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REVIEW ARTICLE

Predictors of treatment response in chronic spontaneous urticaria

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Abstract

The current therapeutic algorithm for chronic spontaneous urticaria (CSU), endorsed by the international guideline, entails treatment escalation from second-generation H_1-antihistamines (sgAHs) to omalizumab and cyclosporine until complete response is achieved. Recently, several predictors of response to these treatment options have been described. Here, we discuss the most promising predictors of response and non-response to these treatments in CSU. A systematic search was performed by two independent researchers using the MEDLINE/PubMed database with specific keywords and 73 studies included in the review. Levels of evidence were categorized as strong (robust predictors), weak (emerging predictors) or no association, based on the outcome and number of studies available. High disease activity, high levels of C-reactive protein and D-dimer are robust predictors for a poor or no response to sgAHs. Poor or no response to omalizumab is robustly predicted by low serum levels of total IgE. A good response to cyclosporine is robustly predicted by a positive basophil histamine release assay, whereas low total IgE is an emerging predictor. The response to treatment with sgAHs, omalizumab and cyclosporine can be predicted by the use of markers that are readily available in routine clinical practice. Further studies are needed to confirm these predictors.

KEYWORDS
antihistamines, biomarker, chronic spontaneous urticaria, cyclosporine, omalizumab, predictors, treatment

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is defined by the unprompted occurrence of wheals, angioedema or both for more than 6 weeks.[1] Globally, CSU affects 1% of the general population.[2] CSU has an unpredictable course and duration, and many patients suffer for more than 1 year, for example 11%–14% for more than 5 years.[3] CSU patients reportedly have an impaired quality of life with marked impact on interpersonal relationships, work, social functioning and sleep.[4,5] Furthermore, patients with CSU frequently develop sexual dysfunction, sleep disorders and psychiatric comorbidities, for example depression and anxiety, which add to the impairment of quality of

Abbreviations: ANA, antinuclear antibodies; ASST, autologous serum skin test; BHRA, basophil histamine release assay; CIndU, chronic inducible urticaria; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; CU-Q2oL, chronic urticaria quality of life questionnaire; sgAHs, second-generation H_1-antihistamines; UAS, urticaria activity score.

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life.[6,7] The management of CSU can be time-consuming and lead to substantial economic burden.[8] Appropriate effective treatment is, therefore, of prime importance.

Second-generation H_1-antihistamines (sgAHs) in standard dose, the first-line therapy according to the EAACI/GA^{2}LEN/EDF/WAO guideline for urticaria, are effective in less than 50% of CSU patients. Increasing the dose of sgAHs improves treatment responses. However, every third to fourth patient will still remain symptomatic.[1,3,9] The third-line therapy, omalizumab, an anti-IgE monoclonal antibody, is more effective with a complete response rate that ranges from 26% to 83% as demonstrated in several landmark studies including XCUISITE, ASTERIA and the recent ligelizumab trial.[10-14] Some omalizumab nonresponders benefit from cyclosporine, the fourth-line therapy.[15,16] The current guideline-recommended treatment algorithm, though useful, is not perfect, given it is based on a trial and error approach. Ideally, the treatment of patients with CSU should be individualized and take into account the likelihood of patients to respond to therapy, based on predictors of response. Clearly, response to treatments varies among subgroups of patients with CSU. Even within these subgroups of CSU, responses differ between patients. By choosing a treatment option tailored to a patient's clinical or biochemical characteristics, treatments that are less likely to be effective may be avoided. This individualized approach saves time and costs.

In recent years, specific markers including clinical and laboratory parameters of CSU that may predict the response to treatment with sgAHs, omalizumab and cyclosporine have been described. Identification of these predictors has only become possible with the availability of patient-reported outcome measures, which are global and validated tools for assessing disease activity, impact and control.[17] For example, low total IgE levels have been reported to be associated with poor response to omalizumab treatment and good response to cyclosporine,[18,19] and response was evaluated using the urticaria activity score over 7 days (UAS7).

With this background, we systematically reviewed the published evidence for biomarkers that predict the response to treatment with sgAHs, omalizumab and cyclosporine in patients with CSU. The use of predictors of the response to treatment, in clinical practice, will improve the management of CSU saving both time and money.

2 | MATERIAL AND METHODS

2.1 | Search strategy, inclusion criteria and exclusion criteria

The review protocol was registered on PROSPERO (Registration number CRD42019142381). A literature search on the MEDLINE/PubMed electronic database was performed in July 2019 independently by two co-authors (PK and JF) using specific keywords *(Chronic urticaria OR Chronic spontaneous urticaria OR Chronic idiopathic urticaria) AND (Antihistamine OR Omalizumab OR Cyclosporine OR Ciclosporin) AND (Marker OR Biomarker OR Predictor OR Predictors OR Predictive OR Treatment response OR Resistance).*

For this systematic review, we included studies with the primary aim of evaluating the association between a potential biomarker or predictor and the response to treatment in CSU patients. In fact, original studies with different types of research design, for example cross-sectional, case-control studies, prospective, open label and retrospective studies, were included. Reviews, case reports and publications with non-English abstract were not considered. Non-English full-text publications with English abstracts were considered. Reference lists of included studies were also searched for additional potentially eligible reports. Summary of literature review is highlighted in Figure S1.

Disagreements about the eligibility of a study for inclusion in the review were resolved by consensus discussion between the two lead investigators (JF, PK), and where necessary, the other co-authors (MKC, MM). After an initial screening of titles and abstracts, studies that did not meet the inclusion criteria were removed. Data were extracted from relevant studies and managed in specially designed tables.

2.2 | Data extraction and bias assessments

Specific information was extracted from each eligible study and documented in tables. The characteristics identified were the name of the investigated predictor, the first author's name, the publication year, study design, sample size, dose of drug, duration of treatment, efficacy of treatment, cut-off value, the association between levels/values of predictors and response to treatment, prediction values and the country the study was performed in.

Results of searches were imported into an Endnote database and duplicates removed. Further discussions among co-authors were carried out to review risk of bias, assess the quality of studies and resolve any discrepancies as explained in section below. The final number of studies included in the systematic review was 73, consisting of 31 prospective studies, 31 retrospective studies, 5 cross-sectional studies, 4 randomized control trials and 2 studies with no information on the design provided (Figure S1).

2.3 | Data analysis and presentation

Results are presented and discussed in a narrative approach. Levels of evidence for the association between a biomarker and treatment response were assessed using a rating system developed by de Croon et al.,[20] which was used in previous studies.[21] The levels of scientific evidence were categorized as 'no evidence', 'inconsistent', 'weak' or 'strong' based on the outcome and number of studies from different centres and teams (e.g. if one team published three studies on the same biomarker that show the same association, we counted it as one study). However, if there were two studies produced by the same team in a different time frame with a different study design, we counted the studies as two separate entities. Some studies showed a significant association for more than one outcome hence were included in more

TABLE 1 Summary of possible markers of nonresponse to second-generation H_1-antihistamines

Parameters	Level of evidence for association	Level of evidence for no association
Age	–	Strong
Sex	–	Strong
Height	–	No / little
Weight	–	Inconsistent
BMI	–	Inconsistent
Concomitant chronic inducible urticaria	Weak	–
Comorbid allergic diseases	Inconsistent	–
Presence of angioedema	Inconsistent	–
Previous cyclosporine treatment	No / little	–
Previous treatment / greater need for corticosteroids	Weak	–
Previous treatment with omalizumab	No / little	–
CSU duration	–	Strong
High UAS7/UAS	Strong	–
High DLQI	–	Inconsistent
Low CU-Q2oL	Weak	–
Type of infiltrate in skin biopsy	–	No / little
Diameter of histamine-induced wheal by SPT	No / little	–
ASST positivity	Inconsistent	–
Positive urticaria HR test	No / little	–
CD63 assay positivity	No / little	–
Basophil FcεRI expression	–	No / little
Basophil CD203c expression	No / little	–
IgG-anti-FcεRI	–	No / little
CU index	Inconsistent	–
Blood leukocyte count	–	No / little
Blood lymphocytes count	–	No / little
Low blood basophil counts	–	Weak
Low blood eosinophil counts	Inconsistent	–
Platelets	–	Inconsistent
High MPV	No / little	–
Low total IgE	–	Weak
ANA positivity	Inconsistent	–
ATA positivity	Inconsistent	–
High TSH	–	No / little
C3	–	Weak
C4	–	Strong
C5a	No / little	–
Single nucleotide polymorphisms (SNPs) in C5AR1	No / little	–
FCεR1A genetic polymorphisms	No / little	–
ORAI1 gene polymorphisms	No / little	–
High D-dimer levels	Strong	–
High C-reactive protein levels	Strong	–
High ESR	Inconsistent	–
ECP	–	No / little
Clusterin	No / little	–
IL–6	No / little	–
LCN2	No / little	–
IL–10, adiponectin, leptin and TNF-α	–	No / little
F1 + 2, TF, TM, HMWK, t-PA, ASO, RF	–	No / little
Total cholesterol, triglycerides, LDL, HDL	–	No / little
Liver enzymes	No / little	–
PAF	No / little	–
Fibrinogen	No / little	

Abbreviations: ANA, antinuclear antibody; ASO, antistreptolysin O; ASST, autologous serum skin test; ATA, antithyroid antibodies; BMI, body mass index; CU-Q2oL, chronic urticaria quality of life questionnaire; CU, chronic urticaria; DLQI, dermatology life quality index; ECP, eosinophil cationic protein; ESR, erythrocyte sedimentation rate; F1+2, prothrombin fragment 1 + 2; HDL, high-density lipoprotein; HR, histamine release; HMWK, high molecular weight kininogen; IL-6, interleukin-6; LDL, low-density lipoprotein; LNC2, lipocalin-2; MPV, mean platelet volume; PAF, platelet-activating factor; RF, rheumatoid factor; sgAHs, second-generation antihistamines; SPT, skin prick test; t-PA, tissue-type plasminogen; TF, tissue factor; TM, thrombomodulin; TSH, thyroid-stimulating hormone.

than one table. The tables include relevant studies with statistically significant and insignificant outcome as determined by a p value of <0.05, and based on this, levels of evidence for association were determined. Data were not adjusted for potential confounders.

Levels of evidence for 'association' are as follows:

(i) *Strong* when three studies available that find an association in the same direction or ≥four studies available, of which >66% find a significant association in the same direction and no more than 25% find an opposite association;
(ii) *Weak* when two studies available that find a significant association in the same direction or three studies available, of which two find a significant association in the same direction and the third study finds no significant association;
(iii) *No / little evidence*: ≤ one study available;
(iv) *Inconsistent* for the remaining cases.

TABLE 2 Potential markers that predict poor response or nonresponse to second-generation antihistamines (sgAHs)

Parameters	First author, year, Ref	N of CSU patients	Methods	Cut-off values
High disease activity	Ulambayar 2019[31]	283	UAS7	N/A
	Trinh 2016[32]	191	UAS7	N/A
	Kim 2016[72]	138	UAS7	N/A
	Magen 2011[24]	385	UAS	N/A
	Curto-Barredo 2018[30]	549	UAS7	N/A
	Kolkhir 2017[35]	84	UAS	N/A
	Yan 2019[27]	145	UAS7	N/A
	Yan 2014[73]	191	UAS7	N/A
High CRP	Yan 2017[23]	605	N/A	Not mentioned
	Kolkhir 2018[22]	1019	Nephelometric method	5 mg/L
	Magen 2011[24]	385	N/A	1–3 mg/L
	de Montjoye 2020[25]	95	N/A	mean 7.7 mg/L
	Kolkhir 2017[35]	84	Nephelometric method	Not mentioned
	Yan 2019[27]	145	N/A	Not mentioned
	Huilan 2015[74]	40	N/A	Not mentioned
High D-dimer	Asero 2013[34]	91	ELISA	500 ng/ml ('normal' or 'elevated')
	Kolkhir 2017[35]	84	ELISA	Not mentioned
	de Montjoye 2020[25]	95	N/A	<500 ng/ml
CU-Q2oL	Trinh 2016[32]	191	CU-QoL	N/A
	Kolkhir 2017[35]	84	CU-Q2oL	N/A
Previous corticosteroid treatment	Ulambayar 2019[31]	283	N/A	N/A
	Trinh 2016[32]	191	N/A	N/A

Results	Limitations	Evidence that a marker predicts nonresponse to sgAHs?
A higher UAS7 score (OR = 1.023, p = 0.024) was a predictor of poor response to antihistamines	Nil (large sample size, prospective study)	Yes
Patients with refractory chronic urticaria had higher UAS scores compared to patients with responsive chronic urticaria; $p < 0.001$	Authors concluded they could not demonstrate a causal link between chronic urticaria and lipocalin−2.	Yes
Higher UAS was found in cases refractory to sgAHs compared to cases responsive to sgAHs; $p < 0.001$	Nil (hospital-based cross-sectional)	Yes
Higher baseline UAS seen in resistant CSU (5.28 ± 0.81) compared with responsive CIU (3.32 ± 1.25); $p < 0.001$	Retrospective study	Yes
Refractory patients showed significantly higher baseline UAS7 compared with non-refractory patients (21.3 ± 13.3 vs. 17.7 ± 12.2; p = 0.035)	Retrospective study	Yes
Responders to levocetirizine had lower UAS scores compared to nonresponders; p = 0.005	Small sample size	Yes
No significant difference between the responder group and nonresponder group regarding UAS7 values; p = 0.521	Authors concluded study limited by sample size and single-centre study	No
The differences in the baseline UAS7 scores between responders and nonresponders were not significant in each monotherapy group; p = 0.964	Nil (prospective study with decent sample size)	No
Patients with lower CRP levels showed better responses to treatment than those with higher CRP levels; $p < 0.05$	Retrospective study	Yes
Of 1019 CSU patients, 31% (n = 313) had elevated levels of CRP (of ≥5 mg/L). CRP levels were significantly higher in nonresponders to sgAHs as compared to responders; $p < 0.001$	Retrospective study	Yes
sgAH-resistant CSU group had higher CRP levels (8.62 ± 3.91 mg/L versus 2.49 ± 1.34 mg/L); $p < 0.001$	Retrospective study	Yes
In nonresponders to sgAHs, CRP serum levels were significantly higher than in responders; $p < 0.0001$	Small sample size	Yes
Responders to levocetirizine had lower CRP compared to nonresponders; $p < 0.001$	Small sample size	Yes
There was no significant difference between the responder group and nonresponder group regarding CRP; $p > 0.6$	Authors concluded study limited by small sample size and being a single-centre study	No
No statistical difference in CRP levels during exacerbation and during remission; $p > 0.05$	Small sample size	No
Patients with elevated D-dimer levels were much more frequently cetirizine-resistant, especially when urticaria severity was moderate ($p < 0.001$ for patients with UAS 3 or 4)	Small sample size	Yes
D-dimer levels were significantly higher in nonresponders as compared to responders; $p < 0.001$	Small sample size	Yes
D-dimer plasma levels were significantly higher in sgAH nonresponders than in sgAH responders; p = 0.009	Small sample size	Yes
Patients with refractory chronic urticaria had lower CU-QoL scores compared to those with responsive chronic urticaria (52.9 vs 69.1, p = 0.001)	Authors concluded they could not demonstrate a causal link between chronic urticaria and lipocalin−2	Yes
Responders had higher CU-Q2oL scores compared to nonresponders; $p < 0.001$	Small sample size	Yes
The percentage of previous corticosteroid use was higher in sgAH nonresponders (93.8%) than sgAH responders (52.1%); $p < 0.001$	Nil (large sample size, prospective study)	Yes
Patients with refractory urticaria had greater needs for antihistamine (mg/day) and systemic corticosteroids (mg/week) than patients with responsive urticaria; $p < 0.001$ In the refractory urticaria group, the percentages of patients who received systemic corticosteroids were 74%.	Authors concluded they could not demonstrate a causal link between chronic urticaria and lipocalin−2	Yes

(Continues)

TABLE 2 (Continued)

Parameters	First author, year, Ref	N of CSU patients	Methods	Cut-off values
Concomitant CIndU	Magen 2011[24]	385	N/A	N/A
	Curto-Barredo 2018[30]	549	N/A	N/A

CIndU, chronic inducible urticaria; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; N/A, not applicable; sgAH, second-generation antihistamines; UAS, urticaria activity score; CU-Q2oL, chronic urticaria quality of life questionnaire.

Levels of evidence for 'no association' are as follows:

(i) *Strong* when >four studies are available, of which >85% find no association;
(ii) *Weak* when >four studies are available, of which >75% find no association.

3 | RESULTS

3.1 | High disease activity, C-reactive protein, D-dimer, concomitant chronic inducible urticaria and previous treatment with corticosteroids are the markers of nonresponse or poor response to sgAHs

For the prediction of good response to sgAHs, neither weak nor strong evidence was demonstrated for any parameters. For nonresponse or poor response to sgAHs, strong evidence was demonstrated for high UAS7 or UAS, raised C-reactive protein (CRP) and raised D-dimer levels to be predictive. High UAS or UAS7 was significantly linked to nonresponse to sgAHs in CSU in two studies, one demonstrating an odds ratio of 1.335 ($p < 0.001$) and the other of 1.008 ($p = 0.02$). Weak evidence was shown for previous treatment with corticosteroids, concomitant chronic inducible urticaria (CIndU) and lower Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) scores. Several other markers with inconsistent strength of evidence were reported (Table 1). There was, however, strong evidence for *no association* of age, sex, disease duration and serum C4 level with responsiveness to sgAHs (Tables 1 and 2; Table S1 and S2).

3.2 | Low total IgE levels are a marker of nonresponse or poor response to omalizumab

As for the prediction of a good response to omalizumab, neither weak nor strong evidence was demonstrated for any parameters. There was strong evidence that low total serum IgE levels at baseline are a predictor for nonresponse or poor response (Table 3). Weak evidence was demonstrated for ASST positivity as a predictor of slow response to omalizumab. The evidence for possible markers of the response to up-dosing of omalizumab was inconsistent. There was strong evidence for *no association* of age, gender and anti-thyroid antibodies as well as weak evidence for *no association* of CRP with the response to treatment with omalizumab (Tables 3 and 4; Table S3–S8).

3.3 | Positive basophil histamine release assay results and low total IgE levels are the markers of good response to cyclosporine

There was strong evidence for positive basophil histamine release assay (BHRA) results and weak evidence for low levels of total IgE to predict a good response to cyclosporine. For the prediction of nonresponse or poor response to cyclosporine, neither weak nor strong evidence was demonstrated for any parameters. Several markers with inconsistent strength of evidence were reported, as summarized in Table 5. There was strong level evidence for *no association* of age with the response to cyclosporine, and weak evidence for *no association* with disease duration (Tables 5 and 6; Table S9 and S10).

Figure 1 highlights predictors of nonresponse to sgAHs and omalizumab and predictors of response to cyclosporine. Table S11 summarizes robust predictors with strong level of evidence for all treatments.

4 | DISCUSSION

This is the first systematic review of potential predictors of the outcome of treatment with all three guideline-recommended therapeutic options in the management of CSU. Our study shows that nonresponse to antihistamines and omalizumab as well as response to cyclosporine can be predicted, albeit with unknown sensitivity and specificity, with readily available clinical and laboratory markers. Our results, therefore, benefit clinicians who help patients to

Results	Limitations	Evidence that a marker predicts nonresponse to sgAHs?
sgAH-resistant CSU group had more cases of concomitant physical urticaria (23.9%) compared with sgAH-responsive CSU group (12.2%); $p = 0.014$	Retrospective study	Yes
Patients with CSU-CIndU required more frequent therapy after 5 years and higher doses of sgAHs than patients with isolated CSU (43.0% vs. 31.3%; $p < 0.05$)	Retrospective study	Yes

manage their CSU, and they guide the development of more targeted and personalized treatment approaches.

4.1 | Potential biomarkers of nonresponse or poor response to second-generation antihistamines

The UAS7 is a diary-based PRO measure recommended by international urticaria guidelines that evaluates disease activity and response to treatment on the basis of wheal number and intensity of itch.[1] Six of eight studies support the hypothesis that high UAS7 (4 studies) or UAS (2 studies) is a marker of sgAH nonresponsiveness (Table 2). What this means is that patients with high disease activity, that is frequent and many wheals with intense pruritus, must expect a less favourable response to sgAH treatment as compared to patients with mild disease, and physicians must be ready to step up the treatment in these patients. On the other hand, the CU-Q2oL is a valid instrument that assesses disease-specific quality of life in patients with CSU. Two studies included in this systematic review demonstrated that nonresponders to sgAHs had lower CU-Q2oL scores. This shows that it is an emerging predictor.

CRP is a sensitive marker of inflammation and up to one-third of CSU patients have elevated levels of CRP.[22] Three retrospective studies provide evidence that CRP levels are higher in sgAH nonresponders.[22-24] One prospective study reported that CRP serum levels were higher in antihistamine nonresponders and in more active disease.[25] High levels of CRP were associated with ASST positivity, high urticaria activity, and elevation of inflammatory and coagulation markers. Of note, a study by Yan et al. revealed that the single nucleotide polymorphism rs216008 mutation may negatively affect the response to the sgAH desloratadine.[26] Additionally, certain CRP single nucleotide polymorphisms, such as those carrying the rs3093059C allele, may be linked to elevated serum CRP levels and a poor response to the sgAH mizolastine.[27]

CIndU, for example symptomatic dermographism and delayed pressure urticaria, may coexist with CSU, and its presence appears to indicate a longer duration of CSU and nonresponse to sgAHs. Indeed, CIndU is a common comorbidity of sgAH-refractory CSU, occurring in 24% of CSU patients.[28] The rates of response to standard doses of sgAHs in CSU were significantly higher than in CIndU.[29] In one study, concomitant CIndU was found in 24% patients with antihistamine-resistant CSU compared to 12% patients with responsive CSU.[24] Furthermore, CSU patients with concomitant CIndU required more frequent therapy after 5 years and higher doses of sgAH.[30] One take away from this finding is that patients with CSU should be explored for comorbid CIndUs. Patients with CSU plus CIndU and their treating physicians should be prepared to move to more effective treatments, if a short trial of sgAHs does not help to achieve disease control.

The international urticaria guideline suggests considering a short course of oral glucocorticosteroids in case of severe CSU exacerbation.[1] Ulambayar and coworkers reported that 94% of patients with sgAH-resistant CSU required corticosteroid use in comparison with 52% of antihistamine responders.[31] A subsequent study by Trinh and coworkers confirmed that the use of systemic corticosteroids and nonresponse to antihistamine treatment are linked.[32] To us, the use of corticosteroids as rescue medication in patients with antihistamine-resistant CSU primarily points to the need to improve their treatment and to switch them to more effective treatment.

D-dimer, a marker of fibrinolysis in chronic inflammation, is elevated in up to 33% of patients with CSU and has been linked to more severe disease and recurrent angioedema.[33,34] D-dimer levels were higher in H_1-antihistamine nonresponders in three studies.[25,34,35] In addition, higher D-dimer plasma levels were associated with the presence of autoantibodies including anti-thyroperoxidase antibodies, antinuclear antibodies and rheumatoid factor.[25]

We classified previous treatment with corticosteroids as an emerging rather than definite predictor of nonresponse to sgAHs as it is supported by only two studies. Further prospective and multicentre studies should assess this marker for its predictive value and properties.

In our literature analysis, we came across several additional markers that may be linked to nonresponse of CSU to sgAHs. For none of them does the evidence available warrant classification as predictors, but further studies may change that. For example, angioedema is frequent in H_1-antihistamine-refractory CSU patients. In a study by Maurer et al., 46% patients were classified as having CSU with angioedema.[28] Antihistamine-resistant chronic urticaria was associated with atopic asthma, rhinitis and rhinosinusitis,

TABLE 3 Summary on possible markers of nonresponse to omalizumab

Parameters	Level of evidence for association	Level of evidence for no association
Age	–	Strong
Gender	–	Strong
High weight and/or BMI	Inconsistent	–
Smoking	–	No / little
Family history of chronic urticaria	–	No / little
Comorbid arterial hypertension	No / little	–
Concomitant chronic inducible urticaria	–	Inconsistent
Comorbid allergic diseases	–	Inconsistent
Comorbid psychiatric disorders	–	No / little
Comorbid hypothyroidism	–	No / little
Comorbid rheumatologic disorders	–	No / little
Comorbid diabetes mellitus	–	No / little
NSAIDs hypersensitivity	–	No / little
Presence of AE or AE in the history	Inconsistent	–
Previous immunosuppressive treatment, primarily cyclosporine	Inconsistent	–
Previous treatment with prednisolone	–	Inconsistent
Previous treatment with montelukast	–	No / little
Previous treatment with antihistamines	Inconsistent	–
CSU duration	Inconsistent	–
Disease evolution (months)	–	No / little
High UAS	Inconsistent	–
High UAS7	Inconsistent	–
Low UCT	Inconsistent	–
High VAS	Inconsistent	–
High DLQI	No / little	–
Low CU-Q2oL	No / little	–
ASST positivity	Inconsistent	–
Basophil tests[b]	Inconsistent	–
Basophil FcεRI expression	Inconsistent	–
Blood leukocyte count	Inconsistent	–
Blood lymphocyte count	–	No / little
Blood neutrophil count	–	Inconsistent
Low blood basophil counts	Inconsistent	–
Low blood eosinophil counts	Inconsistent	–
Platelets	–	Inconsistent
Low total IgE levels	Strong[a]	–
Other immunoglobulins (IgA, IgG, IgM)	–	No / little
ANA positivity	Inconsistent	–
TSH	–	No / little
C3	No / little	–
C4	–	No / little
Antithyroid antibodies	–	Strong
High D-dimer levels	Inconsistent	–
High CRP levels	–	Weak
DHEA-S	–	No / little
FVIIa and FXIIa, prothrombin factors 1 and 2	–	No / little

Abbreviations: AE, angioedema; ANA, antinuclear antibody; ASST, autologous serum skin test; BMI, body mass index; CRP, C-reactive protein; CU-Q2oL, chronic urticaria quality of life questionnaire; DHEA-S, dehydroepiandrosterone sulfate; DLQI, dermatology life quality index; NSAID, nonsteroidal anti-inflammatory drugs; TSH, thyroid-stimulating hormone; UAS, urticaria activity score; UCT, urticaria control test; VAS, visual analogue scale.

[a]See explanation under Table S4

[b]Positive basophil histamine release test or basophil CD203c or CD63 upregulating activity or basophil activation test or CU index.

thyroid disease and hypertension.[36] Prevalence of central obesity, hyperglycemia and hypertriglyceridemia was significantly higher in patients with chronic urticaria compared to normal controls.[37] Logistic regression analysis indicated that an urticaria activity score of ≥13 and the presence of metabolic syndrome were independent predictors of uncontrolled chronic urticaria. In a study by Staubach et al. involving 56 patients, CSU patients with ASST positivity required significantly more antihistamines than ASST-negative CSU patients during a flare (11.1 vs 4.5 antihistamines per week).[38]

Interestingly, basopenia and eosinopenia are common in CSU and have been linked to severe, autoimmune and antihistamine-resistant CSU. For example, we showed that 14% and 10% of CSU patients had basopenia and eosinopenia, respectively, and both parameters strongly correlated. Nonresponders to sgAHs had lower basophil and eosinophil blood counts compared with responders.[39] Additionally, one study demonstrated that the antihistamine-resistant CSU group had more severe basopenia, and another one showed that disease activity negatively correlated to blood basophil counts.[24,25] Both, eosinopenia and basopenia in CSU were associated with being female, high disease activity, ASST positivity, BHRA positivity, low total IgE, high CRP and high IgG anti-thyroperoxidase levels.[24,39-42]

The histamine-induced wheal-and-flare response has been discussed as a useful clinical pharmacologic test to assess dose-response relations for an antihistamine. However, its lack of correlation with

TABLE 4 Potential markers that predict poor response or nonresponse to omalizumab

Parameters	First author, year, Ref	N of CSU patients, assessment of response to omalizumab	Methods	Cut-off values	Results	Limitations	Evidence that a marker predicts nonresponse to omalizumab?
Total IgE	Weller 2018[49]	85 (43 CR, 23 PR, 19 NR), physicians global assessment	Different methods at different centres, therefore measured in percentage scores of the respective upper reference value	NA	Elevated IgE in 77.5% of CR, 31.8% of PR, 20.0% of NR ($p < 0.001$). Low normal IgE in 40.0% NR, 27.3% PR, 2.5% CR ($p < 0.005$)	Retrospective study, different methods to assess the response and to measure total IgE among centres, no cut-off value provided	**Yes**
	Straesser 2018[45]	137, subjectively defined	Method not mentioned, different quartiles of serum IgE assigned: 1st – 0–15.2 IU/ml; 2nd – 15.3–68.8 IU/ml; 3rd – 68.9–168.0 IU/ml; 4th – 168.1–4261 IU/ml	≤15.2 IU/ml	1st quartile: 48.4% response rate 2nd quartile: 86.1% response rate 3rd quartile: 88.2% response rate 4th quartile: 94.1% response rate ($p < 0.001$)	Retrospective study	**Yes**
	Ertas 2018[47]	113, UAS & phyVAS	By nephelometric analysis. Measurements taken before treatment and at the end of 4th week, before 2nd omalizumab injection. Parameters analysed: baseline total IgE, total IgE at end of week 4, increase in total IgE from baseline to end of week 4, total IgE at week 4/ total baseline IgE (w4IgE/bIgE ratio)	43 IU/ml	IgE levels were markedly lower in NR group than in PR ($p = 0.008$) and in CR ($p = 0.032$). Total IgE levels at week 4 were lower in NR than in PR ($p < 0.001$) and in CR ($p < 0.001$). Within first 4 weeks of treatment, total IgE levels increased significantly in PR ($p < 0.001$) and in CR ($p < 0.001$), but not in NR. ROC analyses showed w4IgE/bIgE as a good predictor of response to omalizumab. IgE levels below cut-off of 43 IU/ml were linked to a 33% risk of nonresponse, as compared to 5% in patients with IgE of 433 IU/ml or higher	Nil (good sample size; prospective study)	**Yes**
	Marzano 2019[46]	470, UAS7	By chemiluminescent immunoassay	Levels of 100 kUA/L or greater defined as 'increased'	IgE levels were significantly higher in responders than in nonresponders ($p < 0.0001$).	Retrospective study	**Yes**
	Cugno 2018[18]	25 (divided into NR, PR and CR based on UAS7)	Immunoenzymatic method	NA	Baseline IgE significantly lower in NR than in PR ($p = 0.017$) and CR ($p = 0.004$)	Small sample size	**Yes**

(Continues)

TABLE 4 (Continued)

Parameters	First author, year, Ref	N of CSU patients, assessment of response to omalizumab	Methods	Cut-off values	Results	Limitations	Evidence that a marker predicts nonresponse to omalizumab?
	Jörg 2018[51]	30 (placebo, PR/NR, ER, SR), UAS7	Method not mentioned	NA	Total IgE levels at baseline were lower in PR/NR ($p = 0.182$)[a]	Small sample size	**Yes**[a]
	Deza 2017[52]	47, UAS7	Method not mentioned	NA	Responders presented higher total IgE levels at baseline ($p = 0.003$)	Small sample size	**Yes**
	Magen 2019[48]	106, UAS	Method not mentioned	NA	Higher levels of total IgE in PR vs NR ($p = 0.046$)	Retrospective study, small number of the patients in NR group	**Yes**
	Nettis 2018[54]	322	Immunofluorometric assay	48 KUA/L	Higher pretreatment IgE levels were less likely to be associated with poor treatment response ($p = 0.011$)	Retrospective study	**Yes**
	Ghazanfar 2018[53]	117	Method not mentioned	NA	No correlation between total serum IgE levels at baseline and response to omalizumab ($p = 0.526$)	Nil (good sample size, prospective study)	**No**
	Pinto Gouveia 2017[75]	13, UAS7	Method not mentioned	<100 IU/ml	'No significant differences in IgE in different response group'	Small sample size	**No**
	Metz 2014[13]	51 (divided into CR, 'significant improvement', 'no significant improvement' based on UAS7)	ImmunoCap system	NA	Median total IgE levels were similar in responders and NR	Retrospective study, small sample size	**No**
	Viswanathan 2013[61]	19	Based on 2 commercial labs, with reference ranges: 0–114 IU/ml, and 0–180 IU/ml. Method is not mentioned	Any value above each respective upper limit considered 'IgE elevated'	No statistically significant differences in response to omalizumab were noted between patients with elevated and normal IgE levels ($p = 0.48$)	Retrospective study, small sample size	**No**
	Cildag 2019[76]	41 (divided into complete response, significant improvement or no significant improvement, based on UAS7)	By turbidimetric method	NA	No significant differences in baseline IgE levels when patients were divided into CR and those without complete response ($p = 0.48$)	Retrospective study, small sampe size	**No**

Abbreviations: CR, complete response/complete responder; CSU, chronic spontaneous urticaria; CU, chronic urticaria; ER, early responder; NA, not available; NR, nonresponse/nonresponder; PR, partial response/partial responder; SR, slow responders; UAS, urticaria activity score.

[a]Total IgE levels were lower in nonresponders although the difference did not reach the statistical significance ($p = 0.182$). The reasons for this may be due to many groups being compared, including placebo using Kruskal-Wallis test and also because partial responders being included in the nonresponders group.

TABLE 5 Summary on possible markers of response to cyclosporine

Parameters	Level of evidence for association	Level of evidence for no association
Age	–	Strong
Gender	–	Inconsistent
Race	–	No / little
Comorbid allergic diseases	–	No / little
Comorbid psychiatric disorders	–	No / little
Previous treatment with corticosteroids	–	No / little
Previous treatment with antihistamines	–	No / little
CSU duration	–	Weak
High UAS7	Inconsistent	–
Positive ASST	Inconsistent	–
Positive BHRA or CU index	Strong	–
IgG-anti-FcεRI	–	No / little
IgG-anti-IgE	–	No / little
Blood basophil count	–	No / little
Blood eosinophil count	–	No / little
Low levels of total IgE	Weak	–
ANA positivity	–	Inconsistent
Antithyroid antibodies	–	Inconsistent
High D-dimer levels	No / little	–
High C-reactive protein levels	Inconsistent	–
ESR	–	No / little
Blood T, B, NK cells, immunoglobulins, C3, C4, CICs	–	No / little
High serum IL–2R, TNF-α and IL–5 levels	No / little	–

ANA, antinuclear antibody; ASST, autologous serum skin test; BHRA, basophil histamine release assay; CU, chronic urticaria; ESR, erythrocyte sedimentation rate; IL-2R, interleukin-2 receptor; IL-5, interleukin-5; NK, natural killer; TNF, tissue necrosis factor; UAS7, urticaria activity score over 7 days; CICs: circulating immune complexes.

clinical responses in CSU and chronic inducible urticaria indicates that it should not be used to predict or compare clinical efficacies of antihistamines in these diseases.[43,44]

4.2 | Potential biomarkers of nonresponse or poor response to omalizumab

Numerous studies support low total IgE levels as a predictor of nonresponse or poor response to omalizumab (Table 4). In a study by Straesser et al., serum IgE levels of CSU patients were analysed based on subdivision into 4 different quartiles. It was found that the adjusted odds ratio for response to omalizumab was 13.8 for those with serum IgE levels at the 75th percentile (>168.0 IU/ml) than for those at the 25th percentile (<15.2 IU/ml, $p < 0.001$).[45] In another study that found low baseline IgE levels to be associated with nonresponse to omalizumab, the cut-off level for nonresponders was set at 42 kUA/L.[46] Similar results were also noted in other studies that demonstrated IgE levels were markedly lower in nonresponder group than in partial or complete responders.[47,48] In addition, increases in total IgE levels by twofold or more within the first 4 weeks of omalizumab treatment increase the likelihood of response. Baseline total IgE levels above 43 IU/ml and twofold or more increased IgE levels at week 4 were correlated with the improvement of CSU at week 12 of treatment as assessed by UAS.[47] Weller et al. found that elevated total IgE levels were common in complete responders (77.5%), and rarely detected in nonresponders (20%) to omalizumab ($p < 0.001$).[49] More recently, Asero has confirmed that the majority of early responders to omalizumab have elevated baseline total IgE (>100 UI/ml; $p < 0.05$).[50]

Omalizumab is a monoclonal anti-IgE antibody that inhibits IgE binding to FcεRI receptor on the surface of mast cells and basophils, resulting in a reduction of FcεRI receptors on basophils in CSU patients. Therefore, it may be postulated that FcεRI receptor density may be a parameter for basophil reactivity. Two studies provided evidence that patients demonstrating clinical improvement following omalizumab had significant reduction in FcεRI receptor density on basophils.[51,52] Additionally, there was a lower expression of FcεRI at baseline in nonresponders.

Several studies had demonstrated that previous immunosuppressive treatment might be a predictor of nonresponse or poor response to omalizumab, as illustrated by Ghazanfar et al. in 2018, with azathioprine, cyclosporine and methotrexate being the previous immunosuppressive drugs.[53] This observation was echoed in another study with a larger sample size, which revealed that poor treatment outcome was seen in the group that received previous administration of cyclosporine.[54] However, similar outcomes have not been demonstrated in the remaining studies.[52,55,56] Therefore, current evidence remains inconclusive in this regard.

D-dimer and IL-31 are promising markers for treatment responses to omalizumab in CSU, but evidence is scarce. In one study, all omalizumab responders showed a dramatic decrease in levels of D-dimer after the first administration of omalizumab, as compared to nonresponders who did not show any reduction.[57] In another study, successful omalizumab treatment in CSU patients was associated with lowering of serum IL-31 levels.[58]

The data for other markers, for example ASST, BHRA and ANA, and their link to omalizumab treatment response are inconsistent.[59-61] Further large scale and prospective studies are needed to shed more light on confirming whether or not these markers of IgG autoimmunity are indeed predictors of nonresponse or poor response to omalizumab. We also only found inconsistent evidence for predictors of the response to omalizumab up-dosing.

TABLE 6 Potential markers that predict good response to cyclosporine

Parameters	First author, year, Ref	N of CSU patients	Methods	Cut-off values
Total IgE	Santiago 2019[19]	34	Not mentioned	100 IU/ml
	Endo 2019[69]	34	Not mentioned	88.5 IU/ml
BHRA	Grattan 2000[66]	30	Sera were assayed for HRA on the well-characterized basophils of two donors	>5% histamine release is considered positive
	Iqbal 2012[67]	58	Donor cells were obtained from bloodbank buffy coat cells	<16.5%histamine release is considered negative
	Hollander 2011[68]	24	The CU Index was used[a]	N/A

ASST, autologous serum skin test; BHRA, basophil histamine release assay; CSU, chronic spontaneous urticaria; CU, chronic urticaria; UAS7, urticaria activity score over 7 days.

[a]The CU Index is a nonspecific, histamine release assay in which donor blood cells are mixed with the patient's serum as well as positive and negative control serum.

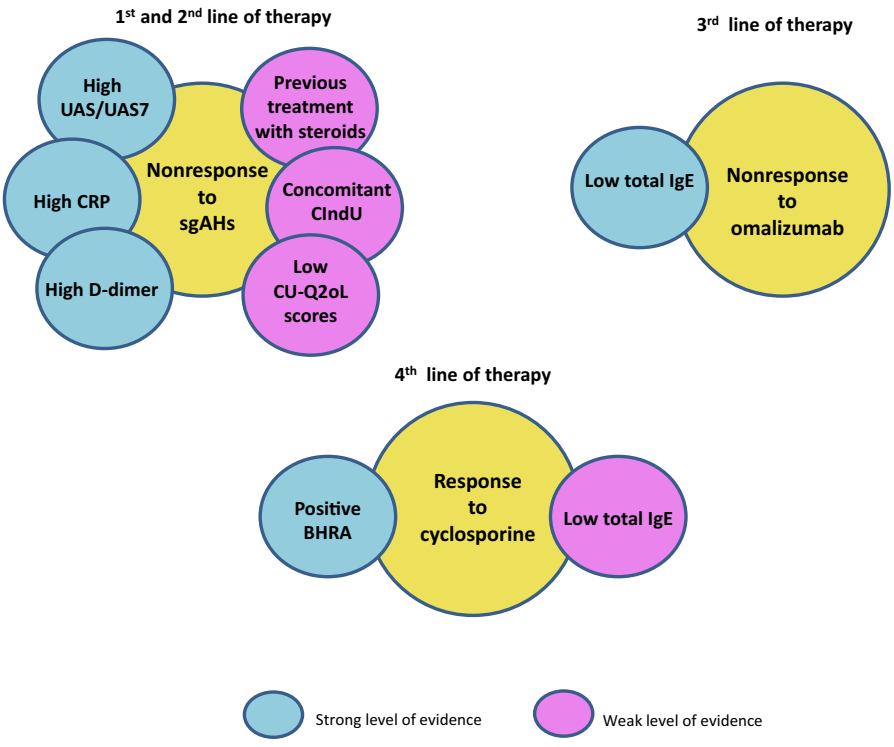

FIGURE 1 Predictors of nonresponse to second-generation antihistamines and omalizumab and response to cyclosporine. BHRA, basophil histamine release assay; CIndU, chronic inducible urticaria; CRP, C-reactive protein; CU-Q2oL, chronic urticaria quality of life questionnaire; sgAHs, second-generation H_1-antihistamines; UAS, urticaria activity score

Results	Limitations	Evidence that a marker predicts good response to cyclosporine?
Mean serum IgE levels were significantly lower in cyclosporine responders vs. nonresponders (p = 0.001). Baseline serum levels of IgE showed a negative correlation with the decrease in UAS7 at month 3 (p = 0.002). When patients were divided into two subgroups based on the normal IgE cut-off, a normal IgE value was associated with a higher probability of response to cyclosporine, with an adjusted odds ratio of 33.9 [95% confidence interval 3.21–357.33; p = 0.003	Retrospective study, small sample size	**Yes**
A significant difference in the change in the UAS7 before and after cyclosporine treatment was observed in patients with a positive ASST and low serum IgE levels (p = 0.0039). The percentage of patients whose UAS7was 6 among all the patients receiving cyclosporine treatment was significantly higher in patients with low IgE levels than in those with high IgE levels (p = 0.009)	Small sample size	**Yes**
13 of 18 clinical responders to cyclosporine were BHRA positive compared with one of nine NR (p = 0.01)	Small sample size	**Yes**
81% of BHRA+patients achieved complete response compared to 19% of BHRA- patients (p < 0.001)	Retrospective study, small sample size	**Yes**
Factors that predicted complete remission of urticaria on cyclosporine were a shorter duration of urticaria (p = 0.03), a history of urticaria (p = 0.01), a positive CU Index (p = 0.05)	Retrospective study, small sample size, subjectively defined, not clear if inducible urticaria was excluded	**Yes**

As for predictors of the time to response to omalizumab in CSU, there is weak evidence in support of ASST positivity being a marker of slow response. Gericke et al. reported that BHRA-positive and ASST-positive omalizumab responders are 4.5 and 5.5 times more likely to have a slow response to treatment compared with BHRA-negative and ASST-negative responders.[62] This study also postulated that omalizumab works via reducing FcεRI expression. In another study, ASST positivity was also linked to slow onset of relief with omalizumab.[54]

The speed of symptom return after omalizumab treatment was independent of duration of CSU, angioedema, previous treatments received or patient demographics. Rather, findings suggest that high baseline UAS7 and slow decrease of symptoms indicate a higher probability of rapid symptom return.[63] In the ASTERIA I and II and GLACIAL trials, patients with lower baseline UAS7 and rapid treatment response (ie high UAS7 area above the curve) had a lower probability of a rapid symptom return and patients with high baseline UAS7 and slower initial response to treatment (ie low UAS7 AAC) had a higher probability of rapid return after treatment discontinuation. Increased IgE levels were linked to faster relapse in patients with omalizumab-discontinued CSU. In contrast, there was no correlation of pre-treatment total IgE levels with time to response to omalizumab and no difference in time to response to omalizumab treatment between patients with increased and normal IgE levels.[64]

4.3 | Potential biomarkers of response to cyclosporine

Type IIb autoimmune CSU is characterized by triple positivity: (i) a positive BHRA, a marker of functional IgG autoantibodies, (ii) a positive ASST, a marker of autoreactivity, and (iii) the presence of IgG anti-FcεRIα autoantibodies as assessed by immunoassay.[65] In BHRA, serum from the patient is incubated with basophils from a healthy donor, and resulting histamine release is expressed as a percentage of total histamine.[66] In a randomized clinical trial, Grattan et al. demonstrated baseline BHRA positivity in 72% of responders to cyclosporine compared with 11% of nonresponders.[66] Iqbal et al. reported that 81% of BHRA-positive patients achieved complete response compared to 19% of BHRA-negative patients.[67] In another study, Hollander et al. showed that BHRA positivity is a predictor of cyclosporine-mediated complete remission.[68]

Recently, Santiago et al. demonstrated that mean serum IgE levels were significantly lower in cyclosporine responders, negatively correlated with the decrease in UAS7 at 3 months and

non-elevated total IgE levels were associated with a higher probability of response to cyclosporine.[19] Endo et al. showed that low baseline total IgE was associated with low UAS7 after treatment with cyclosporine.[69]

Other markers of response to cyclosporine that should be further investigated are CRP, D-dimer and ASST. For example, in one study nine CSU patients with elevated high sensitivity-CRP were found to have a shorter treatment duration.[70] Asero et al. observed elevated baseline D-dimer plasma levels in more than 60% of the patients with severe CSU and D-dimer levels followed the clinical response to cyclosporine treatment in many cases.[71] Although positive ASST has been regarded as a screening marker for type IIb autoimmune urticaria, we found inconclusive evidence of ASST being a potential predictor of treatment response for cyclosporine.

4.4 | Limitations

There was significant heterogeneity among studies, including different antihistamines being used, different cut-off values for the same parameters and different methods for the measurement of the same parameter. Importantly, none of the predictors this study identified have been prospectively validated in terms of their sensitivity and specificity. They should not be used, at this point in time to guide treatment decisions that are not in line with the international guideline treatment algorithm.

5 | CONCLUSION

There are promising clinical and biochemical predictors of nonresponse to sgAHs (high UAS7 or UAS, CRP, D-dimer, concomitant CIndU, previous treatment with corticosteroids and low CU-Q2oL scores) and omalizumab (low total IgE levels) as well as predictors of response to cyclosporine (positive BHRA results and low total IgE levels). Further prospective randomized studies are needed to confirm these predictors and to identify additional ones. The use of these predictors can help to counsel patients on what to expect from their treatment and to prioritize patients at risk of nonresponse for consideration to be switched to more effective therapies.

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CONFLICT OF INTEREST

Jie Shen Fok: no conflicts of interest regarding any aspects of this study. *Pavel Kolkhir*: personal fees from Novartis and Roche, outside the submitted work. *Martin K Church*: a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, Blueprint, Glenmark, Novartis, Pediapharm and Uriach. *Marcus Maurer*: grants and/or personal fees from Allakos, Amgen, Aralez, AstraZeneca, Celldex, CSL Behring, FAES, Genentech, GIInnovation, Innate Pharma, Menarini, Leo Pharma, Lilly, Moxie, MSD, Roche, Sanofi, Third Harmonic Bio, UCB, Uriach, outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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