Original Article

Biopredictors for Omalizumab Response in Patients With Chronic Spontaneous Urticaria

Megan Le, MD, Tara McCaffrey, BA, Li Gao, MD, PhD, and Sarbjit Saini, MD *Baltimore, Md*

What is already known about this topic? Current chronic spontaneous urticaria treatment guidelines recommend omalizumab for patients who are antihistamine-refractory. However, 40% to 50% of patients on omalizumab do not achieve full control, highlighting the need for predictors of omalizumab response.

What does this article add to our knowledge? This study found that basopenia (measured by low blood histamine content) and CU Index positivity individually predicted poorer omalizumab response, with the combination of low IgE and low blood histamine content also linked to reduced omalizumab response.

How does this study impact current management guidelines? This study suggests that negative biopredictors can aid in identifying poor omalizumab responders and may guide earlier use of alternative therapies such as dupilumab and Bruton's tyrosine kinase inhibitors.

BACKGROUND: Proposed negative biopredictors of omalizumab response in patients with chronic spontaneous urticaria are low baseline IgE (≤40 IU/mL), positive CU Index (CUI) test result, and basopenia defined by blood histamine content (BHC) (≤8 ng/mL).

OBJECTIVE: To test the hypothesis that patients with these negative biopredictors will have a poorer response to omalizumab.

METHODS: We performed a retrospective analysis of 3 phase III studies of antihistamine-refractory subjects with chronic spontaneous urticaria who received omalizumab 300 mg every 4 weeks for 12 weeks. The relationship between baseline biopredictors and subjects with excellent symptom control measured by Urticaria Activity Score over 7 days (UAS7 ≤ 6) or poor symptom control (UAS7 > 6) after 12 weeks was examined. We performed χ^2, logistic regression, and receiver-operating characteristic analysis.

RESULTS: In 363 subjects, data were available for IgE and CUI; 266 had BHC measures. Subjects with UAS7 higher than 6 at 12 weeks significantly more often expressed a baseline negative biopredictor: IgE level less than or equal to 40 IU/mL (n = 109 [50%]) versus IgE level more than 40 IU/mL (n = 239 [33%]); CUI positive (n = 98 [55%]) versus negative (n = 263 [32%]); BHC less than 8 ng/mL (n = 64 [55%]) versus BHC more than 8 ng/mL (n = 202 [33%]). CUI positivity significantly predicted a UAS7 higher than 6 at 12 weeks ($P = .0002$; odds ratio, 2.54; 95% CI, 1.55-4.15). According to receiver-operating characteristic curve analysis, a BHC of 6.4 ng/mL was distinguishing nonresponders from responders. Among subjects with low baseline IgE, the presence of low BHC was predictive for nonresponsiveness to omalizumab ($\chi^2 = 4.215$; $P = .040$).

CONCLUSIONS: Subjects with positive CUI, low BHC, or both low IgE and BHC have an increased likelihood of poorer response to omalizumab at 12 weeks. **(J Allergy Clin Immunol Pract 2026;14:495-502)**

Key words: *Urticaria; Omalizumab; Biopredictors*

INTRODUCTION

Chronic spontaneous urticaria (CSU) involves symptoms of urticaria and angioedema on most days for longer than a 6-week period and affects 0.5% to 1% of the US population.[1] Studies support an association with autoimmune diseases, and notably, there is an increased incidence of thyroid autoimmunity with a 5- to nearly 7-fold higher risk of displaying thyroid peroxidase antibody positivity.[2-4] Although disease pathogenesis remains unclear, one theory is that a subset of patients possesses pathogenic IgG autoantibodies that target IgE or its high-affinity IgE receptor.[5] However, standardized tests for autoantibodies remain elusive and current tests often give discordant results.[6,7]

Current guidelines for the treatment of CSU recommend starting with a daily second-generation histamine-1 receptor antagonist and raising the dose up to 4 times the labeled dose as needed.[8] Approximately 50% of patients remain uncontrolled by high-dose antihistamines and are advanced to omalizumab, the

Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md

L.G. was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number R01AI181867.

Conflicts of interest: All the authors declare that they have no relevant conflicts of interest.

Received for publication June 15, 2025; revised September 24, 2025; accepted for publication November 17, 2025.

Available online November 28, 2025.

Corresponding author: Sarbjit S. Saini, MD, Division of Allergy and Immunology, 5501 Hopkins Bayview Circle, Rm 2B.71B, Baltimore, MD 21224. E-mail: ssaini@jhmi.edu.

2213-2198

https://doi.org/10.1016/j.jaip.2025.11.029

Abbreviations used
BHC- blood histamine content
BMI- body mass index
CSU- chronic spontaneous urticaria
CUI- CU Index
ROC- receiver-operating characteristic
UAS7- Urticaria Activity Score over 7 days

first biologic approved for antihistamine-refractory patients.[9] However, 40% to 50% of patients with CSU treated with monthly 300 mg omalizumab injections fail to have complete control after a 3- to 6-month trial and after unsuccessful omalizumab updosing should be offered alternative therapy.[8,10] Thus, there is a need to determine predictors for omalizumab response to permit more rapid advance to effective therapies for patients.

To date, a few predictors for omalizumab response have been examined in small studies. One proposed negative biopredictor for omalizumab response is CU Index (CUI), a commercial assay that tests CSU patient's serum for the ability to evoke histamine release from healthy donor basophils.[11] This serum activity is assumed to be indicative of the presence of functional IgG anti−FceRI or anti-IgE antibodies; however, a positive response does not always agree with other assays that directly measure such autoantibodies.[5-7] CUI positivity can also be observed in healthy controls[11] and other autoimmune diseases.[12] The presence of a positive serologic autoimmune test result with basophils predicted a slower time to respond to omalizumab as compared with a negative test result.[13,14]

Low serum IgE is another negative biopredictor for omalizumab response that has been reported. In a study of 137 patients with CSU undergoing omalizumab therapy, those in the lowest quartile for IgE (≤15.2 IU/mL) have a lower rate of successful response to omalizumab.[15] This lower response with low baseline IgE levels has also been noted by other groups.[16-18]

A third negative biopredictor is a low number of circulating blood basophils or basopenia, a feature also associated with disease severity.[19] In 2 small studies, patients with CSU with reduced baseline blood basophil numbers had a reduced clinical response to omalizumab as compared with those with normal basophil numbers.[20,21]

Given the evidence of these 3 factors, we therefore performed a retrospective analysis that examined the impact of the presence of these 3 biopredictors relative to omalizumab efficacy in antihistamine-refractory patients with CSU.

METHODS

Clinical data sets baseline predictors

This is a retrospective study using data from 3, phase III, randomized, placebo-controlled, clinical trials of the efficacy of omalizumab in antihistamine-refractory subjects with CSU: Asteria I,[22] Asteria II,[23] and Glacial.[24] All subjects in the Asteria trials were on once-a-day standard dose antihistamines as background therapy, whereas Glacial allowed the use of higher doses of antihistamines, histamine-2 receptor antagonists, and leukotriene agents. Subjects were randomized to receive 1 of the following omalizumab doses subcutaneously: placebo, 75 mg, 150 mg, or 300 mg of omalizumab every 4 weeks during the course of the trials (Asteria I, II) or placebo and 300 mg every 4 weeks (Glacial) (Figure 1).

For this study, we extracted data only on those subjects who were receiving the highest US Food and Drug Administration−approved dose of 300 mg given the evidence for maximal benefit from this treatment and the frequent use of this dose in clinical practice.[10] Among the pooled 300-mg recipients, baseline total serum IgE and CUI data were available for nearly all participants, whereas baseline blood histamine content (BHC) (an indirect measure of circulating basophil number) data were limited to US sites due to constraints in assay protocols.[25]

For symptom assessment, we extracted the pretherapy baseline Urticaria Activity Score over 7 days or UAS7, the most widely accepted clinical score to evaluate control of CSU.[26] It is composed of the daily itch score (0-3 max) and the daily hive score (0-3 max, with 0 = no hives, 1 = 1-6 hives, 2 = 7-12 hives, 3 = >12 hives). The maximum daily score is 6, with a maximum of 3 for both itch and hives, with a maximum score of 42 for 7 days. We further extracted UAS7 after 12 weeks of treatment and categorized the clinical response as follows: UAS7 = 0 (complete control of symptoms), UAS7 less than or equal to 6 (well-controlled symptoms), UAS7 more than 6 (poorly controlled symptoms).[27] A total of 49 patients were excluded from the 12-week analysis because of missing raw UAS7 (Figure 1).

Biopredictor outcomes included subgroup analyses based on baseline IgE levels (≤40 IU/mL vs >40 IU/mL), CUI positivity, and BHC (≤8 ng/mL vs >8 ng/mL). Data on histamine content were categorized according to the definition previously published in the Johal et al[20] study, where baseline basophil histamine measures was defined as high (>8 ng/mL) or low (≤8 ng/mL), which is equivalent to 8000 basophils per milliliter blood. Low IgE was determined as less than or equal to 40 IU/mL based on previous literature.[7]

Statistical analysis

Descriptive statistics summarized baseline characteristics and treatment responses. To assess the relationship between the baseline predictors and UAS7 outcomes, we performed χ^2 testing for the single and dual biopredictor presence. In addition, logistic regression analysis was performed comparing responders to nonresponders to omalizumab for each biopredictor; models were adjusted for confounders: age, sex, body mass index (BMI), presence of angioedema, and previous medications. The responsiveness status and baseline blood histamine data were collected for calculating the receiver-operating characteristic (ROC) curve and Youden Index for determining the cutoff value for BHC. The Youden Index is the value that maximizes the sensitivity and specificity, helping to choose an appropriate cutoff point for a diagnostic test.

All statistical analyses were performed using MedCalc Statistical Software version 18.11.3 (MedCalc Software, Ostend, Belgium). Statistical significance was defined as P less than .05.

RESULTS

Demographics

The study population consisted of patients who received 300 mg of omalizumab at 12 weeks, with baseline characteristics analyzed in 2 cohorts: a full cohort of 363 patients and a subset of this larger cohort with 266 subjects for whom BHC levels were available (Table I). The mean age of the larger cohort was 43 years, with 75% of patients identifying as female. The mean body weight and BMI were 82 kg and 29, respectively. For the smaller subset of 266 patients with available BHC data, the demographics were quite similar. The distribution of the

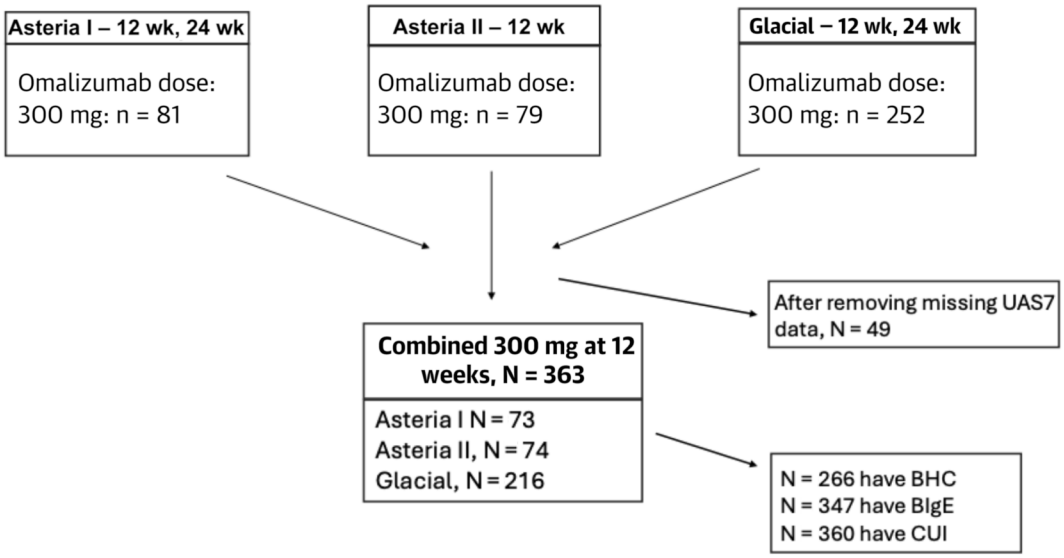


FIGURE 1. Flow diagram of data extraction. Overview of the 3 clinical trials from which 300 mg omalizumab recipient data were extracted.[22-24] *BIgE*, Baseline IgE.

TABLE I. Baseline pooled characteristics of 300-mg recipients

Characteristics at baseline	Subjects with IgE and CUI (N = 363)	Subjects with IgE, CUI, and BHC (N = 266)
Mean age (y)	43 ± 14	42 ± 14
Sex: female	75%	77%
Mean BWT (kg)	82 ± 21	83 ± 22
Mean BMI (kg/m^2)	29 ± 7	30 ± 7
Mean IgE (IU/mL)	168 ± 298	155 ± 253
Median IgE (IU/mL) (range)	82 (1-3050)	84 (1-3050)
Quartiles for IgE (IU/mL) (Q1, Q3)	30, 175	33, 170
Frequency of IgE ≤40 IU/mL	N = 109, 31%	N = 77, 29%
Mean UAS7	31 ± 6	30 ± 7
Median UAS7	31	31
Quartiles for UAS7 (Q1, Q3)	26, 35	26, 35
Frequency of CUI positive	N = 98, 27%	N = 74, 27%
Mean BHC (ng/mL)*	—	15 ± 9
Median BHC (ng/mL)* (range)	—	14 (2.5-55)
Quartiles for BHC (ng/mL) (Q1, Q3)*	—	8, 21
Frequency of BHC ≤8 ng/mL	—	N = 64, 24%

BWT, body weight.
*Because of the nature of obtaining blood histamine, blood histamine samples came only from sites in the United States; thus, the lower sample size.

negative predictors was also examined (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Low baseline IgE

We first examined the impact of low serum baseline IgE on the level of symptom control determined by UAS7 after 12 weeks of 300 mg omalizumab. The average baseline UAS7 in those with low serum IgE (≤40 IU/mL) was 30.24 (n = 109) as compared with 30.78 in those with high serum IgE (>40 IU/mL) (n = 239) (Figure 2, *A*).

After 12 weeks of therapy with monthly 300 mg omalizumab, the group with low IgE had poorer symptom control, week 12 UAS7 mean 11.16 as compared with 6.56 for those with higher baseline IgE (Figure 2, *A*). The frequency of subjects with poor CSU symptom control (UAS7 > 6) at 12 weeks was higher in the subjects with low baseline IgE as compared with subjects with a baseline IgE higher than 40 IU/mL ($\chi^2 = 10.587$; $P = .005$) (Figure 2, *B*).

However, baseline IgE levels were not associated with UAS7 responses, after adjusting for confounders (age, sex, BMI, presence of angioedema, previous medications) ($P = .091$; odds ratio, 1.0; 95% CI, 0.99-1.0) (Table II).

CUI positivity at baseline

We further examined CUI positivity and week 12 UAS7. The average baseline UAS7 in those with positive CUI was 30.35

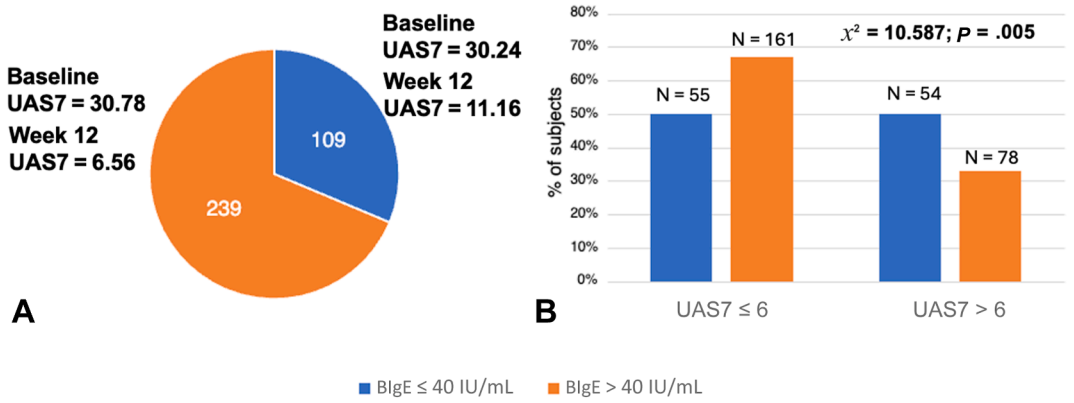


FIGURE 2. (**A**) Baseline IgE and mean UAS7 at baseline and after 12 weeks of omalizumab in those with low or high baseline IgE. (**B**) Percentage of subjects with well-controlled CSU symptoms after 12 weeks of omalizumab treatment (week 12 UAS7 $\leq$ 6) vs poor control (UAS7 $>$ 6) relative to baseline IgE values ($\chi^2 = 10.587$; $P = .005$). *BIgE*, Baseline IgE.

TABLE II. χ^2 testing or logistic regression for biopredictors for omalizumab nonresponse at 12 wk (UAS7 $>$ 6)

Biopredictor(s)	*P* value
Low IgE (≤40 IU/mL)	$P = .091$, odds ratio: 1.0, 95% CI, 0.99-1.0
CUI positivity	$P = .0002$; odds ratio: 2.54; 95% CI, 1.55-4.15
Low BHC (≤8 ng/mL)	$P = .028$, odds ratio: 0.9654, 95% CI, 0.936-0.996
Low IgE (≤40 IU/mL), CUI positivity	$P = .061$, $\chi^2 = 3.5179$
Low IgE (≤40 IU/mL), low BHC (≤8 ng/mL)	$P = .04$, $\chi^2 = 4.2152$
CUI positivity, low BHC (≤8 ng/mL)	$P = .064$, $\chi^2 = 3.4255$
Low IgE (≤40 IU/mL), CUI positivity, low BHC (≤8 ng/mL)	$P = .0001$, $\chi^2 = 16.448$

(n = 98) as compared with 30.64 in those with negative CUI (n = 263) (Figure 3, *A*).

After 12 weeks of omalizumab treatment, the positive CUI group had a higher UAS7 (mean, 12.2) and thus poorer control as compared with the group without baseline CU positivity (mean, 6.47) (Figure 3, *A*). The frequency of subjects with poor CSU symptom control (UAS7 $>$ 6) was higher in the subjects with baseline CUI positivity as compared with subjects with a negative baseline CUI ($\chi^2 = 19.183$; $P < .0001$) (Figure 3, *B*).

CUI positivity corresponds to increasing odds of being a nonresponder (UAS7 $>$ 6 at week 12) ($P = .0002$; odds ratio, 2.54; 95% CI, 1.55-4.15), even after adjusting for confounders (age, sex, BMI, presence of angioedema, previous medications) (Table II).

Low baseline BHC

We next examined baseline BHC, a surrogate for basophil number, and week 12 UAS7. The average baseline UAS7 in those with low BHC (≤8 ng/mL) was 31.59 (n = 64), whereas the average baseline UAS7 in those with high BHC (>8 ng/mL) was 30.05 (n = 202).

After 12 weeks of omalizumab, the low BHC group (≤8 ng/ml) had a higher UAS7 (mean, 12) as compared with a mean UAS7 of 6.89 for the group with high BHC (Figure 4, *A*). The frequency of subjects with poor CSU symptom control (UAS7 $>$ 6) was higher in the subjects with low BHC as compared with subjects with a BHC greater than 8 ng/mL ($\chi^2 = 9.531$; $P = .009$) (Figure 4, *B*).

The probability of being an omalizumab nonresponder (UAS $>$ 6) decreases with each 1-unit increase in BHC, which is a novel finding ($P = .028$; odds ratio, 0.9654; 95% CI, 0.936-0.996), after adjusting for confounders (age, sex, BMI, presence of angioedema, previous medications) (Table II).

We performed the ROC-curve analysis and the corresponding area under the ROC-curve value was used to evaluate how well BHC distinguished nonresponders from responders (Figure 4, *C*). The test demonstrated acceptable discriminative ability with an area under the ROC-curve value of 0.59 ($P < .012$). According to the ROC-curve analysis, the cutoff value defined by the Youden Index for BHC was less than or equal to 6.4 ng/mL for distinguishing nonresponders from responders. The percentage of subjects with a BHC value less than or equal to 6.4 ng/mL was 18.8% (n = 50).

Presence of 2 baseline biopredictors

We further examined the impact of 2 negative predictors at baseline on omalizumab therapy response at 12 weeks. In general, the presence of any 2 biopredictors at baseline led to poorer control at week 12.

IgE and CUI. Nearly two-thirds of subjects with a low baseline IgE and CUI (N = 56) positivity had poor symptom control (UAS7 $>$ 6) after 12 weeks (Figure 5, *A*). However, among all patients with CSU with CUI positivity, low baseline IgE was not predictive for nonresponsiveness to omalizumab ($\chi^2 = 3.5179$; $P = .061$) (Figure 5, *D*).

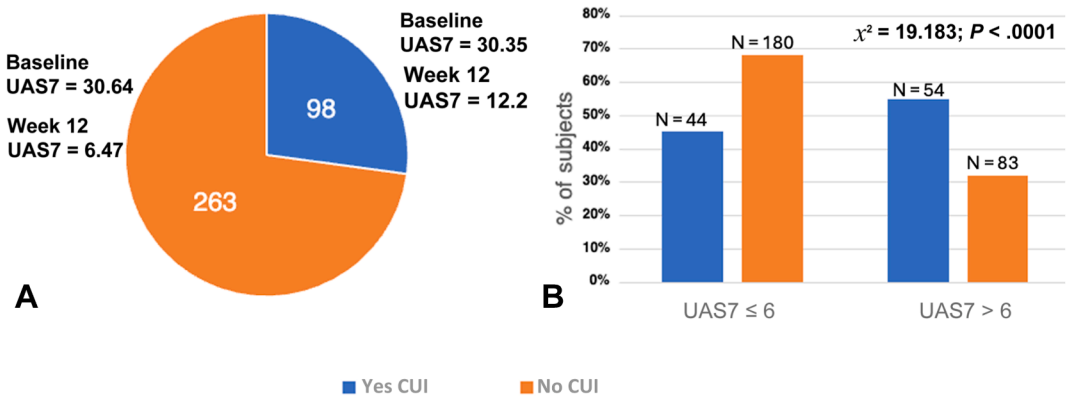
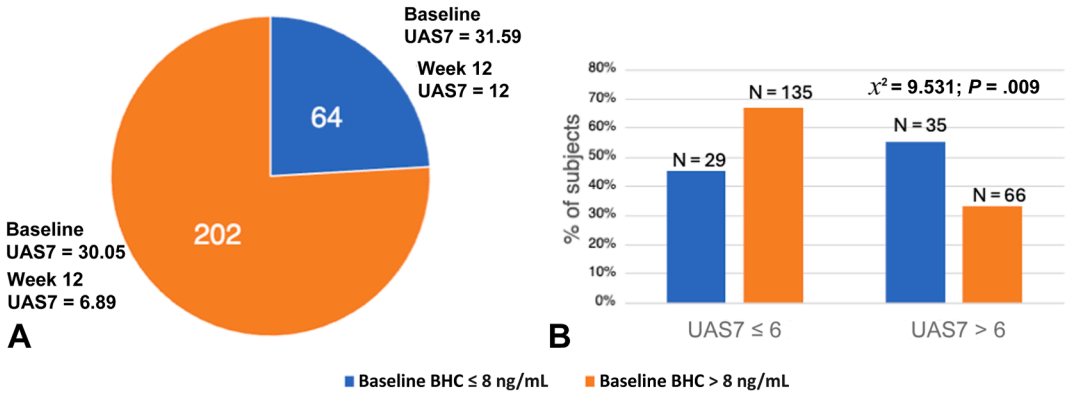


FIGURE 3. (**A**) Baseline CUI result and UAS7 at baseline and after 12 weeks of omalizumab. (**B**) Percentage of subjects with well-controlled CSU symptoms (week 12 UAS7 $\leq$ 6) vs poor control (UAS7 $>$ 6) relative to CUI positivity ($\chi^2 = 19.183$; $P < .0001$).



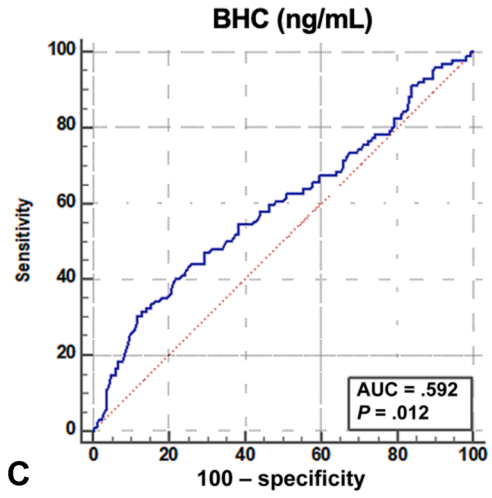


FIGURE 4. (**A**) Baseline BHC and UAS7 at baseline and after 12 weeks of omalizumab. (**B**) Percentage of subjects with well-controlled CSU symptoms (week 12 UAS7 $\leq$ 6) vs poor control (UAS7 $>$ 6) relative to baseline BHC ($\chi^2 = 9.531$; $P = .009$). (**C**) ROC-curve analysis and the corresponding area under the ROC (AUC) for BHC (ng/mL).

IgE and baseline BHC. Among subjects with both low IgE ($\leq$40 IU/mL) and BHC ($\leq$8 ng/mL) (N = 34), 68% had UAS7 higher than 6 at week 12 (Figure 5, *B*). Among all patients with CSU having low baseline IgE, the presence of low BHC was predictive for nonresponsiveness to omalizumab ($\chi^2 = 4.2152$; $P = .04$) (Figure 5, *E*).

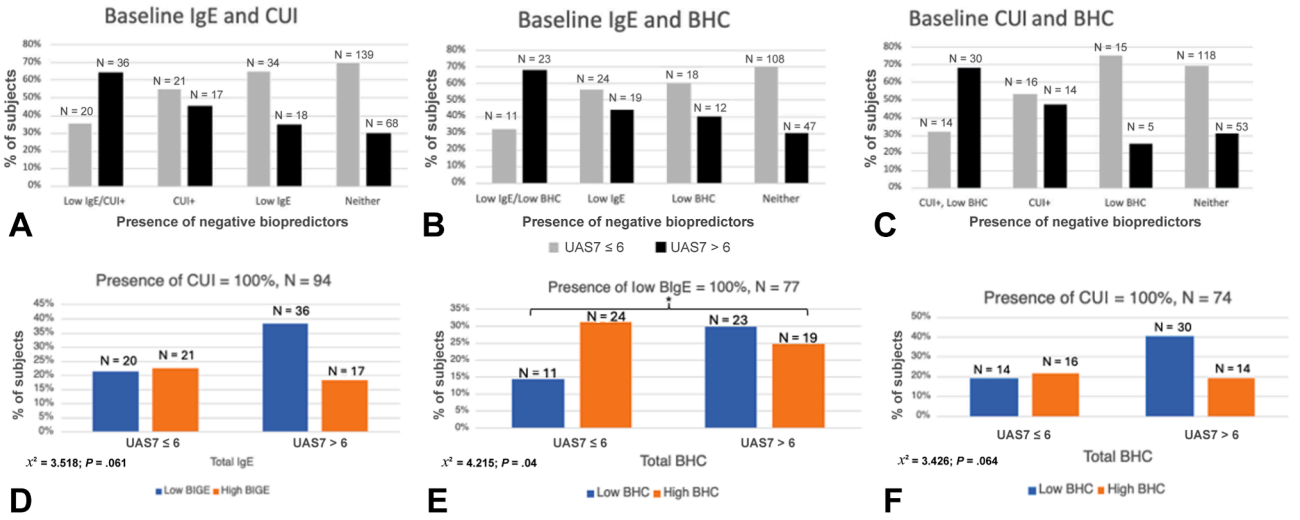


FIGURE 5. (**A-F**) Week 12 UAS7 response relative to the presence of 2 biopredictors. (Fig 5, *A-C*) The frequency of subjects with either well-controlled CSU (UAS $\leq$ 6) or poorly controlled CSU (UAS $>$ 6) relative to the presence of 2 biopredictors, single biopredictor, or none. (Fig 5, *D-F*) The impact of dual biopredictor presence on CSU symptom control at week 12. (Fig 5, *D*) Subjects with CUI positivity were examined for the category of CSU symptoms control (week 12 UAS7 $\leq$ 6 or $>$ 6) relative to the presence of low IgE ($\chi^2 = 3.518$; $P = .061$). (Fig 5, *E*) Subjects with low baseline IgE ($\leq$40 IU/mL) were examined for the category of CSU symptom control (week 12 UAS7 $\leq$ 6 or $>$ 6) relative to the presence of low BHC ($\chi^2 = 4.215$; $P = .04$). (Fig 5, *F*) Subjects with CUI positivity were examined for the category of CSU symptom control (week 12 UAS7 $\leq$ 6 or $>$ 6) with well-controlled CSU symptoms (week 12 UAS7 $\leq$ 6) relative to the presence of low BHC ($\chi^2 = 3.426$; $P = .064$).

CUI and baseline BHC. In those subjects with presence of positive CUI and low BHC ($\leq$8 ng/mL) (N = 44), 68% had UAS7 higher than 6 at week 12 (Figure 5, *C*). Among all patients with CSU with presence of positive CUI, low BHC was not predictive for nonresponsiveness to omalizumab ($\chi^2 = 3.4255$; $P = .064$) (Figure 5, *F*).

Presence of all 3 baseline biopredictors

In subjects who had the presence of 3 negative biopredictors at baseline (N = 32), the average UAS7 at week 12 was 16.54 and 69% had UAS7 higher than 6. In contrast, subjects who lacked all 3 baseline biopredictors, the average UAS7 was 6.25 at week 12 and 70% had a UAS7 of 6 or lower at 12 weeks ($\chi^2 = 16.448$; $P = .0001$) (Figure 6).

DISCUSSION

We conducted this study to examine the impact of 3 proposed negative predictors for omalizumab treatment in antihistamine-refractory patients with CSU to assist medical decisions for choice of optimal therapy for patients with CSU. The goal was to better inform clinicians to permit more rapid advance to alternate therapies beyond omalizumab if there was a high likelihood of poorer response based on biopredictors. Per present guidelines, a trial of 3 to 6 months is indicated to ascertain whether omalizumab is efficacious. The estimated cost of this trial is $4000/mo for 300 mg (a range of $12,000-$24,000). The next step in the treatment algorithm for omalizumab failures is the use of cyclosporine. However, given that other novel agents have emerged as therapeutic options such as dupilumab in the United States and other countries, and remibrutinib (US Food and Drug Administration—approved in October 2025), additional guidance for clinicians for optimal therapy selection is needed.

We found that the subgroups of subjects with CSU treated with omalizumab 300 mg for 12 weeks with either a lower baseline IgE ($\leq$40 IU/mL), presence of CUI positivity, and low baseline BHC of less than 8 ng/mL, all showed higher UAS7 average scores as compared with those with the absence of these features. However, only low BHC and CUI positivity remained as significant predictors after correction of confounders. The aspect of BHC as a predictor is novel and further allowed the construct of an ROC curve with reasonable predictive capacity.

We further found that the presence of 2 negative biopredictors demonstrated a poorer response at week 12 for all pairings (Figure 5, *A-F*) but only the presence of low IgE and low BHC was significant. A major limitation for this dual biopredictor analysis was the smaller numbers of participants with BHC values available. Of note, there are other tests of CSU serum-induced basophil activation (basophil activation test flow-based assay) that are available today but at the time of these studies, they were not available.

In general, in those subjects with a single baseline biopredictor at baseline, 50% to 55% have a UAS7 higher than 6 after 12 weeks of therapy as compared with approximately 33% without the biopredictor. In those with 2 baseline biopredictors present, 65% have poor control at 12 weeks. In those with the presence of all 3 biopredictors at baseline, 69% have poor control after 12 weeks of omalizumab.

To put our findings into context regarding the newer emerging therapies for CSU, in the LIBERTY-CSU CUPID, a study of dupilumab use in antihistamine-refractory subjects, 34% of patients achieved a UAS7 value of 6 or lower at week 12.[28] In clinical trials with rembrutinib, an oral Bruton's

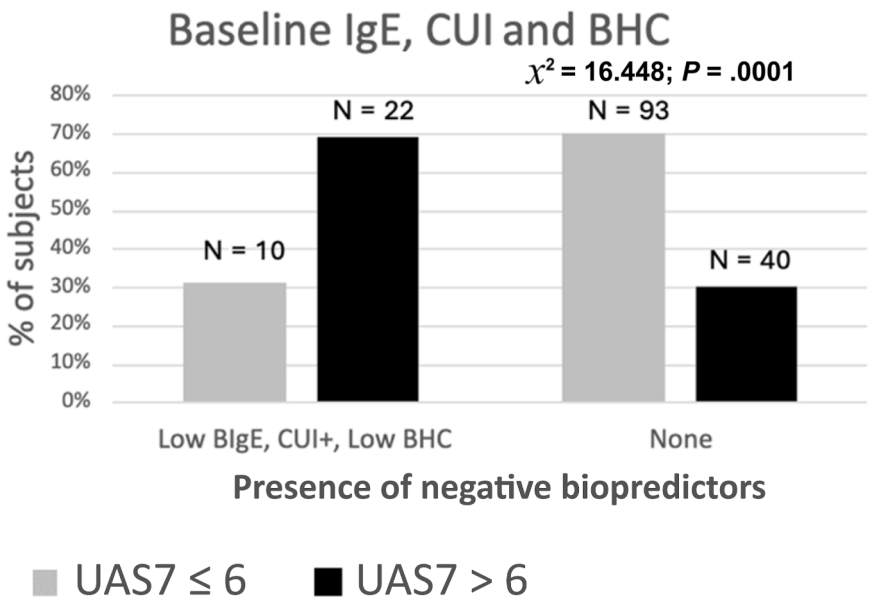


FIGURE 6. Impact of baseline IgE, CUI, and BHC relative to week 12 UAS7 response ($\chi^2 = 16.448$; $P = .0001$). *BlgE,* Baseline IgE.

tyrosine kinase inhibitor, in REMIX-1, 49.8% in the remibrutinib group had a UAS7 value of 6 or lower at week 12, whereas in REMIX-2, 46.8% had a UAS7 value of 6 or lower at week 12.[29]

Of note, a later response can be seen in some patients beyond 12 weeks of omalizumab treatment. Even though patients may not achieve goal UAS7 (≤6) by week 12, there is still a chance that they will achieve control between week 13 and week 24. In both Asteria I and in Glacial, 52% of those on 300 mg of omalizumab achieved the goal UAS7 (≤6) at week 12, whereas 48% did not. However, among the patients who had not achieved goal response of UAS7 at week 12, 58% achieved it between weeks 13 and 24 as compared with 38% of individuals on placebo.[10]

Among the strengths of this study was the use of data from 3 large, multisite, randomized trials of omalizumab versus past smaller, single-site studies. This offers greater generalizability of these results to a broader patient population. Another unique aspect of this study was the examination of multiple negative biopredictors, including the novel use of low BHC, a measure of basopenia, as a predictor. As a sole predictor, BHC had reasonable predictive capacity for week 12 outcomes and attention to accurate blood basophil enumeration is needed.

Among the limitations of this study is the fact that background antihistamine therapy was not uniform across all 3 trials. Two studies (Asteria trials) had the required use of only a single tablet of antihistamine use as compared with more than 2-fold H1 in 60% of patients in the Glacial trial. However, a *post hoc* analysis demonstrated that omalizumab had similar efficacy in subjects with CSU regardless of background therapy administered in these 3 trials.[30] Given the nature of the extracted studies, we have no information on whether updosing with omalizumab would have been effective as has been reported in uncontrolled studies.[31] To date, studies have not been able to identify a biopredictor for those who will respond to updosing.[32] We also appreciated that some baseline biopredictors overlapped in our study population (Figure E1).

Another limitation of our findings is that we selected UAS7 less than or equal to 6, designating patients who are well controlled with only minimal symptoms, as our outcome metric rather than UAS7 = 0, which signifies complete elimination of itch and hives. Although the UAS7 of 0 is the desired target recommended by recent guidelines,[8] it is not achieved by most patients on omazilumab.

In line with our findings, a Korean study of omalizumab response predictors found that low IgE was predictive of nonresponse whereas positive predictors of response at 12 weeks were higher IgE levels (>700 IU) and higher blood basophil counts.[18] In a smaller study of 40 patients, low circulating basophil numbers was predictive of nonresponse.[21]

This study demonstrates that as the presence of individual negative baseline biomarkers increases, the likelihood of treatment nonresponse also rises when judged at 12 weeks of 300 mg omalizumab every 4 weeks. Although some patients with negative biomarkers may still respond, these biomarkers provide useful context for guiding shared therapeutic decision making with patients, particularly as new therapeutic options continue to emerge.

REFERENCES

1. Kolkhir P, Gimenez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. Nat Rev Dis Primers 2022;8:61.
2. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol 2012;129:1307-13.
3. Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M. Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. Autoimmun Rev 2017;16:1196-208.
4. Tienforti D, Di Giulio F, Spagnolo L, Castellini C, Totaro M, Muselli M, et al. Chronic urticaria and thyroid autoimmunity: a meta-analysis of case-control studies. J Endocrinol Invest 2022;45:1317-26.
5. Oliver ET, Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. Immunol Allergy Clin North Am 2024;44:421-38.

6. Asero R, Ferrer M, Kocaturk E, Maurer M. Chronic spontaneous urticaria: the role and relevance of autoreactivity, autoimmunity and autoallergy. J Allergy Clin Immunol Pract 2023;11:2302-8.
7. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, Grattan CEH, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: results of the PURIST study. Allergy 2019;74:2427-36.
8. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA(2)LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022;77:734-66.
9. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J Allergy Clin Immunol 2011;128:567-73.e1.
10. Kaplan A, Ferrer M, Bernstein JA, Antonova E, Trzaskoma B, Raimundo K, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J Allergy Clin Immunol 2016;137:474-81.
11. Eckman JA, Hamilton RG, Saini SS. Independent evaluation of a commercial test for "autoimmune" urticaria in normal and chronic urticaria subjects. J Invest Dermatol 2009;129:1584-6.
12. Cho CB, Stutes SA, Altrich ML, Ardoin SP, Phillips G, Ogbogu PU. Autoantibodies in chronic idiopathic urticaria and nonurticarial systemic autoimmune disorders. Ann Allergy Asthma Immunol 2013;110:29-33.
13. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol 2017;139:1059-61.e1.
14. Mosnaim G, Casale TB, Holden M, Trzaskoma B, Bernstein JA. Characteristics of patients with chronic spontaneous urticaria who are late-responders to omalizumab. J Allergy Clin Immunol Pract 2024;12:2537-9.
15. Straesser MD, Oliver E, Palacios T, Kyin T, Patrie J, Borish L, et al. Serum IgE as an immunological marker to predict response to omalizumab treatment in symptomatic chronic urticaria. J Allergy Clin Immunol Pract 2018;6:1386-8.e1.
16. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy 2018;73:705-12.
17. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, et al. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy 2018;73:2406-8.
18. Lee HY, Jeon HS, Jang JH, Lee Y, Shin YS, Nahm DH, et al. Predicting responses to omalizumab in antihistamine-refractory chronic urticaria: a real-world longitudinal study. J Allergy Clin Immunol Glob 2024;3:100245.
19. Saini SS. Urticaria and basophils. Allergol Int 2023;72:369-74.
20. Johal KJ, Chichester KL, Oliver ET, Devine KC, Bieneman AP, Schroeder JT, et al. The efficacy of omalizumab treatment in chronic spontaneous urticaria is associated with basophil phenotypes. J Allergy Clin Immunol 2021;147:2271-80.e8.
21. Rijavec M, Kosnik M, Koren A, Kopac P, Selb J, Vantur R, et al. A very low number of circulating basophils is predictive of a poor response to omalizumab in chronic spontaneous urticaria. Allergy 2021;76:1254-7.
22. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol 2015;135:925.
23. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368:924-35.
24. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101-9.
25. Saini SS, Omachi TA, Trzaskoma B, Hulter HN, Rosen K, Sterba PM, et al. Effect of omalizumab on blood basophil counts in patients with chronic idiopathic/spontaneous urticaria. J Invest Dermatol 2017;137:958-61.
26. Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2012;108:20-4.
27. Stull D, McBride D, Tian H, Gimenez Arnau A, Maurer M, Marsland A, et al. Analysis of disease activity categories in chronic spontaneous/idiopathic urticaria. Br J Dermatol 2017;177:1093-101.
28. Maurer M, Casale TB, Saini SS, Ben-Shoshan M, Gimenez-Arnau AM, Bernstein JA, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): two randomized, double-blind, placebo-controlled, phase 3 trials. J Allergy Clin Immunol 2024;154:184-94.
29. Metz M, Gimenez-Arnau A, Hide M, Lebwohl M, Mosnaim G, Saini S, et al. Remibrutinib in chronic spontaneous urticaria. N Engl J Med 2025;392:984-94.
30. Casale TB, Bernstein JA, Maurer M, Saini SS, Trzaskoma B, Chen H, et al. Similar efficacy with omalizumab in chronic idiopathic/spontaneous urticaria despite different background therapy. J Allergy Clin Immunol Pract 2015;3:743-50.e1.
31. Metz M, Vadasz Z, Kocaturk E, Gimenez-Arnau AM. Omalizumab updosing in chronic spontaneous urticaria: an overview of real-world evidence. Clin Rev Allergy Immunol 2020;59:38-45.
32. Alizadeh Aghdam M, van den Broek F, Rijken F, Knulst AC, Rockmann H. High-dose omalizumab use in patients with chronic spontaneous urticaria. J Allergy Clin Immunol Pract 2020;8:1426-7.e1.

ONLINE REPOSITORY

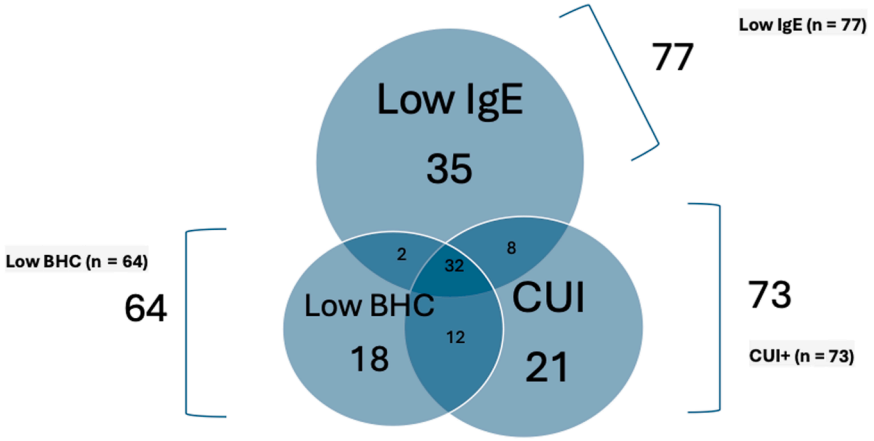


FIGURE E1. Expression of negative biopredictors at baseline (low IgE, BHC, or CUI positivity)