantly longer drug survival compared to cyclosporine and hydroxychloroquine in patients with elevated total IgE level (p = 0.003) (**Figure S1E**). The median drug survival was 19.0 months for omalizumab, versus 6.7 and 4.6 months for cyclosporine and hydroxychloroquine, respectively. In patients with normal total IgE level, no significant differences in drug survival were observed between treatment groups (p = 0.795) (**Figure 2B**).

Table 3. Stratified Cox Regression Analysis for Drug Survival.

	Multivariable (adjusted for age and sex)					
	Hazard ratio of omalizumab users[†]	95%CI	*p*-Value	Hazard ratio of cyclosporine users[†]	95%CI	*p*-Value
Patients with positive ANA[a]	0.64	(0.36-1.13)	0.124	0.97	(0.58-1.63)	0.920
Patients with negative ANA[a]	0.63	(0.45-0.88)	0.006*	0.95	(0.65-1.41)	0.814
Patients with positive ATG or ATPO antibodies[bc]	0.65	(0.38-1.09)	0.100	1.25	(0.62-2.52)	0.530
Patients with negative ATG, and ATPO antibodies[bc]	0.58	(0.37-0.93)	0.024*	0.69	(0.42-1.12)	0.133
Patients with elevated total IgE level[d]	0.48	(0.32-0.72)	<0.001*	0.80	(0.49-1.31)	0.373
Patients with normal total IgE level[d]	0.97	(0.65-1.46)	0.889	0.88	(0.56-1.39)	0.588

[†]Hydroxychloroquine users as a reference group.
*P < 0.05 denotes statistical significance.
[a]ANA antibody was not determined in 9 patients in the omalizumab group, 17 patients in the cyclosporine group, and 10 patients in the hydroxychloroquine group.
[b]ATG antibody was not determined in 18 patients in the omalizumab group, 30 patients in the cyclosporine group, and 33 patients in the hydroxychloroquine group.
[c]ATPO antibody was not determined in 18 patients in the omalizumab group, 27 patients in the cyclosporine group, and 31 patients in the hydroxychloroquine group.
[d]Total IgE level was not determined in 8 patients in the omalizumab group, 27 patients in the cyclosporine group, and 30 patients in the hydroxychloroquine group.
Abbreviations: ANA, Anti-Nuclear antibody; ATG, Anti-Thyroglobulin; ATPO, Anti-Thyroid Peroxidase

Stratified analyses by Cox regression

In patients with negative ANA, as shown in **Table 3**, omalizumab demonstrated a significantly longer drug survival compared to hydroxychloroquine (HR 0.63, 95%CI 0.45-0.88). In ANA-positive patients, neither omalizumab (HR 0.64, 95%CI 0.36-1.13) nor cyclosporine (HR 0.97, 95%CI 0.58-1.63) showed a statistically significant longer drug survival compared to hydroxychloroquine.

In patients negative for thyroid antibodies, omalizumab demonstrated significantly longer drug survival compared to hydroxychloroquine (HR 0.58, 95%CI 0.37-0.93). In patients with positive thyroid antibody, neither omalizumab (HR 0.65, 95%CI 0.38-1.09) nor cyclosporine (HR 1.25, 95%CI 0.62-2.52) showed a longer drug survival compared to hydroxychloroquine.

In patients with elevated total IgE level, we observed a significantly longer drug survival regarding omalizumab compared to hydroxychloroquine (HR 0.48, 95%CI 0.32-0.72). In patients with normal total IgE level, omalizumab (HR 0.97, 95%CI 0.65-1.46) and cyclosporine (HR 0.88, 95%CI 0.56-1.39) showed no significant differences in drug survival compared to hydroxychloroquine.

Discussion

This retrospective cohort study provides real-world evidence regarding drug survival of omalizumab and cyclosporine versus hydroxychloroquine in antihistamine-refractory CSU. Overall, omalizumab had a longer drug survival than cyclosporine and hydroxychloroquine. However, biomarker-stratified analyses revealed a more nuanced picture: the longer drug survival of omalizumab was most pronounced in patients with elevated total IgE levels and negative autoimmune markers. In contrast, for patients with normal total IgE levels or positive autoimmune biomarkers, the inexpensive oral alternatives—hydroxychloroquine and low-dose cyclosporine—demonstrated comparable drug survival to the biologic agent.

Consistent with previous real-world reports on omalizumab drug survival,[16,17,21,32] and supported by landmark randomized control trials establishing its efficacy in antihistamine-refractory CSU,[23,28,29] we found that omalizumab had longer drug survival, but not cyclosporine, versus hydroxychloroquine in antihistamine-refractory CSU patients. Previously, Savic et al. conducted a retrospective multicenter study comparing outcomes in 45 CSU patients based on Dermatology Life Quality Index (DLQI) scores.[30] Omalizumab appeared more effective than cyclosporine despite a large proportion of missing data and patient heterogeneity in prior treatments. Our study enrolled more patients, and the results align with previous findings, although the dosage of our cyclosporine was very low (the median maximum dose: 1.4 mg/kg/day).

According to Kulthanan et al.'s meta-analysis,[19] cyclosporine dosage categories are very low (< 2 mg/kg/day), low (2 to < 4 mg/kg/day), and moderate (4-5 mg/kg/day). Previous studies reported effective CSU treatment with very-low-dose cyclosporine (1.8 ± 1.1 mg/kg/day and 1.5-2.5 mg/kg/day, respectively),[5,14] as well as favorable side effects.[19] Our cyclosporine users received very low doses, resulting in few discontinuations due to adverse effects (7.7%). While international guidelines recommend cyclosporine at 3–5 mg/kg/day,[35] our findings suggest that very-low-dose cyclosporine may be a reasonable option in specific contexts, particularly for patients with autoimmune biomarkers or normal IgE levels where financial access to biologics is limited.

Fok et al. reported inconclusive evidence for ANA in the prediction of therapeutic response to omalizumab and cyclosporine.[11] Our study found that omalizumab had a longer survival than hydroxychloroquine in ANA-negative but not in ANA-positive patients. This finding is noteworthy as we excluded patients with definite autoimmune diseases, indicating that ANA positivity itself is associated with differences in treatment persistence. This aligns with Ertaş et al.'s finding regarding a lower response rate to omalizumab in ANA-positive patients.[9] Our findings may suggest biomarker-associated differences in treatment persistence, which was in line with CSU endotypes.[17,20] Type I CSU (elevated total IgE) might be more omalizumab-responsive,[15] whereas type IIb CSU (positive biomarkers for autoimmunity) might respond better to cyclosporine and hydroxychloroquine. The apparent discrepancy in the predictive value of ANA versus ATG in our analysis may reflect the distinct antigenic targets of these biomarkers—ANA representing systemic nuclear antigens and ATG being organ-specific. Since no single biomarker captures the entire Type IIb (autoimmune) population, ANA likely served as a more sensitive surrogate in this cohort for identifying patients whose disease is driven by mechanisms distinct from the pure IgE-mediated pathway. The statistically significant baseline differences in ANA and ATG positivity across groups may reflect confounding by indication, as clinicians preferentially selected oral immunomodulators for patients with autoimmune markers. This imbalance is consistent with clinicians using these biomarkers to inform treatment selection in real-world practice, reflecting the suspected Type IIb endotype. By employing stratified analyses, we accounted for this selection bias and confirmed that these available biomarkers provide clinical insights into treatment persistence.

We selected hydroxychloroquine for comparisons due to its well-established immunomodulatory effects and favorable side effects.[25] A small, controlled trial found hydroxychloroquine improved quality of life with a trend toward symptom improvement.[26] Our data demonstrated its potential as a viable option in CSU patients with positive biomarkers for autoimmunity, which was implied by a comparable drug survival to very-low-dose cyclosporine. This is noteworthy considering previous inconclusive evidence on hydroxychloroquine use in CSU.[4,16] Our results align with the hypothesis of a type IIb (autoimmune) endotype, where IgG autoantibodies against FcεRI or IgE drive mast cell activation.

Hydroxychloroquine's mechanisms—including lysosomal alkalization, TLR inhibition, and modulation of antigen presentation—may theoretically address autoimmune pathways distinct from IgE-mediated mechanisms targeted by omalizumab.[25] Hydroxychloroquine could be considered a reasonable option for the type IIb endotype, particularly in settings where biologic access is limited.

The similar drug survival observed between omalizumab and hydroxychloroquine in our normal IgE subgroup likely reflects the composite nature of this endpoint. Since omalizumab is not reimbursed in our setting, patients without an immediate 'super-responder' benefit may discontinue it early due to financial burden, whereas the low cost of hydroxychloroquine facilitates longer-term maintenance even with modest efficacy. In this cohort—where omalizumab's biological advantage is less pronounced—out-of-pocket costs may equalize retention rates with more affordable options like hydroxychloroquine. Consequently, longer drug survival in this study should be interpreted as a measure of overall treatment sustainability in a specific socioeconomic context, rather than a direct surrogate for superior clinical efficacy.

Based on these observations, a resource-stratified approach to CSU management may warrant prospective evaluation in Asian populations. For patients with elevated total IgE levels (type I phenotype), omalizumab remains the preferred second-line therapy due to its superior drug survival. In settings where biologic access is severely limited by cost or availability—a common challenge in the Asia-Pacific region—our observations tentatively support consideration of hydroxychloroquine or very-low-dose cyclosporine (1-2 mg/kg/day) as pragmatic alternatives for patients with autoimmune biomarkers or normal IgE, acknowledging the limitations of drug survival as a surrogate for efficacy.

Several limitations should be acknowledged. First, the retrospective design may introduce bias. While standard clinical practice naturally precludes prescribing immunosuppressants to patients with known absolute medical contraindications or severe active infections, we could not systematically control for relative contraindications or transient infections. Furthermore, the choice of second-line therapy was determined by the treating physician through a shared decision-making process with the patient; thus, individual physician preferences and patient-specific factors—which were not captured in this database—may have influenced treatment selection. Since omalizumab, cyclosporine, and hydroxychloroquine were not reimbursed by Taiwan's National Health Insurance and required out-of-pocket payment, their different costs may cause selection bias. The predominantly Han Chinese population and single-center design may limit generalizability. Second, reasons for discontinuation were mostly unknown, which limited the understanding of factors driving differences in drug survival. Third, this study lacked disease activity measures (e.g., UAS7) for comparison or incorporation into the regression model. Consequently, longer drug survival cannot be directly equated to superior clinical efficacy. Furthermore, although prior systemic corticosteroid use was not associated with drug survival in the univariable Cox regression, including these patients means such exposure might have falsely lowered total IgE levels in some cases, potentially misclassifying their baseline endotype. Nevertheless, we did enroll relatively homogeneous antihistamine-refractory CSU patients requiring second-line therapy. Fourth, some physicians may avoid long-term use of cyclosporine due to nephrotoxicity, although the dosage may be more relevant to such toxicity.[10] In our cohort, the median dose of cyclosporine was very low, with a much-lessened risk. Furthermore, per the international and local guidelines,[7,35] long-term use of cyclosporine is listed as a treatment option. Finally, our observational study cannot replace an interventional trial, and head-to-head trials comparing these treatments using standardized efficacy outcomes are needed.

Conclusion

Among antihistamine-refractory CSU patients, omalizumab demonstrated a significantly longer drug survival compared to cyclosporine and hydroxychloroquine, especially for patients with negative biomarkers for autoimmunity and elevated total IgE level. For patients with normal total IgE level, cyclosporine and hydroxychloroquine had a similar drug survival to omalizumab. In patients with positive biomarkers for autoimmunity, hydroxychloroquine demonstrated a comparable drug survival to very-low-dose cyclosporine. These findings are consistent with a biomarker-guided approach to CSU management that reflects a balance between treatment maintenance and real-world socioeconomic considerations, optimizing resource utilization especially in regions where access to biologics is limited.

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Competing Interests

- Sheu H-S: None declared;
- Chen Y-M: None declared;
- Chen J-P: None declared;
- Juan C-K: None declared;
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- Tang K-T: None declared.

Ethics Approval

The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital (approval number: CE24387C).

Consent to participate

Informed consent was waived by the Institutional Review Board of Taichung Veterans General Hospital (CE24387C) due to the retrospective design.

Consent to publish

Not applicable; this article does not contain any identifying individual person's data.

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Author Contributions

- Heh-Shiang Sheu was involved in the conceptualization, methodology, original draft preparation, and reviewing and editing of the manuscript.
- Jun-Peng Chen was involved in statistical analysis.
- Chao-Kuei Juan was involved in reviewing the manuscript.
- Wen-Nan Huang was involved in reviewing the manuscript.
- Yi-Hsing Chen participated in reviewing the manuscript.
- Yi-Ming Chen was involved in the conceptualization of this study.
- Kuo-Tung Tang was involved in the conceptualization of this study, resource acquisition, and reviewing and editing of the manuscript.
- All authors have read and agreed to the published version of the manuscript.

Data availability

De-identified individual data and analysis code are available from the corresponding author upon reasonable request and with institutional approval. Aggregate data are included within the article and its Supplementary Information.

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Supplementary material

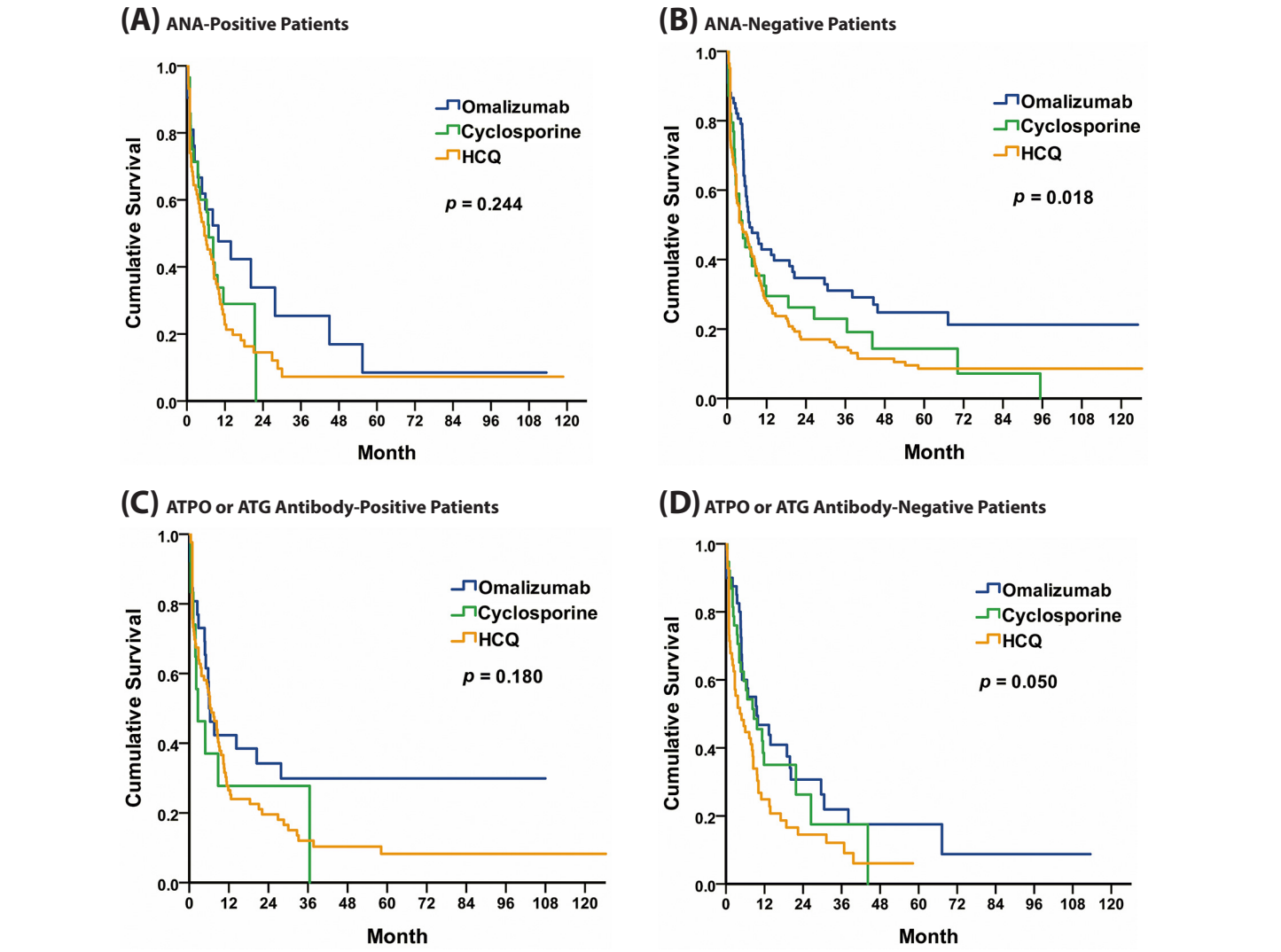

Figure S1. Kaplan-Meier Curves for Drug Survival, (A-B) stratified by ANA positivity, (C-D) stratified by thyroid antibody positivity, and (E) in patient with elevated total IgE level.

[¶]ANA antibody was not determined in 9 patients in the omalizumab group, 17 patients in the cyclosporine group, and 10 patients in the hydroxychloroquine group.

[‖]ATG antibody was not determined in 18 patients in the omalizumab group, 30 patients in the cyclosporine group, and 33 patients in the hydroxychloroquine group.

[#]ATPO antibody was not determined in 18 patients in the omalizumab group, 27 patients in the cyclosporine group, and 31 patients in the hydroxychloroquine group.

[$]Total IgE level was not determined in 8 patients in the omalizumab group, 27 patients in the cyclosporine group, and 30 patients in the hydroxychloroquine group.

Abbreviations: ANA, Anti-Nuclear antibody; ATG, Anti-Thyroglobulin; ATPO, Anti-Thyroid Peroxidase; HCQ, hydroxychloroquine.

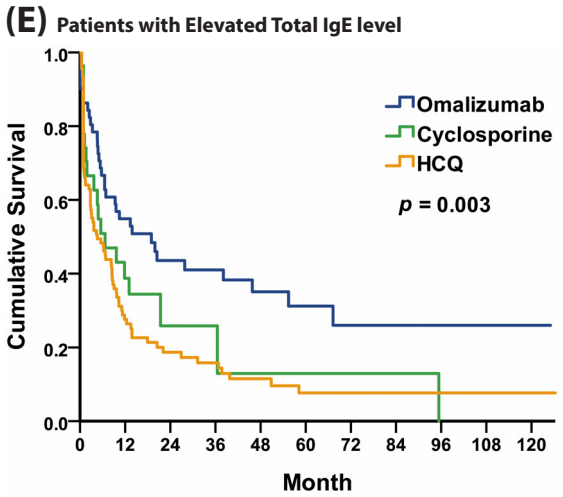

Figure S1. (Continued)

Table S1. Cox regression analysis of risk factors for drug survival.

	Univariable			Multivariable		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (years)	1.00	(1.00-1.01)	0.335	1.00	(0.99-1.01)	0.567
Male gender	0.96	(0.76-1.22)	0.749	0.95	(0.75-1.22)	0.699
Angioedema	0.88	(0.66-1.17)	0.376			
Disease duration (weeks)	1.00	(1.00-1.00)	0.121			
Prior systemic corticosteroids use	0.89	(0.71-1.11)	0.288			
Creatinine (mg/dL)†	0.71	(0.41-1.25)	0.239			
Total IgE level (kU/L)‡	1.00	(1.00-1.00)	0.446			
ATG antibody positivity§	0.90	(0.69-1.18)	0.448			
ATPO antibody positivity¶	0.94	(0.72-1.23)	0.672			
ANA positivity‖	1.11	(0.87-1.41)	0.393			
Omalizumab (reference group: HCQ)	0.68	(0.52-0.89)	0.005*	0.65	(0.50-0.85)	0.002*
Cyclosporine (reference group: HCQ)	0.69	(0.52-0.92)	0.011*	0.85	(0.64-1.13)	0.265

*$P < 0.05$ denotes statistical significance.
†Creatinine was not determined in 2 patients in the omalizumab group, 7 patients in the cyclosporine group, and 13 patients in the hydroxychloroquine group.
‡Total IgE level was not determined in 8 patients in the omalizumab group, 27 patients in the cyclosporine group, and 30 patients in the hydroxychloroquine group.
§ATG antibody was not determined in 18 patients in the omalizumab group, 30 patients in the cyclosporine group, and 33 patients in the hydroxychloroquine group.
¶ATPO antibody was not determined in 18 patients in the omalizumab group, 27 patients in the cyclosporine group, and 31 patients in the hydroxychloroquine group.
‖ANA antibody was not determined in 9 patients in the omalizumab group, 17 patients in the cyclosporine group, and 10 patients in the hydroxychloroquine group.
ANA, Anti-Nuclear antibody; ATG, Anti-Thyroglobulin; ATPO, Anti-Thyroid Peroxidase; HCQ, hydroxychloroquine; HR: hazard ratio; CI: confidence interval.