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Predictors of treatment response in chronic spontaneous urticaria

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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; UAS: Urticaria activity score; sgAHs: Second generation H_1-antihistamines

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Abstract (200 words; 200 max)

The current therapeutic algorithm for chronic spontaneous urticaria (CSU), endorsed by the international guideline, entailstreatment escalationfrom second generation H_1-antihistamines (sgAHs) toomalizumab to cyclosporine until complete response is achieved. Recently, several predictors of response to these treatment options have been described. Here, we discuss the most promisingpredictors of response and non-responseto 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 (CRP) and D-dimer are robust predictors for a poor or no response to sgAHs. Poor or noresponse 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 IgEis 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.

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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]CSUhas an unpredictable course and duration, and many patients suffer for more than one year, e.g. 11 to 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, e.g. depression and anxiety, which add to the impairment of quality of 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/GA²LEN/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 responserate that ranges from 26% to 83% as demonstrated in several landmark studies including XCUISITE,ASTERIA and the recent ligelizumabtrial.[10-14]Someomalizumab non-responders benefit from cyclosporine, the fourth-line therapy.[15, 16]Thecurrent 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 ofCSU,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 individualised approach saves time and costs.

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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 treatmentand good response to cyclosporine,[18, 19] and response was evaluated using the urticaria activity score over 7 days (UAS7).

With this background, we systematically reviewedthe published evidencefor biomarkers that predictthe 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.

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Material and Methods

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, e.g. cross-sectional, case-control studies, prospective, open label and retrospectivestudies, were included. Reviews, case reports and publications with non-English abstract were not considered.Non-English full-text publications with English abstractswere considered. Reference lists of included studies were also searched for additional potentially eligible reports.Summary of literature review is highlighted in Suppl. Figure 1.

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.

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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 studiesand 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 randomised control trials and 2 studies with no information on the design provided (Suppl. Figure 1).

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 than one table. The tables include relevant studies with statistically significant and

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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

(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.

Levels of evidence for 'no association' are

(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.

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Results

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 non-response 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 UAS7was significantly linked to nonresponse to sgAHsin 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(Table 1 and 4; Suppl. Table 1 and 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 baselineis a predictor for nonresponse or poor response(Table 2). Weak evidence was demonstrated for ASST positivity as a predictor of slow response to omalizumab. The evidence for possible markers of the response to updosing of omalizumab was inconsistent. There was strong evidence for *no association*of age, gender and anti-thyroid

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antibodies as well as weak evidence for *no association*of CRPwith the response to treatment with omalizumab (Table 2 and 5, suppl. Table 3-8).

Positive basophil histamine release assay resultsand low total IgElevels 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 non-response 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 summarised in Table 3. There was strong level evidence for *no association*of age with the response to cyclosporine, and weak evidence for *no association*with disease duration (Table 3 and 6; Suppl Table 9 and 10).

Figure 1 highlights predictors of nonresponse to sgAHs and omalizumab and predictors of response to cyclosporine.Suppl. Table 11 summarises robust predictors with strong level of evidence for all treatments.

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

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(one study) is a marker of sgAHnonresponsiveness(Table 4). What this means is that patients with high disease activity, i.e. 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 non-responders 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 sgAHs non-responders.[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

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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 sgAHdesloratadine.[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 sgAHmizolastine.[27]

CIndU, e.g. 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 sgAHs-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]Ulambayarand 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 coworkersconfirmed 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.

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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 multi-centre 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, thyroid disease and hypertension.[36]Prevalence of central obesity, hyperglycemia and hypertriglyceridemia were 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 eosinopeniaare 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

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

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 5). In a studyby 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 foundlow baseline IgE levels to be associated with non-response to omalizumab, the cut-off level for nonresponders was set at 42kUA/L.[46]Similar results were also noted in other studiesthat 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 two-fold or more within the first 4 weeks of omalizumab treatment increase the likelihood of response. Baseline totalIgE levelsabove 43 IU/mL and two-fold or more increasedIgE 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

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(77.5%), and rarely detected in nonresponders(20%) to omalizumab (P <0.001).[49]More recently, Aserohas 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 ofFcεRIat 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, e.g. ASST, BHRA, and ANA, and their link toomalizumab 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

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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.

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]

Potential biomarkers of response to cyclosporine

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Type IIbautoimmune 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 ofcyclosporine-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.

Limitations

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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,

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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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	–

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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	–	Strong
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	–

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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	

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

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Table 2.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	–

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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**	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*	–
Other immunoglobulins (IgA, IgG, IgM)	–	No / little
ANA positivity	Inconsistent	–
TSH	–	No / little
C3	No / little	–
C4	–	No / little
Antithyroid antibodies	–	Strong

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High D-dimer levels	Inconsistent	–
High CRP levels	–	Weak
DHEA-S	–	No / little
FVIIa and FXIIa, prothrombin factors 1 and 2	–	No / little

*See explanation under Suppl. Table 4; **Positive basophil histamine release test or basophil CD203c or CD63 upregulating activity or basophil activation test or CU index; 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:dehydroepiandrosteronesulfate; 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

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Table 3.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 counts	–	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	–

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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

Table 4.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	Results	Limitations	Evidence that a marker predicts nonresponse to sgAHs?
High disease activity	Ulambayar 2019[31]	283	UAS7	N/A	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**
	Trinh 2016[32]	191	UAS7	N/A	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**

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	Kim 2016[72]	138	UAS7	N/A	Higher UAS was found in cases refractory tosgAHscompared to cases responsive to sgAHs; p<0.001	Nil (hospital-based cross sectional)	**Yes**
	Magen 2011[24]	385	UAS	N/A	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**
	Curto-Barredo 2018[30]	549	UAS7	N/A	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**
	Kolkhir 2017[35]	84	UAS	N/A	Responders to levocetirizine had lower UAS scores compared to nonresponders; p = 0.005	Small sample size	**Yes**
	Yan 2019[27]	145	UAS7	N/A	No significant difference between the responder groupand nonresponder group regarding UAS7 values; p=0.521	Authors concluded study limited by sample size and single-centre study	**No**
	Yan 2014[73]	191	UAS7	N/A	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**
High CRP	Yan 2017[23]	605	N/A	Not mentioned	Patients with lower CRP levels showed better responses to treatment than those with higher CRP levels; p<0.05	Retrospective study	**Yes**
	Kolkhir	1019	Nephlometric	5mg/L	Of 1019 CSU patients, 31% (n=313) had elevated	Retrospective study	**Yes**

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	2018[22]		method		levels of CRP (of ≥5mg/L). CRP levels were significantly higher in nonresponders to sgAHs as compared to responders; p<0.001		
	Magen 2011[24]	385	N/A	1-3 mg/L	sgAHs-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**
	de Montjoye 2020[25]	95	N/A	mean 7.7mg/L	Innonresponders to sgAHs, CRP serum levels were significantly higher than in responders(p < 0.0001)	Small sample size	**Yes**
	Kolkhir 2017[35]	84	Nephlometric method	Not mentioned	Responders to levocetirizine had lower CRP compared to nonresponders; p < 0.001	Small sample size	**Yes**
	Yan 2019[27]	145	N/A	Not mentioned	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**
	Huilan 2015[74]	40	N/A	Not mentioned	No statistical difference in CRP levels during exacerbation and during remission; p>0.05	Small sample size	**No**
High D-dimer	Asero 2013[34]	91	ELISA	500ng/mL (“normal” or “elevated”)	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**
	Kolkhir 2017[35]	84	ELISA	Not mentioned	D-dimer levels were significantly higher in nonrespondersas compared to responders; p < 0.001	Small sample size	**Yes**

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	de Montjoye 2020[25]	95	N/A	< 500ng/mL	sgAHsnonresponders:D-dimer plasma levels were significantly higher than in sgAHs responders; p = 0.009	Small sample size	**Yes**
CU-Q2oL	Trinh 2016[32]	191	CU-QoL	N/A	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**
	Kolkhir 2017[35]	84	CU-Q2oL	N/A	Responders had higher CU-Q2oL scores compared to nonresponders; p < 0.001	Small sample size	**Yes**
Previous corticosteroid treatment	Ulambayar 2019[31]	283	N/A	N/A	The percentage of previous corticosteroid use was higher in sgAHsnonresponders (93.8%) than sgAHs responders (52.1%); p<0.001	Nil (large sample size, prospective study)	**Yes**
	Trinh 2016[32]	191	N/A	N/A	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**
Concomitant CIndU	Magen 2011[24]	385	N/A	N/A	sgAHs-resistant CSU group had more cases of concomitant physical urticaria (23.9%) compared with sgAHs-responsive CSU group (12.2%); p=0.014	Retrospective study	**Yes**
	Curto-Barredo	549	N/A	N/A	Patients with CSU-CIndU required more frequent therapy after 5 years and higher doses of sgAHs	Retrospective study	**Yes**

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	2018[30]				than patients with isolated CSU (43.0% vs. 31.3%; p<0.05)		

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

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Table 5.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	Weller2018[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 centers, 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**
	Ertas2018[47]	113, UAS &phyVAS	By nephelometric analysis. Measurements taken before treatment and at the end of 4th week, before 2ndomalizumab injection. Parameters analysed:	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 ($p<0.001$).	Nil (good sample size; prospective study)	**Yes**

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			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)		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. IgElevels below cut-off of 43IU/mL were linked to a 33% risk of nonresponse, as compared to 5% in patients with IgE of 433IU/mL or higher		
	Marzano2019[46]	470, UAS7	By chemiluminescent immunoassay	Levels of 100kUA/L or greater defined as "increased"	IgElevels were significantly higher in responders than in nonresponders ($p<0.0001$).	Retrospective study	**Yes**
	Cugno2018[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**
	Jörg2018[51]	30 (placebo, PR/NR, ER, SR), UAS7	Method not mentioned	NA	Total IgE levels at baseline werelower in PR/NR ($p=0.182$)*	Small sample size	**Yes***
	Deza2017[52]	47, UAS7	Method not mentioned	NA	Responders presented higher total IgE levels at baseline ($p=0.003$)	Small sample size	**Yes**
	Magen2019[48]	106, UAS	Method not mentioned	NA	Higher levels of total IgE in PR vs NR	Retrospective	**Yes**

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					(p =0.046)	study, small number of the patients in NR group	
	Nettis2018[54]	322	Immunofluorometric assay	48 KUA/L	Higher pretreatmentIgE 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 Gouveia2017[75]	13, UAS7	Method not mentioned	<100IU/mL	"No significant differences in IgE in different response group"	Small sample size	**No**
	Metz2014[13]	51 (divided into CR, "significant improvement", "no significant improvement" based on UAS7)	ImmunoCap system	NA	Median total IgElevels were similar in responders and NR	Retrospective study, small sample size	**No**
	Viswanathan2013[61]	19	Based on 2 commercial labs, with reference ranges: 0-114IU/mL, and 0-180 IU/mL.Method is not mentioned	Any value above each respective upper limit considered	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**

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				"IgE elevated"			
	Cildag2019[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**

*****Total IgE levels were lower in non-responders 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 non-responders group.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

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Table 6.Potential markers that predict good response to cyclosporine

Parameters	First author, year, Ref	N of CSU patients	Methods	Cut-off values	Results	Limitations	Evidence that a marker predicts good response to cyclosporine?
Total IgE	Santiago 2019[19]	34	Not mentioned	100 IU/mL	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**
	Endo2019[69]	34	Not mentioned	88.5 IU/mL	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 wassignificantly higher in patients with low IgE levels than in thosewith high IgE levels (p = 0.009)	Small sample size	**Yes**

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BHRA	Grattan 2000[66]	30	Sera were assayed for HRA on the well-characterized basophils of two donors	>5% histamine release is considered positive	13 of 18 clinical responders to cyclosporine were BHRA positive compared with one of nine NR (p = 0.01)	Small sample size	**Yes**
	Iqbal 2012[67]	58	Donor cells were obtained from bloodbank buffy coat cells	<16.5%histamine release is considered negative	81% of BHRA+ patients achieved completeresponse compared to 19% of BHRA- patients (p<0.001)	Retrospective study, small sample size	**Yes**
	Hollander 2011[68]	24	The CU Index was used[1]	N/A	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**

ASST: autologous serum skin test; BHRA: basophil histamine release assay; CSU:chronic spontaneous urticaria; CU:chronic urticaria; UAS7:urticaria activity score over 7 days; [1]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

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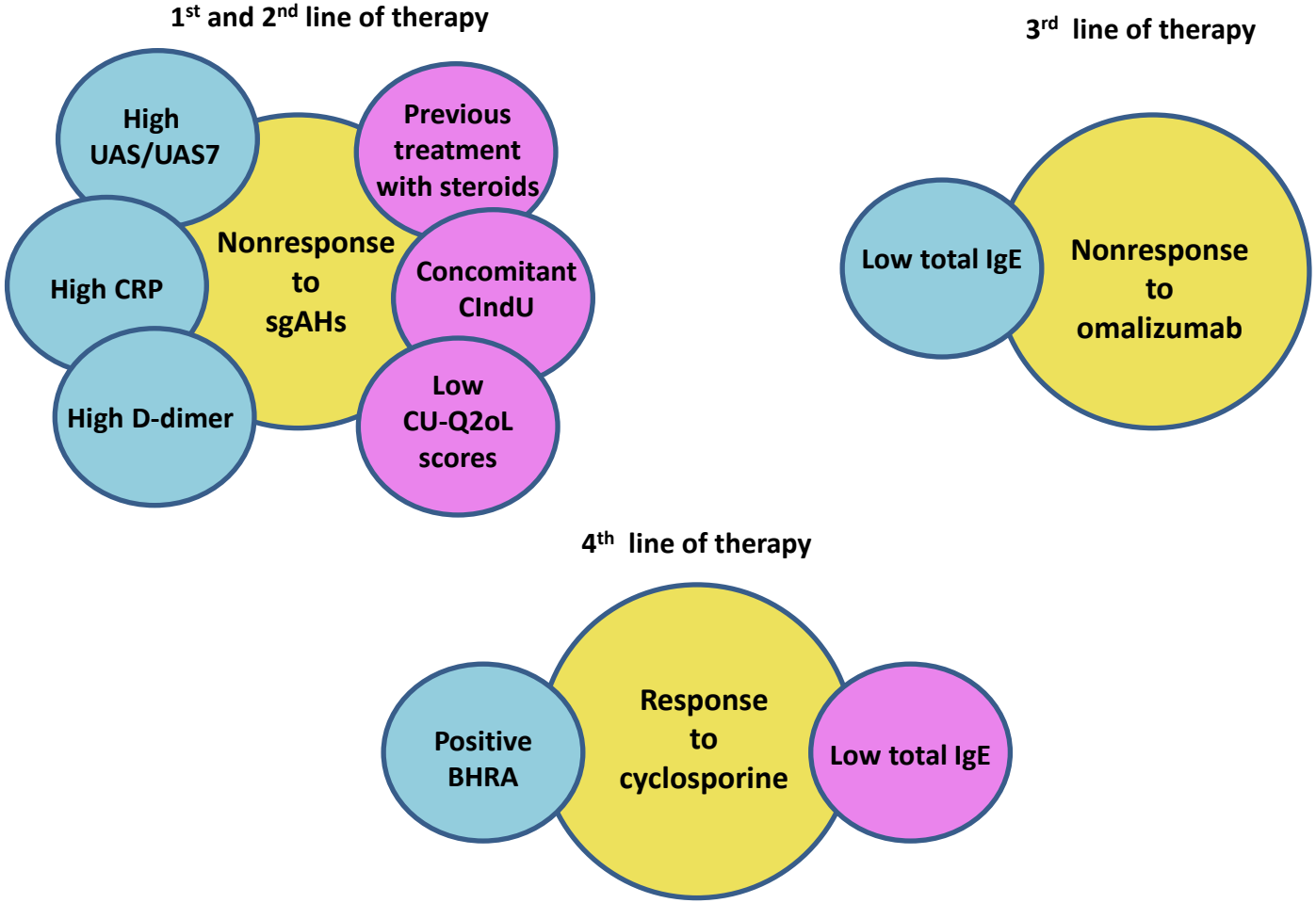
FIGURE LEGEND

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

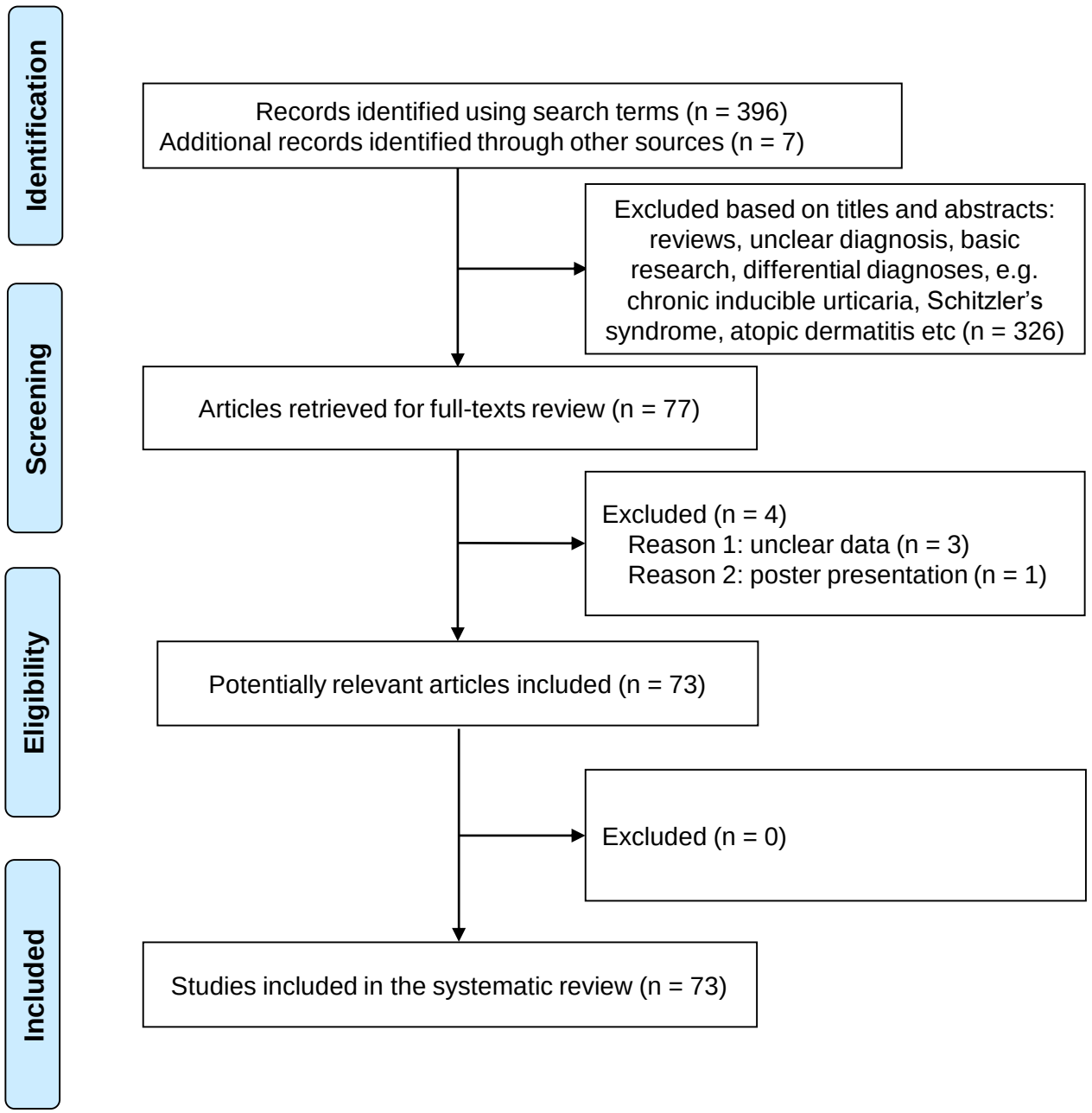
Suppl. Figure 1. Flow chart of study selection process

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Identification
Screening
Eligibility
Included
Records identified using search terms (n = 396)
Additional records identified through other sources (n = 7)
Excluded based on titles and abstracts: reviews, unclear diagnosis, basic research, differential diagnoses, e.g. chronic inducible urticaria, Schitzler's syndrome, atopic dermatitis etc (n = 326)
Articles retrieved for full-texts review (n = 77)
Excluded (n = 4)
Reason 1: unclear data (n = 3)
Reason 2: poster presentation (n = 1)
Potentially relevant articles included (n = 73)
Excluded (n = 0)
Studies included in the systematic review (n = 73)

Suppl. tables

Suppl. Table 1. Potential predictors of response to second generation H_1-antihistamines in patients with CSU

Parameters	First author, Year, Ref	N of CSU patients	Age, years, mean or median (range)	sgAHs name and dosage	When the marker was assessed	How response was evaluated	Results and p-values	Cut-off values	Design of study	Country
Absolute blood eosinophil count, absolute basophil count	Kolkhir 2019[1]	93	>17 (–)	Different, daily, in standard doses	After four weeks of treatment	Patient-based questionnaire	NR to sgAHs had lower blood eosinophils ($p < 0.05$) and basophils ($p = 0.198$) counts compared with R	<0.05 x 10^9/L (eosinophils), <0.01 x 10^9/L (basophils)	Retrospective	Germany, Russia
PAF, UAS7, corticosteroids use, omalizumab use, cyclosporine use	Ulambayar 2019[2]	283	42 (–)	–	Baseline	UAS7	NR had higher blood levels of PAF, UAS7 scores and/or higher need for steroids, omalizumab and/or cyclosporine than R ($p < 0.05$)	5000 pg/mL	Prospective	South Korea
CRP gene polymorphisms	Yan 2019[3]	145	38.2 (18-66)	Mizolastine 10 mg/d, desloratadine 5 mg/d, fexofenadine 120 mg/d (standard dose, 4 weeks)	–	UAS7	rs3093059TT genotype was associated with good response to mizolastine (OR = 4.20, $p = 0.015$)	–	Prospective	China
CRP	Yan 2017[4]	605	–	Mizolastine 10 mg/d, desloratadine 5 mg/d, fexofenadine 120 mg/d	–	UAS7	The patients with lower CRP levels showed better responses to treatment than those with higher CRP levels ($p < 0.05$)	–	Retrospective	China
CRP	Kolkhir 2018[5]	1,019	42 (13-105)	Differ, standard dose	4 weeks after treatment	Subjectively defined	Non-responsiveness to sgAHs in standard and elevated doses was associated with elevated CRP serum levels ($p < 0.05$)	5 mg/L	Retrospective	Germany, Russia

ESR, positive antithyroid antibodies	Choonhakarn 2018[6]	67	43.3 (22-64)	Desloratadine 5 mg or higher	Baseline	UAS7	The patients who had CSU concomitant with antithyroid antibodies (p=0.0002) or high ESR (p = 0.017) had a greater tendency not to respond to the standard dose of sgAHs	ESR: 20 mm/h	Retrospective	Thailand
BHRA	Berti 2017[7]	20	42 (18-67)	Cetirizine 10 mg, desloratadine 5 mg, loratadine 10 mg, bilastine 20 mg, ebastine 10 mg (standard or high doses)	Baseline	UAS	A positive BHRA result at baseline was associated with sgAH treatment withdrawal at 1 year (p = 0.027)	16.5%	Prospective	Italy
Presence of angioedema, UAS7, CU-QoL, LCN2, IL-6, need for corticosteroids	Trinh 2016[8]	191	40 (19-60)	High doses	Baseline	UAS	Patients with sgAH-resistant CSU showed a higher prevalence of angioedema, higher UAS and lower CU-QoL scores, higher IL-6 and lower LCN2 levels and greater needs for systemic corticosteroids compared to those with responsive CSU (p < 0.05)	LCN2: 0.2-10ng/mL IL-6: 9.38-600 pg/mL	Cross-sectional	South Korea
Diameter of histamine-induced wheal	Sanchez 2016[9]	150	28 (14-50)	Daily oral dose of cetirizine (10 mg), fexofenadine (180 mg), bilastine (20 mg), desloratadine (5 mg), or ebastine (20 mg) over 8 weeks; standard or high doses	A histamine SPT was carried out at baseline and 24 hours after the first dose of antihistamine.	UAS, DLQI	Twenty-four hours after administration of antihistamine, inhibition of the histamine wheal by >75% was significantly associated with better UAS and DLQI scores	–	RCT	Colombia
Serum clusterin, ASST, UAS7	Kim 2016[10]	138	39 (19-72)	–, for 3 months	–	UAS7	Refractory CSU was associated higher UAS, lower clusterin leves and ASST negativity (p < 0.05)	Clusterin: 202 mg/mL	Cross-sectional	South Korea

ANA	Magen 2015[11]	569	>40 (–)	Fexofenadine 180 mg/d, cetirizine 10 mg/d, desloratadine 5 mg/d, loratadine 10 mg/d; standard or high doses	–	–	sgAHs were less effective in ANA+ than in ANA- group ($p < 0.05$)	–	Retrospective	Israel
C5a, ASST	Huilan 2015[12]	40[1]	–	–	–	–	Antihistamine-resistant urticaria was associated with higher C5a plasma levels ($p < 0.05$) and higher rates of ASST positivity ($p < 0.05$)	–	Unclear	China
ANA, CU Index	Viswanathan 2012[13]	195	>40 (–)	–	–	Subjectively defined	In patients with positive ANA titers and/or CU index, the percent of refractory patients was higher as compared to those with negative ANA titers and/or CU index ($p < 0.05$)	ANA: >1:160 CU Index: >10	Retrospective	US
Antithyroid antibodies, concomitant CIndU	Amin 2015[14]	211	>40 (–)	Cetirizine 10 mg, fexofenadine 180 mg, loratadine 10 mg, levocetirizine 5 mg, or desloratadine 5 mg once daily	–	Subjectively defined	Antithyroid antibodies or concomitant CIndU were associated with better control using sgAHs ($p < 0.05$)	–	Retrospective	US
Single nucleotide polymorphisms in C5AR1	Yan 2014[15]	191	36 (18-75)	Monotherapy for 4 weeks; desloratadine 5 mg/d, mizolastine 10 mg/d, or fexofenadine 120 mg/d	–	UAS7, DLQI	The -1330GT heterozygous patients had a poor response to desloratadine than the patients with other two genotypes (GG and TT) ($p = 0.001$)	–	Prospective	China
Age	Neverman 2014[16]	46	12.5 (9-18)	Cetirizine 20 mg or hydroxyzine 75 mg twice daily	–	Subjectively defined	Patients who were antihistamine responsive had a median age of 6 years, significantly lower than those who were antihistamine resistant ($p = 0.0001$)	–	Retrospective	US

FCER1A genetic polymorphisms	Guo 2015[17]	191	36 (18-75)	desloratadine 5 mg/d, mizolastine 10 mg/d, or fexofenadine 120 mg/d	–	UAS7	Allele frequency of the rs2298805A was significantly decreased in the ineffective group as compared with the effective group (p = 0.015, OR = 8.328)	–	Prospective	China
D-dimer	Asero 2013[18]	91	47 (11-85)	Cetirizine 10 mg/d for 7 to 14 days	7-14 days after first visit	UAS	NR to sgAHs showed higher rates of elevated D-dimer	500 ng/mL	Prospective	Italy
Presence of angioedema, concomitant CIndU, ASST, UAS, blood basophils count, MPV, CRP, C3, liver enzymes	Magen 2011[19]	291	>40 (–)	Fexofenadine hydrochloride 180 mg q.d.; desloratadine at 5 mg q.d., or cetirizine at 10 mg q.d.	Baseline	UAS7	sgAHs-resistant CSU group was characterized with a higher incidence of angioedema, more cases concomitant CIndU, higher rates of ASST positivity, higher baseline UAS, more severe basopenia, higher MPV, higher serum levels of CRP, C3 and liver transaminases (p < 0.05)	C3: 80-180 mg/dL CRP: 1-3 mg/L	Retrospective	Israel
ASST	Staubach 2006[20]	56	>40 (–)	–	–	UAS7	ASST positivity was associated with higher need for antihistamines (p = 0.02)	–	Prospective	Germany
Concomitant CIndU, UAS7	Curto-Barredo 2018[21]	549	50 (–)	–	Baseline	UAS7	Patients with CSU-CIndU required higher doses of sgAHs than patients with isolated CSU (p < 0.05). NR showed higher baseline UAS7 compared with R (p = 0.03)	–	Retrospective	Spain
Atopic disease	Lee 2011[22]	62	31.8 (18-61)	Levocetirizine 5 mg or desloratadine 5 mg daily, for 6 weeks	–	Subjectively defined	NR were more likely to have allergic rhinitis and/or personal history of atopy (p < 0.05)	–	Prospective	Taiwan

CD63 assay positivity	Irinyi 2007[23]	109	39.8 (13-74)	Cetirizine 10 mg/day in standard or high dose	–	Urticaria score index	Cetirizine was less effective in the group of patients with CD63 assay positivity (12.8%) than in CD63 negative CSU group (68.6%); no p-value provided	Values above 95th percentile of CD63-positive cells induced by 20 control sera were considered as positive	Prospective	Hungary
Basophil CD203c expression	Ye 2013[24]	82	39.2 (–)	–	Baseline	UAS	Basophil CD203c expression was higher in severe CSU patients whose symptoms were not completely controlled with antihistamines ($p = 0.033$)	21.3% and 72.0%	Cross-sectional	Korea
ORAI1 gene polymorphisms	Li 2017[25]	191	36.2 (–)	Desloratadine (5 mg, once per day), mizolastine (10 mg once per day), or fexofenadine (60 mg, twice per day) for 4 weeks	–	UAS7	The allele frequency of rs3741595C was significantly lower in the R than in NR	–	Prospective	China
CRP, D-dimer	Montjoye 2020[26]	95	45.1± 16.2	–	–	UAS7	CRP and D-dimer plasma levels were significantly higher in NR than in R ($p<0.05$)	CRP: <5 mg/L D-dimer: <500 ng/mL	Prospective	Belgium
D-dimer, CRP, fibrinogen, ESR, UAS, CU-Q2oL, IgE	Kolkhir 2017[27]	84	16 to 77	Levocetirizine 5mg daily for 7 days	Baseline (before levocetirizine was given)	UAS CU-Q2oL	Univariate analysis showed D-dimer ($p < 0.001$), CRP ($p < 0.001$), fibrinogen ($p = 0.004$), ESR ($p < 0.001$), UAS ($p = 0.005$), CU-Q2oL ($p < 0.001$) and total IgE ($p = 0.026$) significantly differ for responders and non-responders	-	Prospective	Russia

[1]not clear if inducible urticaria was excluded

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; DLQI: Dermatology Life Quality Index; ESR: erythrocyte sedimentation rate;IL-6: interleukin-6; LCN2: lipocain-2; MPV: mean platelet volume; NR: nonresponders; OR: odds ratio; PAF: platelet-activating factor; R: responders; RCT: randomized controlled trial; sgAHs: second generation H_1-antihistamines; SPT: skin prick tests; UAS: urticaria activity score

Suppl. Table 2. Summary evidence on potential predictors of response to second generation H_1-antihistamines in CSU patients

Parameters	**Difference in baseline values of parameters between NR vs R to sgAHs or in rates of response and nonresponse to sgAHs between patients with high/positive vs low/negative test results**					**Level of evidence for association**	**Level of evidence for *no* association**
	Yes (p<0.05)			*No*			
	Description	*First author*	*N of studies (total/from different teams)*	*First author*	*N of studies (total/from different teams)*		
Age	Higher in NR	Neverman 2014[16]	1/1	Yan 2019[3] Trinh 2016[8] Kim 2016[10] Magen 2011[19] Ulambayar 2019[2] Montjoye 2020[26]	6/6	–	**Strong**
Sex	–	–	0	Yan 2019[3] Trinh 2016[8] Kim 2016[10] Magen 2011[19] Ulambayar 2019[2] Montjoye 2020[26]	6/6	–	**Strong**
Height	–	–	0	Yan 2014[15]	1/1	–	No / little
Weight	–	–	0	Yan 2014[15] Montjoye 2020[26]	2/2	–	Inconsistent
BMI	–	–	0	Yan 2014[15] Magen 2011[19] Ulambayar 2019[2]	3/3	–	Inconsistent
Concomitant chronic inducible urticaria	Better response	Amin 2015[14]	1/1	–	0	**Weak**	–
	Higher rates in NR	Magen 2011[19] Curto-Barredo 2018[21]	2/2	–	0		
Comorbid allergic diseases	Higher rates in NR	Lee 2011[22]	1/1	Kim 2016[10]	1/1	Inconsistent	–
Presence of AE	Higher in NR	Trinh 2016[8] Magen 2011[19]	2/2	Choonhakarn 2018[6] Kim 2016 [10] Montjoye 2020[26]	3/3	Inconsistent	–

Previous cyclosporine treatment	Higher in NR	Ulambayar 2019[2]	1/1	–	0	No / little	–
Previous treatment with corticosteroids / greater need for corticosteroids	Higher in NR	Ulambayar 2019[2] Trinh 2016[8]	2/2	–	0	**Weak**	–
Previous treatment with omalizumab	Higher in NR	Ulambayar 2019[2]	1/1	–	0	No / little	–
CSU duration	–	–	0	Yan 2019[3] Trinh 2016[8] Kim 2016[10] Ulambayar 2019[2] Montjoye 2020[26]	5/5	–	**Strong**
UAS7	Higher in NR	Ulambayar 2019[2] Trinh 2016[8] Kim 2016[10] Magen 2011[19] Curto-Barredo 2018[21] Kolkhir 2017[27]	6/6	Yan 2019[3] Yan 2014[15]	2/1	**Strong**	–
DLQI	–	–	0	Yan 2019[3] Yan 2014[15]	2/1	–	Inconsistent
CU-Q2oL	Lower in NR	Trinh 2016[8] Kolkhir 2017[27]	2/2	-	0	**Weak**	–
Type of infiltrate in skin biopsy	–	–	0	Marques 2016[28]	1/1	–	No / little
Diameter of histamine-induced wheal by skin prick tests	Inhibition of the histamine wheal by >75% associated with response	Sanchez 2016[9]	1/1	–	0	No / little	–
ASST	ASST- rates higher in NR	Kim 2016[10]	1/1	Bélot 2010[29] Montjoye 2020[26]	2/2	Inconsistent	–
	ASST+ rates higher in NR	Huilan 2015[12] Magen 2011[19] Staubach 2006[20]	3/3				
Positive urticaria histamine release test	sgAHs withdrawal at 1 year	Berti 2017[7]	1/1	–	0	No / little	–
CD63 assay positivity	Higher rates in NR	Irinyi 2007[23]*	1/1	–	0	No / little	–

Basophil FcεRI expression	–	–	0	Deza 2019[30]	1/1	–	No / little
Basophil CD203c expression	Higher rates in NR	Ye 2013[24]	1/1	–	0	No / little	–
IgG-anti-FcεRI				Ulambayar 2017[31]	1/1	–	No / little
CU index	Positivity rates higher in NR	Viswanathan 2012[13]	1/1	Neverman 2014[16]	1/1	Inconsistent	–
Blood leukocyte count	–	–	0	Magen 2011[19]	1/1	–	No / little
Blood lymphocytes count	–	–	0	Magen 2011[19]	1/1	–	No / little
Blood basophil counts	Low in NR	Magen 2011[19]	1/1	Kolkhir 2019[1] Kim 2016[10] Montjoye 2020[26]	3/3	-	Weak
Blood eosinophil counts	Low in NR	Kolkhir 2019[1]	1/1	Magen 2011[19]	1/1	Inconsistent	–
Platelets	–	–	0	Magen 2011[19] Ulambayar 2019[2]	2/2	–	Inconsistent
MPV	Higher in NR	Magen 2011[19]	1/1	–	0	No / little	–
Total IgE	Higher in R	Kolkhir 2017[27]	1/1	Trinh 2016[8] Magen 2011[19] Ulambayar 2019[2] Montjoye 2020[26]	4/4	–	Weak
ANA positivity	Higher in NR	Magen 2015[11] Viswanathan 2012[13] Magen 2011[19]	3/3	Ertaş 2019[32] Choonhakarn 2018[6] Montjoye 2020[26]	3/3	Inconsistent	–
ATA positivity	Higher in NR	Choonhakarn 2018[6]	1/1	Viswanathan 2012[13] Montjoye 2020[26]	2/2	Inconsistent	–
	Higher in R	Amin 2015[14]	1/1				
TSH	–	–	0	Magen 2011[19]	1/1	–	No / little
C3	Higher in NR	Magen 2011[19]	1/1	Kim 2016[10] Huilan 2015[12] Ulambayar 2019[2]	3/3	–	Weak
C4	–	–	0	Kim 2016[10] Magen 2011[19] Huilan 2015[12] Ulambayar 2019[2]	4/4	–	**Strong**
C5a	Higher in NR	Huilan 2015[12]	1/1	–	0	No / little	–
Single nucleotide	The -1330GT	Yan 2014[15]	1/1	–	0	No / little	–

polymorphisms in C5AR1	genotype associated with NR						
FCER1A genetic polymorphisms	Allele frequency of the rs2298805A decreased in NR	Guo 2015[17]	1/1	–	0	No / little	–
ORAI1 gene polymorphisms	Allele frequency of rs3741595C higher in NR	Li 2017[25]	1/1	–	0	No / little	–
D-dimer	Higher in NR	Asero 2013[18] Kolkhir 2017[27] Montjoye 2020[26]	3/3	--	0	**Strong**	–
C-reactive protein	Higher CRP levels associated with NR	Yan 2017[4] Kolkhir 2017[27] Kolkhir 2018[5] Magen 2011[19] Montjoye 2020[26]	5/4	Yan 2019[3] Huilan 2015[12]	2/2	**Strong**	–
C-reactive protein gene polymorphisms	rs3093059TT genotype associated with good response to mizolastine	Yan 2019[3]	1/1	–	0	No / little	–
ESR	Higher in NR	Choonhakarn 2018[6] Kolkhir 2017[27]	2/2	Magen 2011[19] Huilan 2015[12]	2/2	Inconsistent	–
ECP	–	–	0	Ulambayar 2019[2]	1/1	–	No / little
Clusterin	Lower in NR	Kim 2016[10]	1/1	–	0	No / little	–
IL-6	Higher in NR	Trinh 2016[8]	1/1	–	0	No / little	–
LCN2	Lower in NR	Trinh 2016[8]	1/1	–	0	No / little	–
IL-10, adiponectin, leptin, and TNF-α	–	–	0	Trinh 2016[8]	1/1	–	No / little
F1 + 2, TF, TM, HMWK, t-PA ASO, RF	-	-	0	Huilan 2015[12]	1/1	-	No / little
Total cholesterol, Triglycerides, LDL, HDL	–	–	0	Ulambayar 2019[2]	1/1	–	No / little
Liver enzymes	Higher in NR	Magen 2011[19]	1/1	–	0	No / little	–
PAF	Higher in NR	Ulambayar 2019[2]	1/1	–	0	No / little	–
Fibrinogen	Higher in NR	Kolkhir 2017[27]	1/1	--	0	No / little	--

*no p-value provided; AE: angioedema; ANA: antinuclear antibody; ASO: anti-streptolysin O; ASST: autologous serum skin test; ATA: antithyroid antibody; BMI: body mass index; CSU: chronic spontaneous urticaria; CU-Q2oL: chronic urticaria quality of life questionnaire; DLQI: dermatology life quality index; ECP: eosinophil cationic protein; ESR: erythrocyte sedimentation rate; F1+2: prothrombin factor 1+2; HDL: high-density lipoprotein; HMWK: high-molecular-weight kininogen; IL: interleukin; LCN2: lipocalin-2; LDL: low-density lipoprotein; MPV: mean platelet volume; NR: nonresponders; PAF: platelet-activating factor; R: responders; RF: rheumatoid factor; sgAHs: second generation H_1-antihistamines; TF: tissue factor; TM: thrombomodulin; TNF: tissue necrosis factor; t-PA: tissue plasminogen; TSH: thyroid stimulating hormone; UAS: urticaria activity score

Suppl. Table 3. Potential predictors of response to omalizumab in CSU patients

Parameters	First author, Year, Ref	N of CSU patients	Age, years, mean or median (range)	CSU severity/ activity, response to antihistamines	Omalizumab, dosage	When the marker was assessed	Evaluation of response	Results	Statistical significance and/or OR	Cut-off values, units	Design of study	Country
ANA	Ertaş 2019[32]	447	38.6 (–)	Severe, AR	300 mg/monthly	–	VAS	ANA+ patients had higher rates of non-response than ANA- patients. ANA titres and treatment responses to omalizumab showed a significant negative correlation	< 0.001	1/100	P	Turkey
Total IgE	Weller 2018[33]	85	44.3 (–)	–	300 mg/monthly	Baseline	Physicians global assessment	Lower in NR vs PR and CR (16.7 vs 65.7 vs 204)	< 0.001	–, percent of upper reference value	R	Multicenter worldwide
Total IgE	Straesser 2018[34]	137	45 (>12)	AR	–	Baseline	Subjectively defined	Lower rates of response in patients with below cut-off levels (48% vs 86-94%)	< 0.001	15.2 IU/mL	R	US
Total IgE,	Ertas 2018[35]	113	40 (–)	AR	300 mg/monthly for 12 weeks	Baseline (bIgE), at the end of the fourth week (w4IgE)	UAS, VAS, TES	Lower bIgE (median: 17.9 vs 82.0 vs 73.7) and w4IgE in NR vs PR and CR (median: 17.9 vs 298.0 vs 290.5). Lower rates of response in patients with below cut-off levels (33% vs 66%)	< 0.05	bIgE: 43 IU/mL, w4IgE: 51 IU/mL, ratio (w4IgE:bIgE) : 1.9 IU/mL	P	Turkey, Germany
Total IgE	Marzano 2018[36]	470	49 (37-61)	Severe, AR	300 mg/monthly for 24 weeks	Baseline	UAS7	Lower in NR than in R (geometric mean: 42.1 vs 131.6)	< 0.0001	Levels of IgE 100 kUA/L or greater were defined as increased	R	Italy
Total IgE	Cugno 2018[37]	25	40.3 (15-69)	Severe, AR	300 mg/monthly for 3 months	Baseline	UAS 7	Lower in NR vs PR and CR (16 vs 115 vs 148)	< 0.05	–, kUA/L	–	Italy

Total IgE	Jörg 2017[38]	25	41.8 (18-70)	AR	300 mg	Baseline	UAS7	Lower in PR/NR vs CR (median: 25 vs 113-296)	ns, 0.182	–, kU/L	RCT	Switzerland
Total IgE	Deza 2017[39]	47	51 (41-64)	moderate-to-severe, AR	300 mg	Baseline	UAS7	Lower in NR vs R (median: 20 vs 151)	0.0003	–, kU/L	P	Spain
Total IgE	Magen 2019[40]	63	40 (–)	Severe, AR	300 mg/monthly for at least 24 weeks	Baseline	UAS	Lower in NR vs PR (mean: 109 vs 159)	0.046	–, IU/mL	R	Israel
Total IgE	Nettis 2018[41]	322	46.5 (12-85)	AR	300 mg/monthly for at 24 weeks	Baseline	UAS	Poor treatment response after 24 weeks was associated with low levels of total IgE	< 0.05	48 KUA/L	R	Italy
ASST	Deza 2017[39]	47	51 (41-64)	moderate-to-severe, AR	300 mg	Baseline	UAS7	Higher rates of ASST positivity in NR vs R (100% vs 60%)	0.022	–, % positivity	P	Spain
Basophil FcεRI expression	Deza 2017[39]	47	51 (41-64)	moderate-to-severe, AR	300 mg	Baseline, 2nd, 3rd, 6th and 12th injections	UAS7	Lower in NR vs R (Baseline median: 577 vs 12,227)	< 0.0001	–, mean fluorescence intensity (MFI)	P	Spain
FcεRI receptor density	Jörg 2017[38]	25	41.8 (18-70)	AR	300 mg	Baseline	UAS7	Lower in PR/NR vs CR (median: 55.9 vs 104-113.7)	ns, 0.09	–, receptors per basophil	RCT	Switzerland
CU-BAT: CD63 positivity	Jörg 2017[38]	25	41.8 (18-70)	AR	300 mg	Baseline	UAS7	Higher in PR/NR vs CR (median: 26% vs 17-20%)	ns, 0.438	–, %	RCT	Switzerland
BAT	Straesser 2018[34]	137	45 (>12)	AR	–	Baseline	Subjectively defined	A trend towards lower likelihood of omalizumab response in patients with a positive BAT	0.074	–	R	US
Basophil CD203c upregulating activity	Palacios 2016[42]	41	45.9 (–)	AR	300 mg/monthly for at least 3 months.	Baseline	Subjectively defined	Higher rates of response in patients without CD203c upregulating activity	0.02	5%	R	US
Histamine release test	Ghazanfar 2016[43]	137	>30 (–)	–	150 every 2 weeks or 300 mg/monthly	–	Subjectively defined	A larger fraction of CR to omalizumab among patients with a negative test (77% vs. 27%)	< 0.01; OR: 9.07 (95% CI [2.80–29.32])	–	R	Denmark

D-dimer	Cugno 2018[37]	25	40.3 (15-69)	Severe, AR	300 mg/monthly for 3 months	Baseline	UAS 7	Lower in NR vs PR vs CR (162 vs 676 vs 619)	< 0.05	–, ng/mL	–	Italy
D-dimer	Berard 2019[44]	136	44.4 (18-75)	Moderate-to-severe, AR	300 mg/monthly	Baseline, weeks 4, 8.	UAS7, UCT	A weak correlation of D-dimer and UCT at week 12 (positive) and UAS7 at week 12 (negative)	–	500 ng/mL	P, OL, nr	France
Gender	Straesser 2018[34]	137	45 (>12)	AR	–	Baseline	Subjectively defined	A trend towards greater likelihood of response to omalizumab treatment by men compared to women	0.052, adjusted OR for response 4.79 (95% CI [0.99-23.18])		R	US
CSU duration	Weller 2018[33]	85	44.3 (-)	–	300 mg/monthly	Baseline	UAS7	Lower in NR vs PR vs CR (median: 18 vs 93 vs 53)	< 0.05	–, months	R	Multicenter
CSU duration	Vadasz 2017[45]	280	44 (21-68)	severe AR	150-450 mg/monthly	Baseline	UAS7	Higher in PR/NR vs CR (24-60 vs 6-18)	–	–, months	R	Israel
CSU duration	Nettis 2018[41]	322	46.5 (12-85)	AR	300 mg/monthly for at 24 weeks	Baseline	UAS	Poor treatment response after 24 weeks was associated with longer CSU duration	< 0.05	–	R	Italy
CSU duration	Cubiro 2018[46]	48	49.2 (16-76)	AR	300 mg/monthly	Baseline, at 12 and 24 weeks	UAS7	Patients with long-term urticaria (≥ 18 months' duration) were less likely to achieve a clinical response at week 12	OR: 0.25 (95% CI [0.06-0.96])	–, months	R	Spain
Presence of AE	Ertas 2018[35]	113	40 (–)	AR	300 mg/monthly for 12 weeks	Baseline and at the end of the fourth week, before the second omalizumab injection	UAS, VAS, TES	More common in NR than in PR and CR (93.3% vs 56.4% vs 55.8%)	< 0.05	–	P	Turkey, Germany
Presence of AE	Serarslan 2018[47]	40	43.1 (19-76)	AR	300 mg/monthly	–	Subjectively defined	CR was more frequently did not	< 0.05	–	R	Turkey

								have AE				
Presence of AE	Ghazanfar 2016[43]	137	>30 (–)	–	150 every 2 weeks or 300 mg/monthly	–	Subjectively defined	A larger fraction of CR to omalizumab among patients without AE (72.3% vs. 56.1%)	0.07; OR: 2.05 (95% CI [0.95–4.40])	–	R	Denmark
Presence of AE or AE in the history	Nettis 2018[41]	322	46.5 (12-85)	AR	300 mg/monthly for at 24 weeks	Baseline	UAS	Poor treatment response after 24 weeks was associated with presence of AE or AE in the history	< 0.05	–	R	Italy
Previous immunosuppressive therapy	Ghazanfar 2018[48]	117	42 (12-77)	AR	300 mg/monthly	Baseline, at three and six months	UAS7, UCT	Previous immunosuppressive treatment was associated with poor treatment response to omalizumab at three months	< 0.001	–	P	Denmark
Previous immunosuppressive therapy	Ghazanfar 2016[43]	137	>30 (–)	–	150 every 2 weeks or 300 mg/monthly	–	Subjectively defined	A larger fraction of CR to omalizumab among patients with no previous history of immunosuppressive therapy (71.4% vs. 56.8%)	0.10; OR: 1.91 (95% CI [0.87–4.17])	–	R	Denmark
Previous treatment with cyclosporine	Nettis 2018[41]	322	46.5 (12-85)	AR	300 mg/monthly for at 24 weeks	Baseline	UAS	Poor treatment response after 24 weeks was associated with previous cyclosporine use	< 0.05	–	R	Italy
Previous immunsuppressive therapy	Cubiro 2018[46]	48	49.2 (16-76)	AR	300 mg/monthly	Baseline, at 12 and 24 weeks	UAS7	Previous immunosup-pressive treatment tended to be associated with a lower probability of complete response at week 12	OR: 0.27 (95% CI [0.07-1.02])	–	R	Spain
Previous treatment with antihistamines	Cubiro 2018[46]	48	49.2 (16-76)	AR	300 mg/monthly	Baseline, at 12 and 24 weeks	UAS7	Antihistamine treatment was associated with lower probability of	OR: 0.1 (95% CI [0.01-0.88])	–	R	Spain

								response to omalizumab at week 24				
Disease activity (Physician VAS)	Ertas 2018[35]	113	40 (–)	AR	300 mg/monthly for 12 weeks	Baseline and at the end of the fourth week, before the second omalizumab injection	UAS, VAS, TES	Higher in NR vs PR and CR (median, 10 vs 9 vs 8)	< 0.05 (only for NR vs CR)	–	P	Turkey, Germany
Disease activity (UAS7)	Vadasz 2017[45]	280	44 (21-68)	severe AR	150-450 mg/monthly	Baseline	UAS7	Higher in PR/NR vs responders (20-32 vs 12-18)	–	–	R	Israel
Disease activity (UAS7)	Salman 2019[49]	42	39.4 (17-75)	AR	300 mg/monthly	Baseline	UAS7 and UCT CU-Q2oL, DLQI	Higher in NR/PR vs CR	< 0.05	–	R	Turkey
Disease activity (UAS)	Magen 2019[40]	63	40 (–)	Severe, AR	300 mg/monthly for at least 24 weeks	12 weeks	UAS	Higher in NR vs PR and/or CR	< 0.001	–	R	Israel
UCT	Salman 2019[49]	42	39.4 (17-75)	AR	300 mg/monthly	Baseline	UAS7 and UCT CU-Q2oL, DLQI	Lower in NR/PR vs CR	< 0.05	–	R	Turkey
DLQI	Salman 2019[49]	42	39.4 (17-75)	AR	300 mg/monthly	Baseline	UAS7 and UCT CU-Q2oL, DLQI	Higher in NR/PR vs CR	< 0.05	–	R	Turkey
CU-Q2oL	Salman 2019[49]	42	39.4 (17-75)	AR	300 mg/monthly	Baseline	UAS7 and UCT CU-Q2oL, DLQI	Higher in NR/PR vs CR	< 0.05	–	R	Turkey
Arterial hypertension, obesity, BMI	Magen 2019[40]	63	40 (–)	Severe, AR	300 mg/monthly for at least 24 weeks	Baseline	UAS	Higher in NR vs PR and/or CR	< 0.05	%, %, BMI 27.0 kg/m^2	R	Israel
White blood cell count	Magen 2019[40]	63	40 (–)	Severe, AR	300 mg/monthly for at least 24 weeks	Baseline	UAS	Higher in NR vs PR or CR	< 0.05	11.0 x10^3 cells/mL	R	Israel
C3 level	Magen	63	40 (–)	Severe,	300	Baseline	UAS	Higher in NR vs PR	< 0.001	160.0 mg/dL	R	Israel

	2019[40]			AR	mg/monthly for at least 24 weeks			or CR				
C-reactive protein	Magen 2019[40]	63	40 (–)	Severe, AR	300 mg/monthly for at least 24 weeks	Baseline	UAS	Higher in NR vs CR	< 0.05	3.0 mg/L	R	Israel
Absolute blood eosinophil and basophil count	Kolkhir 2019[1]	147	43 (13-105)	AR	300 mg/monthly	Baseline, after 4 weeks, and after 8 weeks	UAS7	NR had significantly lower blood eosinophil count compared with PR and CR. Patients with eosinopenia or basopenia more often were NR to omalizumab.	< 0.05	<0.05 x 10^9/L for eosinophils, <0.01 x 10^9/L for basophils	R	Germany

AE: angioedema; ANA: antinuclear antibody; AR: antihistamine-resistant; ASST: autologous serum skin test; BAT: basophil activation test; CR: complete responders; CSU: chronic spontaneous urticaria; CU-Q2oL: chronic urticaria quality of life questionnaire; DLQI: dermatology life quality index; nr: non-randomised; NR: nonresponders; ns: non significant; OL: open-label; OD: odds ratio; P: prospective; PR: partial responders; R: retrospective; RCT: double-blind placebo controlled randomized study; TES: treatment effectiveness score; UAS: urticaria activity score; UCT: urticaria control test; VAS: visual analog scale

Suppl. Table 4. Summary evidence on potential predictors of response to omalizumab in CSU patients

Parameters	**Difference in baseline values of parameters between NR vs R to omalizumab or in rates of response and nonresponse to omalizumab between patients with high/positive vs low/negative test results or prediction of response**					**Level of evidence for association**	**Level of evidence for *no* association**
	Yes (p<0.05)			*No*			
	Description	*First author*	*N of studies (total/from different teams)*	*First author*	*N of studies (total/from different teams)*		
Age	–	–	0	Magen 2019[40] Weller 2018[33] Ertas 2018[35] Marzano 2018[36] Deza 2017[39] Ghazanfar 2018[48] Nettis 2018[41] Asero 2017[50] Avci 2019[51] Straesser 2018[34] Serarslan 2018[47] Pinto Gouveia 2017[52] Palacios 2016[42] Viswanathan 2013[53]	14/13	–	Strong
Gender	Worse response in female patients	Straesser 2018[34]	1/1	Magen 2019[40] Weller 2018[33] Ertas 2018[35] Marzano 2018[36] Deza 2017[39] Ghazanfar 2018[48] Nettis 2018[41] Asero 2017[50] Ghazanfar 2016[43] Serarslan 2018[47] Viswanathan 2013[53] Pinto Gouveia 2017[52] Palacios 2016[42]	13/12	–	Strong
Weight and/or BMI	Higher in NR	Magen 2019[40]	1/1	Straesser 2018[34]		Inconsistent	–
Smoking	–	–	0	Ghazanfar 2018[48] Ghazanfar 2016[43]	2/1	–	No / little
Family history of chronic urticaria	–	–	0	Deza 2017[39]	1/1	–	No / little
Concomitant arterial	Higher in NR	Magen 2019[40]	1/1	–	0	No / little	–

hypertension							
Concomitant CIndU	–	–	0	Deza 2017[39] Ghazanfar 2018[48]	2/2	–	Inconsistent
Concomitant allergic diseases	–	–	0	Magen 2019[40] Ghazanfar 2018[48]	2/2	–	Inconsistent
Concomitant psychiatric disorders	–	–	0	Ghazanfar 2018[48]	1/1	–	No / little
Concomitant hypothyroidism	–	–	0	Magen 2019[40]	1/1	–	No / little
Concomitant rheumatologic disorders	–	–	0	Magen 2019[40]	1/1	–	No / little
Concomitant diabetes mellitus	–	–	0	Magen 2019[40]	1/1	–	No / little
NSAIDs hypersensitivity	–	–	0	Asero 2017[50]	1/1	–	No / little
Presence of AE or AE in the history	Association with poor response or rates are higher in NR	Nettis 2018[41] Ghazanfar 2016[43] Serarslan 2018[47] Ertas 2018[35]	4/4	Magen 2019[40] Deza 2017[39] Ghazanfar 2018[48] Asero 2017[50]	4/4	Inconsistent	–
Previous immunosuppressive treatment primarily cyclosporine	Lower probability of complete response or poor response	Nettis 2018[41] Ghazanfar 2018[48]	2/2	Deza 2017[39] Cubiró 2018[46] Ghazanfar 2016[43]	3/3	Inconsistent	–
Previous treatment with prednisolone	–	–	0	Ghazanfar 2018[48] Nettis 2018[41]	2/2	–	Inconsistent
Previous treatment with montelukast	–	–	0	Ghazanfar 2018[48]	1/1	–	No / little
Previous treatment with antihistamines	Lower probability of response	Cubiró 2018[46]	1/1	Nettis 2018[41]	1/1	Inconsistent	–
CSU duration	Longer duration associated with non response	Cubiró 2018[46] Nettis 2018[41] Vadasz 2017[45]	3/3	Magen 2019[40] Ertas 2018[35] Marzano 2018[36] Ghazanfar 2018[48] Asero 2017[50] Avci 2019[51] Serarslan 2018[47] Pinto Gouveia 2017[52]	8/7	Inconsistent	–
	Shorter duration associated with non response	Weller 2018[33]	1/1				
Disease evolution (months)	–	–	0	Deza 2017[39]	1/1	–	No / little
UAS	Higher in NR	Magen 2019[40]	1/1	Magen 2019[40] Ertas 2018[35]	2/2	Inconsistent	–
UAS7	Higher in NR or NR+PR	Salman 2019[49] Vadasz 2017[45]	2/2	Marzano 2018[36] Deza 2017[39]	2/2	Inconsistent	–
UCT	Lower in NR/PR	Salman 2019[49]	1/1	Deza 2017[39]	1/1	Inconsistent	–

VAS	Higher in NR	Ertas 2018[35]	1/1	Ertas 2018[35]	1/1	Inconsistent	–
DLQI	Higher in NR/PR	Salman 2019[49]	1/1	–	0	No / little	–
CU-Q2oL	Higher in NR/PR	Salman 2019[49]	1/1	–	0	No / little	–
ASST	Positive ASST associated with nonresponse	Deza 2017[39]	1/1	Nettis 2018[41] Metz 2014[54]	2/2	Inconsistent	–
Histamine release test or basophil CD203c or CD63 upregulating activity or basophil activation test or CU index	Negative histamine release test or CD2003c or CD63 upregulating activity associated with good response	Ghazanfar 2016[43] Palacios 2016[42] Jörg 2017[38]	3/3	Ghazanfar 2018[48] Viswanathan 2013[53]	2/2	Inconsistent	–
	Positive BAT associated with good response	Straesser 2018[34]	1/1				
Basophil FcεRI expression	Lower in NR	Deza 2017[39]	1/1	Jörg 2017[38]	1/1	Inconsistent	–
Blood leukocyte count	Higher in NR	Magen 2019[40]	1/1	Ghazanfar 2018[48]	1/1	Inconsistent	–
Blood lymphocyte count	–	–	0	Çildağ 2019[55]	1/1	–	No / little
Blood neutrophil count	–	–	0	Ghazanfar 2018[48] Çildağ 2019[55]	2/2	–	Inconsistent
Blood basophil counts	Lower in NR	Kolkhir 2019[1]	1/1	Magen 2019[40]	1/1	Inconsistent	–
Blood eosinophil counts	Lower in NR	Kolkhir 2019[1]	1/1	Magen 2019[40] Çildağ 2019[55]	2/2	Inconsistent	–
Platelets	–	–	0	Magen 2019[40] Çildağ 2019[55]	2/2	–	Inconsistent
Total IgE	Low levels associated with poor response	Nettis 2018[41] Magen 2019[40] Deza 2017[39] Jörg 2017[38] Cugno 2018[37] Marzano 2018[36] Ertas 2018[35] Straesser 2018[34] Weller 2018[33]	9/8	Ghazanfar 2018[48] Pinto Gouveia 2017[52] Metz 2014[54] Viswanathan 2013[53] Çildağ 2019[55]	5/5	**Strong***	–
Other immunoglobulins (IgA, IgG, IgM)	–	–	0	Çildağ 2019[55]	1/1	–	No / little

ANA positivity	Higher in NR	Ertaş 2019[32]	1/1	Magen 2019[40] Asero 2017[50] Viswanathan 2013[53]	3/3	Inconsistent	–
TSH	–	–	0	Magen 2019[40]	1/1	–	No / little
C3 complement component	Higher in NR	Magen 2019[40]	1/1	–	0	No / little	–
C4 complement component	–	–	0	Magen 2019[40]	1/1	–	No / little
Antithyroid antibodies (IgG-anti-TPO/TG)	–	–	0	Marzano 2018[36] Asero 2017[50] Straesser 2018[34] Palacios 2016[42] Viswanathan 2013[53] Ertas 2018[35] Magen 2019[40]	7/6	–	Strong
D-dimer	Higher levels associated with better response	Berard 2019[44] Cugno 2018[37]	2/2	Marzano 2018[36]	1/1	Inconsistent	–
C-reactive protein	Higher in NR	Magen 2019[40]	1/1	Ghazanfar 2018[48] Berard 2019[44] Pinto Gouveia 2017[52]	3/3	–	Weak
DHEA-S	–	–	0	Avci 2019[51]	1/1	–	No / little
Factors VIIa and XIIa, prothrombin factors 1 and 2	–	–	0	Berard 2019[44]	1/1	–	No / little

* There are 9 studies that show the association of low tIgE and nonresponse to omalizumab (5 of them include more than 100 patients) and 5 studies that did not show this. Some studies that did not show significant differences in serum IgE concentrations between omalizumab responders and non-responders are small (2 studies <20 patients, 2 studies <60 patients) and retrospective. Moreover, they did not stratify low versus normal/high IgE levels and then analyze for differences in clinical response to omalizumab. Of 9 studies where the association was shown, 2 studies were from the same team (Marzano 2018 and Cugno 2018) so we count them as 1 study according to our rating system. Of 5 studies contra, 1 was from our group (Metz et al. 2014), which was later followed by the study of Weller 2018 (pro). Therefore, we do not take into account this early paper from Metz et al. In total, we have 8 studies pro and 4 studies contra. It corresponds 66.6% of evidence that supports the hypothesis of low total IgE as a marker of nonresponse to OMA. Therefore, according to the rating system, the level of evidence for low total IgE is strong.

ANA: antinuclear antibody; ASST: autologous serum skin test; BAT: basophil activation test; BMI: body mass index; CIndU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; CU-Q2oL: chronic urticaria quality of life questionnaire; DHEA-S: dehydroepiandrosterone sulfate; DLQI: dermatology life quality index; NR: nonresponders; R: responders; TG: thyroglobulin; TPO: thyroid peroxidase; TSH: thyroid stimulating hormone; UAS: urticaria activity score; UCT: urticaria control test; VAS: visual analog scale

Suppl. Table 5. Potential predictors of need for omalizumab updosing in CSU patients

Parameters	First author, Year, Ref	N of CSU patients	Age, years, mean or median (range)	CSU severity/ activity	Omalizumab dosage, mg	When the marker was assessed	Evaluation of response	Results	p-value	Cut-off values	Design of study	Country
Total IgE	Salman 2019[56]	72	>40 (17-81)	AR, severity differs	300-450 mg/monthly	Baseline	UAS7 and UCT	The number of patients with low baseline IgE levels was significantly higher in 450 mg group of CSU patients as compared to 300 mg group	0.006	43 IU/ mL	Retrospective	Turkey
BMI, UCT, duration of the disease, presence of angioedema	Kocartürk 2017[57]	172	>40 (–)	AR	150-600 mg/monthly	Baseline	UAS7, UCT	The duration of disease and angioedema frequency was found to be higher in patients receiving 150-300 mg vs 450-600 mg. BMI was higher and pre-oma UCT was lower in patients receiving 450-600 mg	< 0.05	–	Retrospective	Turkey, Spain
Age, BMI, previous treatment with cyclosporine	Curto-Barredo 2018[21]	286	44.6 (–)	–	300-600 mg/monthly	Baseline	UAS7	Predictors of good response with 450-600 mg of omalizumab were previous treatment with cyclosporine, obesity and age > 57 years old	< 0.01	–	Retrospective	Spain

AR: antihistamine-resistant; BMI: body mass index; CSU: chronic spontaneous urticaria; UAS: urticaria activity score; UCT: urticaria control test

Suppl. Table 6. Summary evidence on potential predictors of omalizumab updosing in CSU patients

Parameters	**Difference in baseline values of parameters between patients on standard dose vs high dose of omalizumab**					**Level of evidence for association**	**Level of evidence for *no* association**
	Yes (p<0.05)			*No*			
	Parameter values in 'updosing' group	*First author*	*N of studies (total/from different teams)*	*First author*	*N of studies (total/from different teams)*		
Age	Higher	Curto-Barredo 2018[21]	1/1	Kocartürk 2017[57] Salman 2019[56] Curto-Barredo 2018[21]	3/3	–	Weak
Gender	–	–	0	Kocartürk 2017[57] Salman 2019[56] Curto-Barredo 2018[21]	3/3	–	Inconsistent
BMI	Higher	Kocartürk 2017[57] Curto-Barredo 2018[21]	2/2	Salman 2019[56] Curto-Barredo 2018[21]	2/2	Inconsistent	–
Smoking	–	–	0	Salman 2019[56]	1/1	–	No / little
Concomitant atopic diseases	–	–	0	Salman 2019[56]	1/1	–	No / little
Concomitant inducible urticaria	–	–	0	Kocartürk 2017[57] Curto-Barredo 2018[21]	2/2	–	Inconsistent
Previous immunosuppressive treatment		Curto-Barredo 2018[21]	1/1	–	0	No / little	–
CSU activity	–	–	0	Kocartürk 2017[57] Salman 2019[56] Curto-Barredo 2018[21]	3/3	–	Inconsistent
CSU duration	Shorter	Kocartürk 2017[57]	1/1	Salman 2019[56]	1/1	Inconsistent	–
Presence of angioedema	Lower frequency	Kocartürk 2017[57]	1/1	Salman 2019[56] Curto-Barredo 2018[21]	2/2	Inconsistent	–
UCT	Lower	Kocartürk	1/1	Salman 2019[56]	1/1	Inconsistent	–

		2017[57]					
ESR	–	–	0	Salman 2019[56]	1/1	–	No / little
C-reactive protein	–	–	0	Salman 2019 [56]	1/1	–	No / little
Total IgE	Lower	Salman 2019[56]	1/1	Kocartürk 2017[57] Curto-Barredo 2018[21]	2/2	inconsistent	
D-dimer	–	–	0	Salman 2019[56] Curto-Barredo 2018[21]	2/2	–	Inconsistent

BMI: body mass index; CSU: chronic spontaneous urticaria; ESR: erythrocyte sedimentation rate; UCT: urticaria control test

Suppl. Table 7. Potential predictors of speed of omalizumab action in CSU patients

Parameters	First author, year, Ref	N of CSU patients	Age, years, mean or median (range)	CSU severity/ activity	Omalizumab dosage, mg	When the marker was assessed	Evaluation of response	Results	p-value	Cut-off values	Design of study	Country
BHRA, ASST	Gericke 2017[58]	46	47 (23-85)	AR	Omalizumab 300 mg/monthly for 3 months	Baseline	UAS7	Slow response was associated with positive BHRA and/or ASST	0.05	BHRA: >16.5%	OL P	Germany
CSU duration	Syrigos 2018[59]	20	54.5 (19-85)	AR	–	Baseline	UAS7	Late response to omalizumab correlated with shorter disease duration before initiation of omalizumab	0.026	–, months	R	Greece
CSU duration	Vadasz 2017[45]	280	44 (21-68)	Severe, AR	150-450mg/monthly	Baseline	UAS7	Higher in LR vs FR	–	–, months	R	Israel
ASST	Nettis 2018[41]	322	46.5 (12-85)	AR	300 mg/monthly for at 24 weeks	Baseline	UAS	ASST+ patients were 4.30 times more likely to have a slow response to omalizumab treatment as compared with	0.001	–	R	Italy

								ASST-patients				

AR: antihistamine-resistant; ASST: autologous serum skin test; BHRA: basophil histamine release assay; CSU: chronic spontaneous urticaria; FR: fast responders; LR: late responders; OL: open-labelled; P: prospective; R: retrospective; UAS: urticaria activity score

Suppl. Table 8. Summary evidence on potential predictors of time of response of omalizumab in CSU patients

Parameters	**Difference in baseline values of parameters between fast vs slow responders to omalizumab**					**Level of evidence for association**	**Level of evidence for *no* association**
	Yes (p<0.05)			*No*			
	Parameter values in slow responders to omalizumab	*First author*	*N of studies (total/from different teams)*	*First author*	*N of studies (total/from different teams)*		
Age	–	–	0	Syrigos 2018[59] Gericke 2017[58]	2/2	–	Inconsistent
BMI	–	–	0	Gericke 2017[58]	1/1	–	No / little
Comorbidities	–	–	0	Syrigos 2018[59]	1/1	–	No / little
CSU activity	–	–	0	Gericke 2017[58]	1/1	–	No / little
CSU duration	Shorter	Syrigos 2018[59]	1/1	Gericke 2017[58]	1/1	Inconsistent	–
	Longer	Vadasz 2017[45]	1/1				
Presence of angioedema	–	–	0	Syrigos 2018[59]	1/1	–	No / little
ASST	Positive	Gericke 2017[58] Nettis 2018[41]	2/2	–	0	**Weak**	
BHRA	Positive	Gericke 2017[58]	1/1	–	0	No / little	–
ESR	–	–	0	Syrigos 2018[59]	1/1	–	No / little
C-reactive protein	–	–	0	Syrigos 2018[59]	1/1	–	No / little
Total IgE	–	–	0	Marzano 2018[36] Syrigos 2018[59] Gericke 2017[58] Ertas 2017[60]	4/4	–	Strong
TSH	–	–	0	Syrigos 2018[59]	1/1	–	No / little
Autoimmunity	–	–	0	Syrigos 2018[59]	1/1	–	No / little

ASST: autologous serum skin test; BHRA: basophil histamine release assay; BMI: body mass index ; CSU: chronic spontaneous urticaria; ESR: erythrocyte sedimentation rate; TSH: thyroid-stimulating hormone

Suppl. Table 9. Potential predictors of response to cyclosporine in CSU patients

Parameters	First author, Year, Ref	N of CSU patients	Age, years, mean or median (range)	CSU severity/ activity, response to sgAHs	Cyclosporine dose (mg/kg/day), duration	When the marker was assessed	Evaluation of response	Results	Cut-off values	Design of study	Country
Total IgE	Santiago 2019[61]	34	45 (–)	Moderate-to-severe, AR	3, for a minimum of 3 months.	–	UAS7	Mean serum IgE was significantly lower in cyclosporine responders vs NR (p=0.001)	100 IU/mL	R	Portugal
CRP	Ohtsuka 2010[62]	15	40 (16-60)	Severe, AR	3-5 .	Baseline	Subjectively defined	All patients responded to oral cyclosporine. All nine patients with elevated high CRP showed decrease in CRP levels after the start of oral cyclosporine therapy (p-value is not indicated). Shorter treatment duration in patients with high CRP (8.7 months vs 22.7 months, $p < 0.05$)	0.07 mg/l	P	Japan
D-dimer	Asero 2015[63]	29	46 (11-75)	Severe, AR	3-5, for ≥3 months	Baseline, during and/or at the end of the treatment.	Subjectively defined	Baseline D-dimer levels showed a highly significant negative correlation with the response to cyclosporine. 10 of 11 (91%) patients with normal D-dimer plasma levels versus 7 of 18 (39%) patients with elevated D-dimer plasma levels showed a completely successful response to the treatment ($p = 0.008$)	500 ng/mL	P	Italy
BHRA	Grattan 2000[64]	30	33 (19-72)	ASST+, severe, AR	4, for 4 weeks	Baseline and after treatment	UAS7	13 of 18 clinical responders to cyclosporine were BHRA positive compared with one of 9 NR ($p = 0.01$)	5%	RCT	UK
BHRA	Iqbal 2012[65]	58	–	AR	4, for 3-4 months	Baseline	Subjectively defined	81% of BHRA+ patients achieved complete response compared to 19% of BHRA- patients ($p < 0.001$)	16.5%	R	UK
A history of urticaria, duration of urticaria, CU Index	Hollander 2011[66]	68*	40 (–)	AR	1 with increasing the dose over time	Baseline	Subjectively defined	Factors that predicted complete remission of CU on cyclosporine were a shorter duration of urticaria ($p = 0.03$), a history of urticaria ($p = 0.01$), a positive CU Index ($p = 0.05$)	–	R	US
UAS7	Curto-Barredo 2018[21]	549	50 (–)	–	–	Baseline	UAS7	85% of patients with baseline UAS7>16 needed cyclosporine or omalizumab combined with antihistamines in order to	–	R	Spain

								control CSU symptoms (p = 0.0013)			
ASST, total IgE	Endo 2019[67]	34	47 (18-82)	AR	3, for 4 weeks	–	UAS7	Therapeutic efficacy of cyclosporine in CSU patients with ASST-positive results was significantly higher than that in patients with ASST-negative results (p = 0.0048). 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 UAS7 was 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)	88.5 IU/mL for IgE	P	Japan
IL-2R, IL-5, TNF alpha	Serhat Inaloz 2008[68]	27	36 (17-59)	AR	2.5, in two divided doses for 4 weeks	Baseline	UAS	Serum IL-2R, TNF-α and IL-5 levels of patients before cyclosporine treatment were statistically higher than those of control group and significantly decreased after 4 weeks of treatment (p = 0.001)	–	P	Turkey
ASST	Baskan 2004[69]	20	-	Severe, AR, ASST+	4, 4-12 weeks	Baseline, post-Rx	UAS	ASST wheal diameter was significantly smaller 2 weeks after stopping cyclosporine than at baseline for the 4-week group (p = 0.020), and the 12-week group (p < 0.0001)	–	P	Turkey
ASST	Di Gioacchino 2003[70]	40	-	AR, ASST+	4-5, for 16 weeks	Baseline, post-treatment	Clinical severity score	The ASST was negative in 13 patients and positive in 3 of 16 patients, with total remission of symptoms	–	RCT	Italy

*not clear if inducible urticaria was excluded; AR: antihistamine-resistant; ASST: autologous serum skin test; BHRA: basophil histamine release assay; CR: compete responders; CRP: C-reactive protein; CSU: chronic spontaneous urticaria; CU: chronic urticaria; IL: interleukin; NR: nonresponders; P: prospective; R: retrospective; RCT: randomized controlled trial; TNF: tumor necrosis factor; UAS: urticaria activity score

Suppl. Table 10. Summary evidence on potential predictors of response to cyclosporine in CSU patients

Parameters	**Difference in baseline values of parameters between NR vs R to cyclosporine or in rates of response and nonresponse to cyclosporine between patients with high/positive vs low/negative test results or prediction of response**					**Level of evidence for association**	**Level of evidence for *no* association**
	Yes (p<0.05)			*No*			
	A change in parameter values for responders to cyclosporine	*First author*	*N of studies (total/from different teams)*	*First author*	*N of studies (total/from different teams)*		
Age	–	–	0	Santiago2019[61] Asero 2015[63] Endo 2019[67] Hollander 2011[66]	4/4	–	Strong
Gender	–	–	0	Hollander 2011[66] Asero 2015[63] Endo 2019[67]	3/3	–	Inconsistent
Race	–	–	0	Hollander 2011[66]	1/1	–	No / little
Concomitant allergic diseases	–	–	0	Hollander 2011[66]	1/1	–	No / little
Concomitant psychiatric disorders	–	–	0	Hollander 2011[66]	1/1	–	No / little
Previous treatment with corticosteroids	–	–	0	Hollander 2011[66]	1/1	–	No / little
Previous treatment with antihistamines	–	–	0	Hollander 2011[66]	1/1	–	No / little
CSU duration	Shorter	Hollander 2011[66]	1/1	Santiago2019[61] Asero 2015[63] Endo 2019[67]	3/3	–	Weak
UAS7	>16	Curto-Barredo 2018[21]	1/1	Endo 2019[67]	1/1	Inconsistent	–
ASST	Positive	Endo 2019[67] Baskan 2004[69]* Di Gioacchino 2003[70]*	3/3	Toubi 1997[71] Hollander 2011[66] Grattan 2000[64] Boubouka 2011[72]	4/4	Inconsistent	–
BHRA or CU index	Positive	Iqbal 2012[65] Grattan 2000[64] Hollander 2011[66]	3/3	–	0	**Strong**	–
IgG-anti-FcεRI	–	–	0	Endo 2019[67]	1/1	–	No / little
IgG-anti-IgE	–	–	0	Endo 2019[67]	1/1	–	No / little
Blood basophil	–	–	0	Endo 2019[67]	1/1	–	No / little

counts							
Blood eosinophil count	–	–	0	Loria 2001[73]	1/1	–	No / little
Total IgE	Low	Endo 2019[67] Santiago2019[61]	2/2	–	0	**Weak**	–
ANA positivity	–	–	0	Hollander 2011[66] Santiago2019[61]	2/2	–	Inconsistent
Antithyroid antibodies	–	–	0	Hollander 2011[66] Santiago2019[61] Asero 2015[63]	3/3	–	Inconsistent
D-dimer	Normal	Asero 2015[63]	1/1	–	0	No / little	–
C-reactive protein	High	Ohtsuka 2010[62]	1/1	Santiago2019[61] Asero 2015[63]	2/2	Inconsistent	–
ESR	–	–	0	Asero 2015[63]	1/1	–	No / little
Blood T, B, NK cells, Igs, C3, C4, CICs	–	–	0	Loria 2001[73]	1/1	–	No / little
Serum IL-2R, TNF-α & IL-5 levels	Decreased after treatment	Serhat Inaloz 2008[68]	1/1	–	0	No / little	–

*Studies had some limitations (see Suppl. Table 9); ANA: antinuclear antibody; ASST: autologous serum skin test; BHRA: basophil histamine release assay; CICs: circulating immune complexes; CSU: chronic spontaneous urticaria; CU: chronic urticaria; ESR: erythrocyte sedimentation rate; Igs: immunoglobulins; IL: interleukin; NK: natural killer; NR: nonresponders; R: responders; TNF: tumor necrosis factor; UAS: urticaria activity score

Suppl. Table 11. Summary for potential predictors with *strong* level of evidence in CSU patients

Parameters	Response outcome to treatment involved	Total CSU patients assessed	Total studies included	Studies done prospectively to identify predictors?	Parameters identified in *ad hoc* analysis?
High UAS7	Poor response to sgAHs	1882	7	5 prospective	Nil
Elevated CRP	Poor response to sgAHs	2289	6	2 prospective	Nil
Low total IgE	Poor response to omalizumab	1576	14	8 retrospective	Relevance of IgE was found in ad hoc analysis in 1 study
Positive BHRA	Good response to cyclosporine	112	3	2 retrospective	Nil

BHRA: basophil histamine release assay; CRP: C-reactive protein; sgAHs: second generation antihistamines; UAS: urticaria activity score

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