

Emerging Biomarkers and Therapeutic Pipelines for Chronic Spontaneous Urticaria



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Learning objectives:

1. To recognize potential biomarkers related to important aspects of chronic spontaneous urticaria (CSU).
2. To discuss the mechanisms of action and therapeutic effectiveness of the latest agents available or under investigation for the management of antihistamine-refractory CSU.

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Chronic spontaneous urticaria (CSU) is defined as the appearance of evanescent wheals, angioedema, or both, for at least 6 weeks. CSU is associated with intense pruritus and poor quality of life, with higher odds of reporting depression, anxiety, and sleep difficulty. As of yet, the assessment of the activity and course of the disease along with the response to several treatments in CSU are based purely on the patient's medical history and the use of the patient-reported outcomes. Recently,

several reports have suggested that certain parameters could be considered as potential disease-related biomarkers. Moreover, with the advent of such biomarkers, newer biologic agents are coming forth to revolutionize the management of potential refractory diseases such as CSU. The purpose of this article is to review the most promising biomarkers related to important aspects of CSU, such as the disease activity, the therapeutic response, and the natural history of the disease, and discuss the

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Abbreviations used

ASST-	Autologous serum skin test
ATA-	Antithyroid antibody
BHRA-	Basophil histamine release assay
Btk-	Bruton tyrosine kinase
CAPS-	Cryopyrin-associated periodic syndrome
CRP-	C-reactive protein
CRT _{H2} -	Chemoattractant receptor homologous molecule expressed on the T _{H2} cell
CSU-	Chronic spontaneous urticaria
EU-	European Union
F1+2-	Prothrombin fragment 1+2
FcεRI-	High-affinity IgE receptor
FDA-	Food and Drug Administration
IV-	Intravenous
IVIg-	Intravenous immunoglobulin
mAb-	Monoclonal antibody
MPV-	Mean platelet volume
OCS-	Oral corticosteroid
PGD2R-	Prostaglandin D2 receptor
SC-	Subcutaneous
Syk-	Spleen tyrosine kinase

mechanisms of action and therapeutic effectiveness of the latest agents available or currently under investigation for the management of antihistamine-refractory CSU. The knowledge of these features could have an important impact on the management and follow-up of patients with CSU. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1108-17)

Key words: Urticaria; Biomarkers; CRP; IL-6; MPV; D-dimer; F1+2; Biologics; Omalizumab; ASCENT-I; ASCENT-II; GLACIAL; IL-1 antagonists; TNF-α inhibitors; Intravenous immunoglobulin; Rituximab; Ligelizumab; Quilizumab

Chronic spontaneous urticaria (CSU) represents the most common subtype of chronic urticaria and is defined as the appearance of evanescent wheals, angioedema, or both, which occurs suddenly and persists for longer than 6 weeks.¹ Although CSU is usually not a life-threatening condition, its symptoms (cutaneous swelling, itch, and pain) may have a deep impact on various aspects of patients' everyday life.²

As of yet, the assessment of the activity and course of the disease along with the response to several treatments in CSU are based purely on the patient's medical history and the use of the patient-reported outcomes.^{1,3,4} Although these questionnaires are validated and widely used tools for the evaluation of patients with CSU, their main limitation is their subjective nature. For this reason, several studies have investigated objective measurable parameters that allow the assessment and monitoring of different important aspects of CSU.⁵⁻⁸ However, to date, no reliable indicators of such features are fully implemented for its use in clinical practice.

First-line therapy for CSU is based on second-generation H1 antihistamines, often required at 2 to 4 times the recommended dose.¹ Unfortunately, many patients will fail antihistamines and

will require alternative therapies to control their symptoms. For these subjects, biologic agents, which include monoclonal antibodies (mAb), recombinant antagonists, and donor immunoglobulin, have proven to be relatively safe and efficacious and may play an important role in the treatment of urticarial diseases.⁹

The purpose of this article is to review the most promising biomarkers related to important aspects of CSU, such as the disease activity, the therapeutic response, and the natural history of the disease, and discuss the therapeutic effectiveness of the biologic agents available or currently under investigation for antihistamine-refractory CSU.

EMERGING BIOMARKERS IN CSU

According to the National Institute of Health Biomarkers Definitions Working Group, a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention."¹⁰ In this sense, essential characteristics of a good biomarker are its sensitivity, specificity, and reproducibility for the identification and/or measurement of a particular disease state.¹⁰ In addition, the ease with which the biomarker can be collected and measured at the point of care is another crucial feature to take into consideration for an ideal biomarker.¹¹ Thereby, the identification and validation of reliable biomarkers in CSU could help to better evaluate the patient's disease status, which could eventually lead to a more individualized and personalized treatment and follow-up not only in everyday clinical care but also in clinical trials (Table I).

Biomarkers for disease activity

Several markers have been investigated for their possible link to CSU activity. Inflammatory mediators, such as the C-reactive protein (CRP) and IL-6, seem to be promising biomarkers, because their plasma levels are increased in patients with more active CSU and are significantly lower on spontaneous remission.^{12,13,25-33} Likewise, levels of mean platelet volume (MPV), which is considered a marker of platelet reactivity, also show a positive correlation with CSU activity.³⁷⁻³⁹ These observations support the fact that CSU should be considered an immune-mediated chronic inflammatory disease resulting from immunological activation events after the exposure to different triggers.⁴⁹ The detection of increased levels of D-dimer and prothrombin fragment 1+2 (F1+2) in patients with more active disease also demonstrates the crucial involvement of the coagulation cascade and fibrinolysis in CSU, positioning themselves as other potential biomarkers of disease activity.^{12-24,34,35}

On the other hand, various abnormalities related to basophils and their functions have also been described in patients with active disease. For example, a negative correlation between blood basophil count and CSU activity has been reported in several investigations, suggesting that circulating basophils may be recruited from blood into urticarial skin lesions during the activity of the disease.⁵⁰⁻⁵³ Increased levels of basophil CD63 or CD203c expression induced by CSU serum or a basophil responder phenotype to anti-IgE stimulation, which reflect abnormalities on the basophil activation/degranulation pathway, may also predict the highest CSU activity reflected by significant impairment in quality of life, higher frequency of emergency department use, and higher itch severity.⁵⁴⁻⁵⁶ Several studies also support the notion that a positive autologous serum skin test (ASST), which is a simple in vivo clinical test for the

TABLE I. Most promising biomarkers in CSU

Biomarker	CSU feature	No. of studies showing significant association*	Comment	References
D-dimer	Disease activity	13	Higher levels are associated with more active disease	12-24
C-reactive protein	Disease activity	11	Higher levels are associated with more active disease	12,13,25-33
Prothrombin fragment 1+2	Disease activity	8	Higher levels are associated with more active disease	14,16,17,22-24,34,35
IL-6	Disease activity	4	Higher levels are associated with more active disease	28,29,33,36
Mean platelet volume	Disease activity	3	Higher levels are associated with more active disease	37-39
D-dimer	Response to antihistamines	2	Higher levels are associated with insufficient clinical response	13,40
Basophil histamine release assay	Response to cyclosporine	2	Positive result is associated with satisfactory clinical response	41,42
D-dimer	Response to cyclosporine	1	Lower levels are associated with satisfactory clinical response	43
IL-31	Response to omalizumab	1	Lower levels are associated with satisfactory clinical response	44
Basophil FcεRI receptor	Response to omalizumab	1	Lower expression is associated with insufficient clinical response	45
Total IgE levels	Response to omalizumab	1	Lower baseline levels and a lesser increase after start of treatment are associated with insufficient clinical response	46
Antithyroid antibodies	Disease course	2	Its presence is associated with longer disease duration	7,47
CD63 expression	Disease course	1	Higher levels are associated with earlier spontaneous resolution in pediatric CSU	48

CSU, Chronic spontaneous urticaria; FcεRI, high-affinity IgE receptor.

*Information adapted from Ref. 5.

detection of basophil histamine-releasing activity, is linked to active CSU.⁵⁷⁻⁶⁰

In summary, and although many other clinical or laboratory parameters have been claimed to correlate with CSU activity, we believe that the aforementioned markers, particularly CRP, IL-6, MPV, D-dimer, and F1+2, are the most promising candidates and deserve further exploration for their value as biomarkers of disease activity based on the high level of evidence (ie, several studies from different centers showing the same association), consistency (ie, reproducibility), feasibility, and clinical relevance. Nevertheless, it should be taken into account that certain biomarkers, especially those related to inflammation and coagulation, are not specific enough for urticaria, as they can be elevated in many other conditions that are often comorbidities or even an underlying cause of CSU (eg, chronic infections, autoimmune disorders, vascular diseases, among others). For this reason, their interpretation in CSU should always be done with caution.

Biomarkers of response to treatment

The establishment of personalized treatment plans remains one of the biggest challenges in CSU. In this regard, and given the emergence of new therapies in CSU, there is a growing interest to look for objective markers that reliably predict the disease prognosis and the effectiveness of a specific therapeutic intervention. However, only a few studies have shown a

significant association between levels of a certain biomarker and response to treatment.

In the case of antihistamine therapy, D-dimer levels seem to be the most promising biomarker. In an Italian study, patients with insufficient response to antihistamines were more likely to present elevated D-dimer levels, suggesting that this parameter could be a biomarker for severe CSU with antihistamine-resistant disease.⁴⁰ This observation was confirmed by Kolkhir et al,¹³ who suggest that the evaluation of not only D-dimer but also fibrinogen, CRP, and erythrocyte sedimentation rate should be considered before starting treatment with nonsedating antihistamines, because high levels of these markers may predict an unsatisfactory therapeutic response. Another investigation reported that antihistamine-resistant CSU may show increased complement C5a fraction, higher disease activity, longer duration of wheals, and higher positivity of ASST.⁶¹

Baseline levels of D-dimer have also been linked to response to cyclosporine. In a recent study, D-dimer levels showed a highly significant negative correlation with response to cyclosporine treatment and were also considered a useful tool to monitor this clinical response.⁴³ Another potential biomarker for cyclosporine responsiveness is the basophil histamine release assay (BHRA). Thus, 2 independent investigations, including a double-blind placebo-controlled study, showed that patients with a positive BHRA are more likely to show a satisfactory response to cyclosporine than those with a negative BHRA.^{41,42}

Finally, some biomarkers have been proposed for patients undergoing treatment with omalizumab. A significant association has been shown between levels of IL-31, a major dermal pruritogen, and response to anti-IgE therapy, with lower baseline levels observed in patients showing a satisfactory clinical response.⁴⁴ Levels of total serum IgE and the high-affinity IgE receptor (FcεRI) expression on basophils are also interesting biomarkers for omalizumab responsiveness. In a recent Spanish study, all nonresponders to omalizumab showed significantly lower baseline levels of basophil FcεRI expression than responders, suggesting that the deficient FcεRI downregulation experienced during treatment could be an explanation for the nonresponder status.⁴⁵ Ertas et al⁴⁶ postulated that omalizumab responsiveness may also be predicted by total IgE levels and their change during treatment, particularly by the week 4/baseline ratio of total IgE. Lastly, Palacios et al⁶² observed that the lack of basophil CD203-c upregulating activity, which is thought to reflect the presence of autoantibodies to IgE and/or FcεRI receptor, might also correlate with the clinical response to anti-IgE therapy. In addition to the response to treatment, recent studies have also investigated potential biomarkers for different categories of omalizumab response. For example, a positive BHRA and ASST have been proposed as predictors of slow therapeutic response,⁶³ whereas increased IgE levels seem to be linked to faster relapse in patients with omalizumab-discontinued CSU.⁶⁴

Biomarkers for the disease course

Some biomarkers have been discussed in the literature by their usefulness to predict the course of the disease, that is, the time to spontaneous remission. However, the level of evidence is still low due to the small number of available studies. Having said that, the most promising biomarker for the CSU course seems to be the presence of serum antithyroid antibodies (ATA). Two independent studies suggested that disease duration is significantly longer if ATA are detected in patients with CSU.^{7,47} Levels of vitamin D and total IgE have also been linked to disease duration. In this regard, Woo et al⁶⁵ showed that serum vitamin D levels are more likely to be critically low in patients with CSU and can also be inversely related to disease duration. These findings have led some authors to propose the use of vitamin D as adjuvant therapy for CSU.⁶⁶ Meanwhile, Kessel et al⁶⁷ showed a significant association between increased total serum IgE levels and urticarial duration lasting more than 2 years.

Because of limited published data and different methodologies and/or study designs used, there is sometimes conflicting evidence for a particular biomarker. For example, profound basopenia has been linked to increased serum autoreactivity, greater impairment in quality of life, and poorly controlled disease in adult patients with CSU.⁵⁰ However, the same markers have been associated with a better prognosis in pediatric CSU. Thus, Netchiporouk et al⁴⁸ recently reported that children with CSU showing high scores on the basophil activation test using CD63 marker expression and absence of blood basophils are more likely to exhibit an earlier spontaneous resolution of urticaria. The authors suggested that this favorable prognosis associated with higher CD63 expression could be related to autoantibody production induced by transient viral and bacterial infections, which are quite common in children and represent well-known and relevant triggers of urticaria. Although possible differences in etiologic and/or pathogenic factors (eg, differences in the mechanism of autoimmunity) in both groups of patients could

partially explain such results,⁶⁸⁻⁷⁰ further research is needed to clarify the disparate findings in adults and children. These studies should be performed in children and adults with CSU and should assess basopenia, basophil-activating serum activity, and other markers of “autoimmune” CSU for their possible link to the duration and severity of the disease.

In addition to laboratory values, some clinical markers have also been linked to CSU duration. For example, several investigations have suggested that patients with CSU who present with concomitant angioedema or inducible urticaria may show longer disease duration, longer time to remission, and/or lower resolution rates.^{7,8,71-74} Similarly, disease activity, evaluated through clinical scores, could also be related to CSU duration.^{7,60,67,75} Lesser-known clinical features, such as the presence of arterial hypertension or hypersensitivity reactions to nonsteroidal anti-inflammatory drugs, may also result in a distinct CSU phenotype showing a longer disease duration.^{76,77}

To conclude, special attention should be given to modern techniques that have allowed the identification of potential useful CSU biomarkers, such as RNA sequencing, microarrays, and proteomic or metabolomic analysis.⁷⁸⁻⁸³ For example, by proteomics analysis, serum clusterin, a protein involved in multiple functions including modulation of the complement system, regressing angiogenesis, and cleaning bioactive cell debris, has been found to be increased in patients with a positive ASST and in those showing a satisfactory clinical response to antihistamine therapy.⁷⁹ Similarly, the rs2298805 polymorphism of the *FCER1A* gene, which encodes the α -chain of the FcεRI receptor, has been associated with the therapeutic efficacy of nonsedating H1-antihistamines in Chinese patients with CSU.⁸⁰ Recently, certain microRNAs have been found to be significantly increased in patients with positive chronic urticaria index (a functional anti-FcεRI test that supports the autoimmune basis of the disease).⁸¹ These microRNAs, which may be considered potential biomarkers for chronic autoimmune urticaria, target some genes that are associated with several biologic functions such as cellular movement, tissue development, regulation of leukocyte migration, or inflammatory response.⁸¹ Although larger population sizes and multicenter studies are needed to confirm such preliminary observations, the implementation of these techniques might help in the near future to not only identify potential disease biomarkers but also increase our knowledge regarding the pathogenesis of CSU.

CSU TREATMENT OVERVIEW

First-line treatment for CSU involves high-dose second-generation antihistamines; however, more than 50% of patients remain uncontrolled despite this therapy.^{84,85} Oral corticosteroids (OCS) may be indicated in individuals with CSU whose disease remains refractory despite H1 antihistamines and leukotriene antagonists. Only short courses of OCS are recommended (typically ≤ 10 days) because of their systemic side effects with continual or long-term use.^{1,85} In some patients, there is a reliance on repeated courses of OCS because discontinuation may lead to CSU flares. Although OCS may be an adequate temporary therapy, the authors feel that this therapy should not be a mainstay of treatment for patients with CSU given their potential systemic side effects and increased health care costs associated with these side effects. For patients with refractory CSU, a number of biologic agents are also being used during the

TABLE II. Overview of biotherapeutics currently in clinical trials for management of CSU

Biologic agent	Drug category	CSU dosing/frequency	Mechanism of action in CSU	Clinical trials identifier	References
Omalizumab*	Anti-IgE	FDA approved: 150 or 300 mg every 4 wk Off-label: doses up to 600 mg every 4 wk or 300 mg every 2 wk have been used successfully in refractory cases	Binding of IgE at the Fc region reduces free IgE levels leading to downregulation of FcεRI expression on mast cells, basophils, and dendritic cells, resulting in decreased mediator release	N/A	86-89
IVIg	IVIg	0.15 g/kg every 4 wk for 6-51 mo or 2 g/kg over 2 d every 4-6 wk	Blocks FcεRI activity on mast cells, which prevents IgE binding and degranulation. Also may decrease B-cell autoantibody production	N/A	90
TNF-α inhibitors (etanercept, adalimumab, infliximab)	TNF-α inhibitor	Etanercept: 50 mg SC weekly Adalimumab: 40 mg SC every 2 wk Infliximab: 5 mg/kg IV every 8 wk	Used in the treatment of CSU or urticarial vasculitis because TNF-α may be upregulated in the lesional and nonlesional skin of patients with CSU	N/A	91-93
Rituximab	Chimeric murine/human anti-CD20 mAb	375 mg/m ² weekly injections for 4 wk	B-cell depletion via complement and antibody-dependent cytotoxicity results in decreased circulating autoantibody levels	N/A	94
IL-1 inhibitors (anakinra, canakinumab)	IL-1 inhibitor	Anakinra: 100 mg SC Canakinumab: 150 mg SC every 8 wk	Inhibition of IL-1β may modify the clinical course of urticarial lesions in CSU	NCT01635127	9,11,95
Ligelizumab (QGE031)	Anti-IgE	QGE031 every 4 wk × 13 wk	Similar to omalizumab excepts binds to free IgE with greater affinity	NCT02477332 NCT02649218	96
GSK2646264	Syk inhibitor	Topical application for 28 d	Upregulates transcription factors responsible for the synthesis and degranulation of proinflammatory mediators	NCT02424799	95,97
AZD1981	PGD ₂ antagonist	40 mg orally 3 times daily for a total of 7 d	CRT _{H2} inhibition could reduce frequency and severity of urticarial lesions because of overexpression of CRT _{H2} on eosinophils in patients with CSU	NCT02031679	98
GDC-0853	Btk inhibitor	Oral administration twice daily for a total of 56 d	Unknown	NCT03137069	99

Btk, Bruton tyrosine kinase; *CRT_{H2}*, chemoattractant receptor homologous molecule expressed on T_{H2} cell; *CSU*, chronic spontaneous urticaria; *FDA*, Food and Drug Administration; *IVIg*, intravenous immunoglobulin; *PGD₂*, prostaglandin D₂ receptor; *SC*, subcutaneous; *Syk*, spleen tyrosine kinase.

Table adapted from Refs. 9 and 95.

*FDA approved in the United States for the treatment of CSU in 2014.

past few years to achieve a satisfactory disease control. We will focus on the therapeutic effectiveness of these biologic agents (Table II).^{9,95}

Omalizumab

In 2014, omalizumab was the first US Food and Drug Administration (FDA)-approved biologic agent for the management of CSU.¹⁰⁰ It is a humanized mAb that binds to free IgE at the Fc region, thus preventing the interaction with FcεRI receptor on effector cells, such as mast cells and basophils. Although the exact mechanisms for the therapeutic effects of omalizumab remain unclear, one proposed mechanism involves the inhibition of the effects of IgG autoantibodies to IgE or the α subunit of FcεRI, resulting in dampened skin mast cell activation.^{101,102}

The benefits of omalizumab were demonstrated in patients with CSU with and without autoantibodies in proof of concept and phase II studies.¹⁰³⁻¹⁰⁵ After the results of these trials, 3 large

phase III clinical trials (ASTERIA I, ASTERIA II, and GLACIAL) were performed.⁸⁶ These trials showed that patients with CSU who received omalizumab had significant improvements in urticaria and quality-of-life measures compared with placebo.⁸⁷⁻⁸⁹ The effects were dose dependent, and a complete resolution of urticarial symptoms was found in a significant number of patients who received the highest dose of omalizumab, 300 mg administered subcutaneously (SC) monthly. In the ASTERIA II trial, the omalizumab 150 mg and 300 mg groups achieved primary efficacy endpoint significance in weekly itch severity scores at 12 weeks from baseline compared with placebo.⁸⁸ Omalizumab was also effective regardless of patient demographics or background therapy.¹⁰⁶

On the basis of these trials, the US FDA approved the use of omalizumab 150 mg or 300 mg, whereas the licensed dose in the European Union (EU) is 300 mg SC every 4 weeks for individuals with antihistamine-refractory CSU aged 12 years and older, independent of serum IgE or body weight.^{107,108} Higher

(600 mg) doses of omalizumab were explored in the phase II MYSTIQUE trial; however, there was no difference in outcomes compared with the 300 mg omalizumab group.¹⁰⁵ As per US guidelines, omalizumab is now included as a fourth step in the management of CSU after failure of standard and high-dose antihistamines, addition of an H₂-antihistamine and leukotriene antagonist, and failure of a high-potency antihistamine, such as doxepin or hydroxyzine.⁸⁵ In contrast, omalizumab is recommended as a third step for CSU management after failure of standard and high-dose nonsedating antihistamines as per EU guidelines.¹ Omalizumab is safe and well tolerated, with most common adverse events including headache (6.1%), sinusitis (4.9%), arthralgia (2.9%), and injection-site reactions (2.7%).^{109,110} There were no reports of anaphylaxis in any of the phase III urticaria clinical trials. Omalizumab appears effective at therapeutic durations of >1 year.¹¹¹

Questions that remain unanswered include why there are a large number of individuals who are partial or nonresponders to omalizumab, up-and-down dose-titration recommendations, and the duration of time that omalizumab should be continued once therapeutic efficacy is attained. In partial responders, there are reports of improved symptom control with increased frequency of omalizumab dosing of 300 mg SC every 2 to 3 weeks.^{111,112} Omalizumab nonresponders are proposed to be those who fail to achieve symptom control after 4 doses of omalizumab 300 mg SC every 4 weeks, because the response rate is similar to placebo after this 16-week period.¹¹³ To date, there is no universal agreement on weaning strategies or duration of therapy for omalizumab once disease control is optimized.

A phase IV XTEND-CIU (NCT02392624) trial partially addressed this knowledge gap by evaluating omalizumab treatment efficacy after 48 weeks compared with 24 weeks.^{114,115} This was a US-based, multicenter, randomized, double-blind, placebo-controlled trial that enrolled patients aged 12-75 years with antihistamine-refractory CSU and a 7-day urticaria activity score ≥ 16 during the 7 days before baseline. Results showed that omalizumab treatment prevented symptom recurrence and achieved sustained control through 48 weeks. Also, the percentage of subjects experiencing clinical worsening during the 12 weeks after withdrawing therapy was similar in those subjects treated for 24 weeks before withdrawal compared with those treated for 48 weeks before withdrawal, thus suggesting a possible clinical benefit with a longer treatment interval.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been used successfully for the treatment of antihistamine-refractory CSU because of its role as an immune modulator in autoimmune diseases. Its immunoregulatory effects include Fc receptor blockade, enhancement of regulatory T cells, accelerated clearance of autoantibodies, and an increase in Fc γ RII expression.¹¹⁶⁻¹¹⁸ A number of case series have demonstrated remission of CSU with IVIg administration, with the largest conducted by Pereira et al.⁹⁰ This study demonstrated that monthly infusions of low-dose IVIg (0.15 g/kg) in 29 subjects resulted in improvement in urticaria or angioedema in 90%, with almost two-thirds achieving complete remission after 6-51 months of therapy. Clinical use of IVIg is somewhat limited because of the high cost, prolonged infusion times, and limited data on efficacy. Therefore, unless another indication exists for use of IVIg, alternative biologic agents should be considered.

TNF- α antagonists

Because TNF- α has been found to be upregulated in the lesional and nonlesional skin of patients with CSU, TNF- α inhibitors (etanercept, adalimumab, and infliximab) have been used in the treatment of CSU or urticarial vasculitis.^{91,119} One of the first cases that described the efficacy of TNF- α inhibitors was usage of etanercept in a patient with refractory delayed pressure urticaria and psoriasis.¹²⁰ Since then, multiple case reports and case series have shown promising results in individuals with CSU, physical urticarias, and urticarial vasculitis.^{92,121} One retrospective study showed that treatment with etanercept or adalimumab in 25 patients with CSU resulted in resolution of urticaria or angioedema in 60%.⁹³ TNF- α inhibitors may be useful in patients with CSU who are refractory to omalizumab; however, no head-to-head studies have been performed to date. TNF- α inhibitors may be limited by their increased risk for infections, including tuberculosis and fungal infections, along with an increased risk for lymphomas and other malignancies.⁹

Rituximab

Rituximab is a chimeric murine/human anti-CD20 mAb approved for use in several hematologic and autoimmune disorders. By targeting the CD20 antigen on the B-cell surface, B-lymphocytes are depleted. This mechanism results in inhibition of autoantibody production important in some patients with CSU. Some promising results have been demonstrated in case reports for individuals with CSU and physical urticarias. Rituximab has also shown benefit in hypocomplementemic urticarial vasculitis.⁹⁴ However, given the lack of randomized, double-blind, placebo-controlled trials, rituximab is not a current FDA-licensed therapy for the treatment of antihistamine-refractory CSU.

IL-1 inhibitors

Cryopyrin-associated periodic syndromes (CAPS) is a spectrum of autoinflammatory syndromes including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.¹²² CAPS is associated with altered synthesis of cryopyrin and subsequent overproduction of IL-1 β via autosomal dominant mutations of the nucleotide-binding domain, leucine-rich family, pyrin domain containing 3 gene (NLRP3). This overproduction of IL-1 β often leads to formation of urticarial lesions. Therapies directed against IL-1 β have been FDA-approved for the treatment of CAPS, including anakinra, a recombinant human IL-1R α antagonist; canakinumab, a humanized anti-IL-1 β mAb; and rilonacept, a soluble decoy receptor that blocks IL-1 β signaling.⁹ Two studies have also shown a critical role for anakinra and canakinumab in the treatment of Schnitzler syndrome, which is often manifested by urticaria, fever, myalgias, and lymphadenopathy.^{123,124} Various clinical trials are underway to elucidate the role of IL-1 inhibitors in CSU therapy, including a phase II randomized, double-blind placebo-controlled single center study evaluating the use of canakinumab versus placebo in CSU (NCT01635127).^{11,95}

Anti-IgE mAb: ligelizumab and quilizumab

Given omalizumab's positive impact on CSU management, alternative anti-IgE mAbs have also been investigated. Ligelizumab is a humanized IgG₁ mAb that has a similar mechanism of action to omalizumab, but binds to free IgE with greater

affinity.⁹⁶ Two studies are currently underway to examine the efficacy and safety of ligelizumab as add-on therapy for patients with CSU compared with placebo and omalizumab (NCT02477332), along with the use of ligelizumab for CSU over a 1-year period (NCT02649218).

Quilizumab is a humanized IgG₁ that targets the M1 prime segment of membrane-expressed IgE, resulting in diminished IgE-switched B cells and plasmablasts that may last up to 6 months after completion of therapy.¹²⁵ Despite its initial positive effects, further development of quilizumab has since been discontinued.

Other investigational agents

Spleen tyrosine kinase (Syk) upregulates transcription factors that are responsible for the synthesis and degranulation of proinflammatory mediators, and studies have demonstrated increased Syk expression in certain subsets of patients with CSU.^{97,126,127} GSK2646264 is a topical Syk inhibitor that is currently under investigation in a randomized, double-blind, single and repeat ascending trial to determine its efficacy in patients with CSU and cold urticaria (NCT02424799).⁹⁵

Chemoattractant receptor homologous molecule expressed on T_H2 cells (CRT_H2) is a prostaglandin D2 receptor (PGD2R) that has been reported to be overexpressed on eosinophils in patients with CSU.⁹⁸ Inhibition of CRT_H2 could reduce the frequency and severity of urticarial lesions because of its anti-inflammatory properties. AZD1981 is a PGD2R antagonist currently under investigation in a phase IIa, randomized, placebo-controlled, double-blind study to determine its efficacy as a potential therapy in CSU (NCT02031679).

Bruton tyrosine kinase (Btk) is a nonreceptor tyrosine kinase that transmits signals crucial for B-cell development.⁹⁹ Genetic Btk deletion causes B-cell immunodeficiency, making this kinase an attractive target for B-cell disorders, in particular malignancies such as chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenström's macroglobulinemia. Given some promising results in case reports with the use of rituximab in CSU, there is belief that Btk inhibitors could potentially play a role in refractory CSU management. A phase IIA multicenter, randomized, double-blind, placebo-controlled pilot study is currently in process to evaluate the efficacy, safety, and pharmacodynamics of the Btk inhibitor, GDC-0853, compared with placebo in individuals with antihistamine-refractory CSU (NCT03137069).

As mentioned previously, IL-6 plays a pivotal role in immune and inflammatory responses and may be an important biomarker for disease activity in CSU. Case reports have suggested the utility of tocilizumab (IL-6 antagonist) in patients with urticarial vasculitis and Schnitzler's syndrome.^{128,129} To date, no trials have been performed to determine the effectiveness of anti-IL-6 therapy against CSU. The authors believe that future investigations could elucidate unanswered questions regarding whether circulating IL-6 contributes to the pathogenesis of CSU and biologic agents targeting IL-6 could expand the therapeutic pipeline in CSU.

SUMMARY

Although there is a growing interest in the search of reliable indicators of different aspects of CSU, the current level of evidence to support the available biomarkers is still low (except for biomarkers of disease activity). This is probably due, in part, to the wide variability and heterogeneity in the data collected from

the published studies, which often show differences in selection of patient populations and/or data analysis. Nevertheless, there are some biomarkers that appear to be the best candidates, according to the published evidence and the authors' opinion, that should be explored in further studies as potential predictors of different features of the disease (Table 1).

Moreover, with the advent of biomarkers, newer biologic agents are coming forth to revolutionize management of potential refractory diseases such as CSU. Omalizumab is the most studied and first FDA-approved biologic agent for the treatment of CSU in 2014. Several other agents have shown promising results in clinical case reports and case series, but more randomized, controlled studies are necessary to elucidate the effectiveness of these drugs in CSU. Furthermore, investigational trials are ongoing with ligelizumab, canakinumab, a topical Syk inhibitor, a CRT_H2 antagonist, and a Btk inhibitor to define their use in CSU. Despite their costs, as precision medicine continues to advance, biologics will play an even more important role in the management of CSU, especially in patients with biomarkers that predict a higher likelihood of success.

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