Utility of serum biomarkers in real-world practice for predicting response to omalizumab therapy in patients with chronic spontaneous urticaria

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Background: Omalizumab (OMA), a recombinant humanized IgG monoclonal anti-IgE antibody, is approved for treatment for chronic spontaneous urticaria (CSU) refractory to second-generation H_1-antihistamine (SGAH) therapy. However, currently, there are no validated serum biomarkers to reliably predict response to OMA treatment.

Objective: We explored the real-world clinical utility of using serum biomarkers for predicting response to OMA for CSU patients with disease refractory to high-dose SGAH therapy.

Methods: A single-center, retrospective chart review of CSU patients treated with OMA enrolled patients who had at their initial evaluation collection of a basophil histamine release assay for detecting IgG antibodies targeting FcεR1α subunit before starting OMA treatment. In addition, total IgE, IgG–anti–thyroid peroxidase (TPO), C-reactive protein, and absolute eosinophil count, if available, were analyzed as predictors for OMA response. The validated Outcome and Assessment Information Set Database (OASIS-D) rating system was used to assess responsiveness to OMA.

Results: High levels of IgG–anti-TPO were significantly associated with a poor response to OMA. However, basophil histamine release assay, total IgE, C-reactive protein, and absolute eosinophil count, as well as IgG–anti-TPO/total IgE ratios, were not predictive of a response to OMA therapy.

Conclusions: This real-world study confirms previous reports that a high IgG–anti-TPO level is a reliable predictor of poor response to OMA. However, better validation of basophil histamine release assay and other immunoassays that measure IgG antibodies to FcεR1α subunit are required before they can be recommended as predictors for OMA response. Whether any of these biomarkers are relevant for predicting response to novel advanced therapeutics under current development requires further investigation. (J Allergy Clin Immunol Global 2025;4:100386.)

Key words: *Chronic spontaneous urticaria, autoimmune urticaria, omalizumab, biomarkers, CU Index, TPO, IgE*

Chronic spontaneous urticaria (CSU) is defined by the presence of recurrent wheals and/or angioedema of more than 6 weeks' duration.[1] The prevalence of CSU in the general population has been estimated to range from 0.5% to 5%.[2] This high prevalence represents a significant burden on national health care systems and patient quality of life, particularly for patients with difficult-to-treat disease.

The clinical symptoms of CSU are primarily driven by activation of skin mast cells, which release histamine, cytokines, and other vasoactive mediators (ie, platelet-activating factor, prostaglandin D_2) through constitutive exocytosis and piecemeal degranulation.[3,4] This in turn leads to the recruitment of effector cells (T cells, eosinophils, basophils), nerve activation, and vasodilation seen at the site of wheals.[5] The way mast cells are activated to release bioactive mediators is thought to occur via multiple pathways, with at least 2 autoimmune endotypes currently being recognized.[6] In the type I autoimmune CSU endotype (type I aiCSU), also known as autoallergic CSU, IgE antibodies are produced against self-antigens (autoallergens) such as thyroid peroxidase (TPO), IL-24, eosinophil peroxidase, and double-stranded DNA.[7-10] The type IIb autoimmune CSU (type IIb aiCSU) endotype, in contrast, is characterized by IgG autoantibodies directed against the high-affinity IgE receptor (FcεR1α subunit) on mast cells and basophils or to IgE itself.[6,11] Previous literature has suggested that patients with type IIb aiCSU tend to have low levels of total IgE and high levels of TPO autoantibodies, and their disease is frequently refractory to second-generation H_1-antihistamines (SGAH) and omalizumab (OMA).[12,13]

There are no curative treatments available for CSU, and currently approved therapies focus on providing symptom control. Second-generation H_1-antihistamines are considered first-line therapy, followed by updosing to 4 times the US Food and Drug Administration–approved daily dosage if not effective. However, the disease of a significant portion of patients does not respond, or only partially responds, to this treatment. OMA, a recombinant humanized IgG monoclonal anti-IgE antibody, is currently considered the next step in treating refractory CSU.[1] OMA inhibits binding of IgE to FcεR1 on the surface of mast cells and basophils, thereby downregulating FcεR1 density and preventing IgE and IgG antibody-mediated cross-linking of adjacent

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Abbreviations used

AEC: Absolute eosinophil count
aiCSU: Autoimmune CSU
BHRA: Basophil histamine release assay
CRP: C-reactive protein
CSU: Chronic spontaneous urticaria
CU Index: Chronic Urticaria Index
OASIS-D: Outcome and Assessment Information Set Database
OMA: Omalizumab
OR: Odds ratio
SGAH: Second-generation H_1-antihistamine
TPO: Thyroid peroxidase

alpha subunits.[14,15] Studies evaluating the overall efficacy of OMA therapy in patients with CSU have varied in their results, though a recent meta-analysis found an average complete response rate of 72.2% across 45 different studies.[16] However, OMA comes with a significant economic cost, and it can take multiple injections to result in a clinical response. Thus, the value of effectively being able to predict response and nonresponse to this treatment would be an important clinical benefit.

Currently, there are no validated serum biomarkers for the diagnosis and treatment of CSU. Many studies to date have explored the use of a variety of serum biomarkers to help stratify patients according to severity, prognosis, endotype, and responsiveness to different treatments, with mixed results. One such measure is the basophil histamine release assay (BHRA), referred to as the Chronic Urticaria (CU) Index. This method mixes patient serum with donor basophils, and the released histamine levels are measured through a quantitative enzyme immunoassay.[17] A positive CU Index finding suggests the presence of IgG autoantibodies in the patient's serum targeting FcεR1α subunit on donor basophils, leading to degranulation. A positive BHRA/basophil activation test result has been proposed to be the best indicator of chronic autoimmune (type IIb) CSU and has been strongly correlated with a low total IgE and basopenia, but these assays are not yet standardized.[18] Other serum biomarkers have also been evaluated in patients with CSU, with varying results, including but not limited to total IgE, IgG–anti-TPO, C-reactive protein (CRP), and absolute eosinophil count (AEC).[7,12,19-23]

Further insight into the value of obtaining such biomarkers in clinical practice to help guide treatment decisions for patients with SGAH-refractory CSU would be highly useful. In this retrospective, real-world observational chart review, we sought to determine if there was a significant correlation between those with disease with full, partial, and no response to OMA and the levels of these biomarkers, with a special focus on the CU Index.

METHODS

Patients and procedures

This was a retrospective real-world observational chart review of CSU patients being treated at a large single-site allergy/immunology group practice. Information was recorded through chart review of the electronic medical record, with all patient identifiers excluded in the analysis, allowing for an institutional review board exemption. Patients initiated OMA therapy to treat CSU between October 2016 and January 2023; to be included in the analysis, their data had to include a CU Index result obtained before OMA initiation. Despite its current approval for CSU in patients aged 12 years and older, patients under 12 who received OMA off label were included in the analysis because studies have found OMA to be safe and effective in this age group.[24] Patients were allowed to continue SGAH therapy but could not be receiving an immunosuppressive treatment such as hydroxychloroquine or cyclosporin.

Responsiveness to OMA was assessed using the validated Outcome and Assessment Information Set (OASIS-D), which is used by Medicare and Medicaid to assess control of a disease from clinical records at 2 points in time.[25] This assessment tool (Table I) was utilized because patient-reported outcome measure data were not uniformly available for all patients. Patients required a baseline rating of 3 or 4 before initiation of OMA. OMA response was defined as follows: no response, rating unchanged or worsened; partial response, rating improvement to 2; and complete response, rating improvement to 1. OMA was continued for a minimum of 4 months before OASIS-D rating, and dosing intervals were allowed to increase to every 2 weeks (from every 4 weeks) during this period.

Biomarker analysis

All patients included in the study had a CU Index level obtained before the initiation of OMA. Other laboratory data that were analyzed included total IgE, IgG–anti-TPO, CRP, and AEC, although complete data were not available for all patients. All biomarkers were classified as being either high or low, given the lack of interlaboratory standardization for reporting measurements of CU Index, IgG–anti-TPO, and CRP. Thus, any laboratory value greater than its reference range was considered high for these 3 biomarkers. A cutoff value of ≤40 IU/mL was used to differentiate low from high total IgE. For AEC, a cutoff value of ≤150 cells/μL was used to differentiate low from high. IgG–anti-TPO/total IgE ratios were also analyzed on the basis of a previous report by Brás et al.[26] Ratios were also defined using a high and low classification system for each biomarker, given laboratory variations for reporting measurements of IgG–anti-TPO. For example, if a patient had an IgG–anti-TPO level lower than the laboratory reference range (low) and a total IgE level greater than 40 kU/L (high), then the patient would be classified as having a low IgG–anti-TPO/total IgE ratio.

Objectives

The primary objective of this study was to look for differences in the response to OMA treatment (no response vs partial response vs full response) based on serum levels of specific biomarkers (CU Index, total IgE, IgG–anti-TPO, AEC, and CRP) for patients with CSU refractory to 4 times the recommended dose of SGAH therapy. Secondary objectives included predicting response to treatment with OMA based on the IgG–anti-TPO/total IgE ratio. Individual biomarkers were analyzed according to OMA full and partial response in one group compared to nonresponse to assess for any improvement in CSU symptoms. We compared patients with OMA full/partial response to nonresponse according to the CU Index level (low and high) in conjunction with levels of other biomarkers. Finally, we analyzed individual biomarkers according to OMA full response compared to nonresponse and partial response in one group to assess if there were differences between patients with complete response compared to those without.

TABLE I. OASIS-D rating system for degree of symptom control[25]

Score	Description
0	Asymptomatic; no treatment needed at this time.
1	Symptoms well controlled with current therapy.
2	Symptoms controlled with difficulty, affecting daily functioning; patient needs ongoing monitoring.
3	Symptoms poorly controlled; patient needs frequent adjustment in treatment and dose monitoring.
4	Symptoms poorly controlled; patient has history of rehospitalizations.

Statistical analysis

In the analysis of categorical variables, total counts, proportions, and generated frequency tables were computed. For continuous variables, the mean values along with the standard errors were calculated. To explore the bivariate relationships between categorical predictors and the outcomes of interest, chi-square tests were used. In the case of continuous variables, logistic regression analyses were conducted. All *P* values and 95% CIs were reported.

RESULTS

Patient demographics

A total of 46 patients with CSU met the inclusion criteria for analysis (Table II). None of these patients had disease with an adequate response to maximum-dose SGAH therapy. The mean age of the patients was 39.46 ± 2.42 years, with the youngest patient being 8 and the oldest 72. Two patients were younger than 12 (8 and 9 years, respectively). Patients were predominately female (36 patients, 78.26%). The average duration of chronic urticaria symptoms before initiation of OMA was 5.07 ± 0.95 years, with durations ranging from 3 months to 30 years. All the patients had an OASIS-D rating of 3 or 4 at baseline, with an average rating of 3.07 ± 0.05, indicating uncontrolled disease.

Primary objective

Of the 46 study patients, the disease of 22 (47.83%) exhibited no response, 8 (17.39%) partial response, and 16 (34.78%) full response to treatment with OMA (Table III). For CU Index, 63.64% (14/22 patients) of those with no response had an elevated level compared to 56.25% (9/16 patients) of those with full response and 37.5% (3/8 patients) of those with partial response, although these differences were not found to be statistically significant ($P = .646$ for no response vs full response). Biomarker levels for total IgE, AEC, and CRP were also not found to be statistically significant for full and partial response compared to no response. We found that among the 40 patients with IgG–anti-TPO data, 92.31% (12/13 patients) in the full response group had low IgG–anti-TPO levels compared to 50% (10/20 patients) in the no response group, which was found to be statistically significant, with an odds ratio (OR) of 0.08 (95% CI, 0.01 to 0.77; $P = .0283$). Those with partial response also had lower IgG–anti-TPO levels (85.71%; 6/7 patients), but this group was not significantly different from no response ($P = .1254$).

Secondary objectives

We also aimed to evaluate the utility of the IgG–anti-TPO/total IgE ratio in predicting disease response to OMA (Table III). Eighteen patients were identified as having either a low (n = 11) or high (n = 7) ratio. Five (83.33%) of the 6 with full response, 2 (66.67%) of the 3 with partial response, and 4 (44.44%) of the 9 with no response in this subgroup had a low IgG–anti-TPO/total IgE ratio. Although there was a trend for differences between those with full response compared to those with partial or no response to have a low ratio, the numbers for each group were small and did not reach statistical significance.

Patients were also analyzed according to full/partial response (as one group) compared to no response to assess for any improvement in CSU symptoms with OMA treatment (Fig 1). Results were similar to those of the 3 response groups analyzed separately (Table III). For full/partial response, no significant differences were seen in levels of CU Index (OR, 0.57 [95% CI, 0.18 to 1.86]; $P = .353$), total IgE (OR, 1.1 [95% CI, 0.28 to 4.26]; $P = .8902$), AEC (OR, 0.91 [95% CI, 0.26 to 3.25]; $P = .8897$), and CRP (OR, 1 [95% CI, 0.27 to 3.74]; $P = 1.0$) compared to those with no response. However, full/partial response (90%; 18/20 patients) was again significantly more likely to occur with a low IgG–anti-TPO level compared to those with no response (50%; 10/20 patients), with an OR of 0.11 (95% CI, 0.02 to 0.61; $P = .0115$).

Given that all patients in the study had CU Index data, we compared patients with full/partial response to those with no response according to their CU Index level (low and high) in conjunction with levels of other biomarkers (specifically, total IgE and IgG–anti-TPO) (Fig 2). A total of 20 patients had a low CU Index level compared to 26 patients who had a high CU Index level. Among those with no response with a high CU Index level, 66.67% (8/12 patients) had a high IgG–anti-TPO level, while only 11.11% (1/9 patients) of full/partial response with a high CU Index level had a high IgG–anti-TPO level (OR, 0.06 [95% CI, 0.01 to 0.69]; $P = .0236$). Conversely, comparisons between those with full/partial response and those with no response according to CU Index levels in conjunction with total IgE levels were similar across all groups and were not found to be significant.

Finally, biomarkers were also analyzed according to full response compared to partial/no response (as one group), given that a partial response is considered inadequate by many CSU patients. The results from this analysis were similar to the analysis of those with full/partial response compared to no response. Among partial/no response to OMA, 40.74% (11/27 patients) had a high IgG–anti-TPO versus 7.69% (1/13 patients) of those with full response. Although a trend was observed, this difference did not reach the threshold for statistical significance, likely because of the small numbers of patients per group.

DISCUSSION

In this observational study, we sought to explore the real-world clinical utility of obtaining serum biomarkers before initiation of OMA for the treatment of CSU to predict which patients have disease most likely to respond to this therapy. Disease treated with OMA was classified as having no response, partial response, and full response according to the OASIS-D rating system for degree of symptom control after treatment. Specific biomarkers that were analyzed before starting OMA were CU Index, total IgE, IgG–anti-TPO, AEC, and CRP. Our findings did not detect any

TABLE II. Demographic information of 46 study patients

Characteristic	All patients	CU Index low	CU Index high	Logistic OR (CI)	Logistic *P* value
Age (years)	39.46 ± 2.42	41.5 ± 3.57	37.88 ± 3.3	0.99 (0.95-1.02)	.4555
Sex				0.71 (0.18-2.91)	.6389
Female	36 (78.26)	15 (41.67)	21 (58.33)		
Male	10 (21.74)	5 (50)	5 (50)		
Race†					
White	41 (89.13)	18 (90)	23 (88.46)		
African American	3 (6.52)	1 (5)	2 (7.69)		
Asian Indian	1 (2.17)	0	1 (3.85)		
Other‡	1 (2.17)	1 (5)	0		
CSU duration (years)	5.07 ± 0.95	6.57 ± 1.82	3.92 ± 0.9	0.93 (0.84-1.03)	.1801
OASIS-D rating					
Before OMA	3.07 ± 0.05	3.1 ± 0.1	3.04 ± 0.04	0.55 (0.09-3.48)	.5272
After OMA	2.17 ± 0.13	2.1 ± 0.2	2.23 ± 0.18	1.18 (0.61-2.27)	.6226

Data are presented as nos. (%) or means ± SDs. Patient characteristics were recorded at time of OMA initiation.
†Race was reported by patients.
‡Patient declined to answer.

TABLE III. Response to OMA for each biomarker

Biomarker	Total, no. (%)	Low, no. (%)	High, no. (%)	Chi-square *P* value	Logistic OR (CI)	Logistic *P* value*
CU Index						
No response	22 (47.83)	8 (36.36)	14 (63.64)	.4423		
Partial response	8 (17.39)	5 (62.5)	3 (37.5)		0.34 (0.06-1.83)	.2102
Full response	16 (34.78)	7 (43.75)	9 (56.25)		0.73 (0.2-2.74)	.646
Total IgE						
No response	22 (47.83)	11 (61.11)	7 (38.89)	.668		
Partial response	8 (17.39)	5 (71.43)	2 (28.57)		0.63 (0.09-4.18)	.6309
Full response	16 (34.78)	5 (50)	5 (50)		1.57 (0.33-7.48)	.5702
IgG–anti-TPO						
No response	22 (47.83)	10 (50)	10 (50)	.0211		
Partial response	8 (17.39)	6 (85.71)	1 (14.29)		0.17 (0.02-1.65)	.1254
Full response	16 (34.78)	12 (92.31)	1 (7.69)		0.08 (0.01-0.77)	.0283
AEC						
No response	22 (47.83)	12 (63.16)	7 (36.84)	.767		
Partial response	8 (17.39)	6 (75)	2 (25)		0.57 (0.09-3.64)	.5537
Full response	16 (34.78)	9 (60)	6 (40)		1.14 (0.28-4.59)	.8508
CRP						
No response	22 (47.83)	12 (63.16)	7 (36.84)	.4644		
Partial response	8 (17.39)	5 (83.33)	1 (16.67)		0.34 (0.03-3.56)	.3701
Full response	16 (34.78)	7 (53.85)	6 (46.15)		1.47 (0.35-6.17)	.599
IgG–anti-TPO/total IgE ratio						
No response	9 (50)	4 (44.44)	5 (55.56)	.3107		
Partial response	3 (16.67)	2 (66.67)	1 (33.33)		2.5 (0.16-38.6)	.5117
Full response	6 (33.33)	5 (83.33)	1 (16.67)		6.25 (0.5-77.5)	.1537

*Calculated with "no response" as reference group.

differences in response rates to OMA when the CU Index level alone was used as a predictive biomarker. An elevated CU Index level was found in 56.25% of those with full response compared to 63.64% of those with no response.

High levels of IgG–anti-TPO, an autoimmune test that has previously been found to be a useful diagnostic biomarker for type IIb aiCSU,[13,27] were associated with a poor response to OMA in our study. We found this association to be significant when comparing those with no response to those with full response and with full/partial response, respectively. This observation is in agreement with findings by Kolkhir et al, who found that the prevalence of a positive antinuclear antibody and/or IgG–anti-TPO was significantly higher in those with no response to OMA treatment (71%, 5/7 patients) compared to those with complete response (20%, 4/16 patients).[28] Likewise, Türk et al found that among those with full response to OMA (8 patients), none had a positive IgG–anti-TPO finding.[29]

Given the association between IgG–anti-TPO presence and type IIb aiCSU, we sought to analyze whether using IgG–anti-TPO and CU Index levels in combination would increase specificity for predicting OMA response. A high CU Index level but not a low CU Index level in combination with a high IgG–anti-TPO significantly predicted nonresponse to OMA. Collectively, these findings demonstrate that IgG–anti-TPO by itself and in combination with CU Index level can significantly predict response to OMA. However, given the strong level of significance of a high IgG–anti-TPO alone in predicting nonresponse to OMA and the lack of significance of CU Index level as an independent

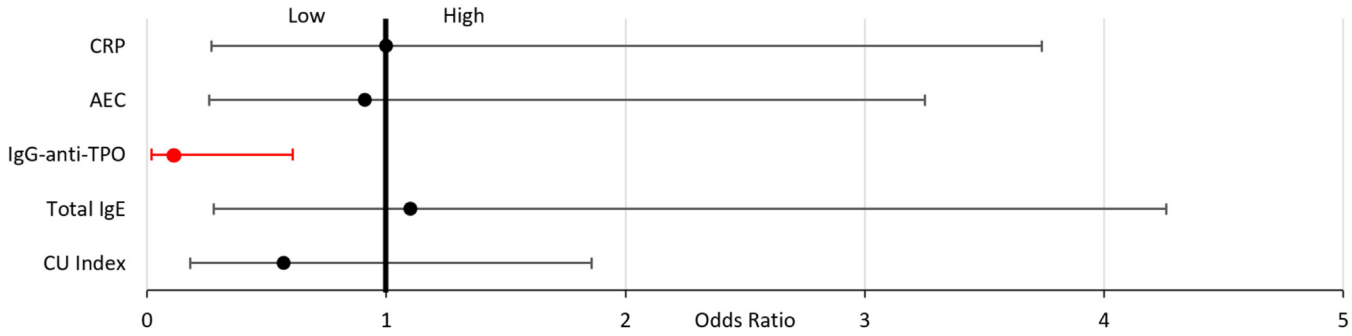

FIG 1. Logistic regression model showing ORs and 95% CIs of combined full/partial response to OMA compared to no response for each biomarker. CIs that exclude null value of 1 indicate significant biomarker level for patients with disease that had full/partial response to OMA.

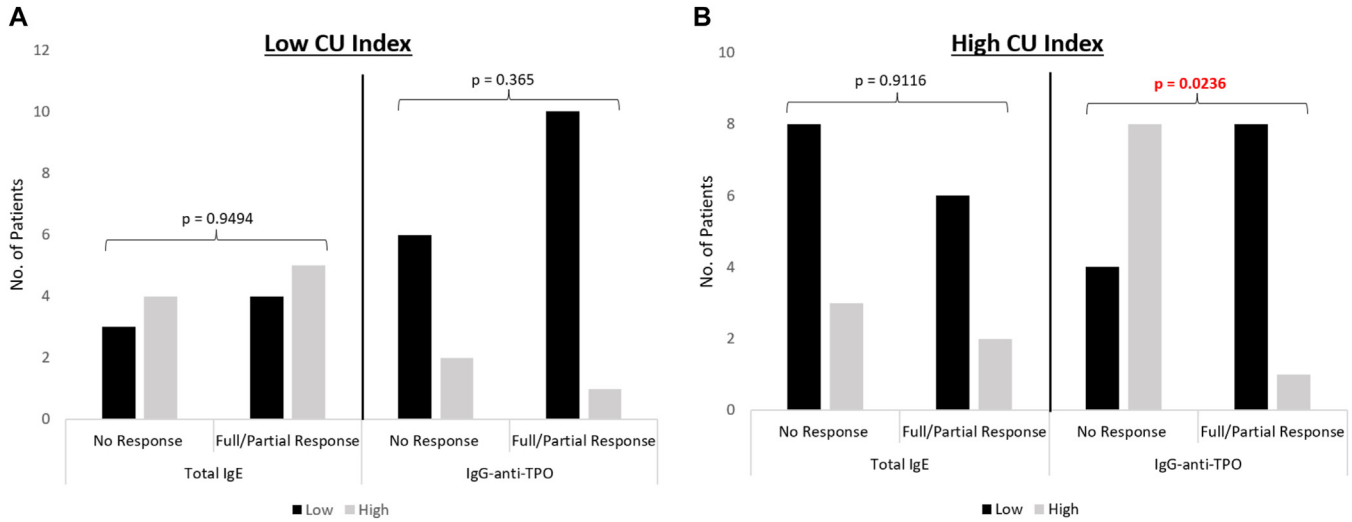

FIG 2. Full/partial response to OMA compared to no response according to CU Index level plus total IgE or CU Index level plus IgG–anti-TPO level. **(A)** Absolute patient numbers of full/partial response versus no response to OMA with low CU Index level and low *(black)* versus high *(gray)* total IgE or low *(black)* versus high *(gray)* IgG–anti-TPO level. **(B)** Absolute patient numbers of full/partial response versus with no response to OMA with high CU Index level and low *(black)* versus high *(gray)* total IgE or low *(black)* versus high *(gray)* IgG–anti-TPO level. Logistic *P* values are shown for each subgroup.

biomarker in predicting response, obtaining a CU Index level in CSU patients with disease refractory to maximum-dose SGAH therapy appears to have limited clinical utility for making treatment decisions regarding initiation of OMA in these patients. These data suggest that standardized assays with increased specificity for IgG autoantibodies to FcεR1α subunit or to IgE itself are still required to confirm type IIb aiCSU.

There has been increasing evidence demonstrating an association between increased total IgE levels (frequently seen in type I aiCSU) and clinical responsiveness to OMA treatment.[20,23,30,31] This association was also demonstrated in a recent systematic review and meta-analysis.[32] Conversely, low total IgE levels have been associated with nonresponse to OMA.[30] Studies have identified total IgE thresholds ranging from 15.2 IU/mL to 43 IU/mL for predicting clinical response to OMA in patients with CSU.[23,30,32-35] In our study, we used a cutoff of ≤40 IU/mL to indicate low total IgE levels because for many laboratories, this is the lower level of detection reported for the assay. We also investigated whether there was an inverse or direct correlation between total IgE levels and CU Index levels to predict treatment response with OMA. These analyses did not detect any between-group differences.

In a recent study of 175 patients by Brás et al evaluating IgG–anti-TPO/total IgE ratio's utility in OMA response prediction for CSU, a high ratio was found to be predictive of a poor response to OMA.[26] This finding was also highlighted in another study of 138 patients by Chen et al.[36] In a subgroup analysis of high versus low ratios, our study observed similar findings among full, partial, and no response. Although a trend was observed, given the small sample size in this subgroup of patients with these biomarkers obtained before treatment with OMA, statistical significance was not achieved.

CRP is an acute-phase reactant and inflammatory marker that has been found to be elevated in patients with CSU compared to healthy controls.[37] Furthermore, higher levels of CRP have been associated with greater disease activity, quality-of-life impairment, and nonresponsiveness to SGAH therapy.[21,38] Previous studies have shown a significant decrease in CRP levels in patients

treated with OMA,[19,39] but little is known about the ability of CRP levels to predict response before treatment. Findings from our study did not detect any meaningful differences between response groups. Finally, eosinophils are often found in both lesional and nonlesional biopsy samples of patients with CSU.[40] Kolkhir et al found blood eosinopenia to be associated with type IIb aiCSU, high disease activity, and poor response to OMA.[22] However, our study did not demonstrate any significant differences between response groups with regards to AEC in peripheral blood.

This study has several limitations of note. First, the sample size was relatively small, given that patients were excluded if they did not have a baseline CU Index level recorded before initiation of OMA. In addition, this was a single-center study, which limits generalizability. However, our population sizes for the groups analyzed in this study are similar to or larger than studies reporting similar findings by other investigators.[27,29] Second, we used binary data (high vs low) or a common "level of detection denominator" cut point rather than absolute laboratory values for all biomarker analysis, given the lack of laboratory standardization and the potential for discordance between interlaboratory reporting measurements of the biomarkers analyzed. For example, cutoff values of ≤40 IU/mL and ≤150 cells/μL were used to define low total IgE and AEC, respectively, because these values were the level of detection reported by some commercial laboratories. Third, we did not subclassify patients by their disease's clinical phenotype (ie, urticaria predominant vs angioedema predominant vs both) to detect differences in response rates. Finally, the results were presented without any adjustments for multiple comparisons, thus increasing the potential for type I error.

A strength of this study was that we used a validated tool to extract data from the electronic medical records (OASIS-D rating system), which has been shown to more accurately assess demographic and outcome data compared to self-reported patient information.[41] Another strength of this study is that our results are concordant with what other investigators have previously reported.

Given the significant association between high levels of IgG–anti-TPO and poor OMA response in our study, a warranted area for future research should be to evaluate its effectiveness as a biomarker for novel biologic and immunosuppressive therapies currently in development for CSU treatment across the spectrum of patient phenotypes/endotypes, from histaminergic to type IIb aiCSU. In general, the inconsistency of our results with other studies likely reflects differences in the populations selected, the prespecified criteria used in the study designs, and the methodologies applied for data analysis.[42] In our study, which was a retrospective and real-world one with restrictive inclusion criteria, we believe that the results add to the ongoing discussion on how biomarkers should currently be used to determine treatment choices after H_1-antihistamines prove ineffective. Currently, the choices for second- and third-line treatment options are limited to OMA and cyclosporine, respectively. In the future, however, as the armamentarium for CSU treatments expands, the relevance of ours and other biomarker studies may influence clinicians to select a therapy where autoimmunity does not influence treatment outcomes. Preliminary data suggest that Bruton tyrosine kinase inhibitors and c-kit inhibitors are effective irrespective of these biomarkers, whereas data related for dupilumab response in the context of OMA nonresponse are confounding.[43-45] Because elevated IgG–anti-TPO antibodies can be found in 12% to 26% of euthyroid subjects without CSU, determining the relevance of this biomarker and others is forthcoming from completed or ongoing large placebo-controlled trials that are investigating these novel therapies for CSU treatment.[46]

In conclusion, high IgG–anti-TPO level as an independent biomarker was associated with poor response to OMA, whereas high CU Index, total IgE, CRP, and AEC were not found to be clinically useful. This finding of high IgG–anti-TPO level, type IIb aiCSU, and OMA refractoriness is consistent with the previously reported literature. Larger, well-controlled prospective studies are needed to confirm the clinical utility of biomarkers, alone or in combination, for predicting response to the advanced therapeutics currently in development.

DISCLOSURE STATEMENT

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Key messages

- **The real-world clinical utility of obtaining serum biomarkers for predicting response to OMA for patients with CSU refractory to SGAH therapy is not well established, and previously reported literature on this topic is limited.**
- **High IgG–anti-TPO levels were a strong predictor of a poor response to OMA, whereas a high CU Index level was not.**
- **These findings are consistent with other studies, thus supporting recommendations for obtaining an IgG–anti-TPO level before initiating OMA therapy for patients with CSU refractory to maximum-dose SGAH therapy, because patients with high levels may be better candidates for treatment with immunosuppressive therapy and other novel biologics currently under development.**
- **Further validation of BHRA and other immunoassays as markers for IgG anti-FcεR1α subunit antibodies is required to determine their utility as biomarkers for chronic autoimmune urticaria.**

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