



Advances in the pathogenesis representing definite outcomes in chronic urticaria

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Purpose of review

We reviewed in this article, the recent advances in CSU physiopathology and potential clinical and laboratory biomarkers in CSU.

Recent findings

In addition to the central role of mast cells in urticaria physiopathology, increased interest in basophils has arisen. Recent data corroborate the autoimmunity pathway as one of the main pathways in mast cell activation. The association of inflammatory cytokines, heat shock proteins and *staphylococcal* infection with CSU are also reviewed. C-reactive protein, D-dimers, autologous serum skin test, IgE levels and FcεRI expression in basophils have shown their potential as biomarkers for disease duration, activity, severity and/or response to treatment.

Summary

A comprehensive understanding of chronic spontaneous urticaria mechanisms is essential to find novel biomarkers and treatments. The use of these biomarkers in clinical practice will guide us in choosing the best treatment option for our patients.

Keywords

biomarkers, therapeutics, urticaria

INTRODUCTION

Urticaria is a condition characterized by the development of wheals, angioedema or both. It is classified as chronic when symptoms persist for more than 6 weeks, and spontaneous when there is no specific eliciting factor. Chronic spontaneous urticaria (CSU) must be differentiated from other diseases that can manifest with wheals and/or angioedema but have other pathophysiologic mechanisms, such as urticaria vasculitis, maculopapular cutaneous mastocytosis, nonhistaminergic angioedema and autoinflammatory syndromes [1]. A detailed history and physical examination are essential to identify significant aspects of the disease and to guide any further laboratory assessment that may be useful to confirm or exclude underlying causes or diseases [2].

The diagnosed prevalence of chronic urticaria has been estimated to be 0.53% in the United States, 0.63% in Europe and 0.41% in Brazil [3–5]. Although not life-threatening, chronic urticaria has been associated with a negative impact in the quality of life [6]. As CSU may last for many years, it is imperative to control the disease until it is gone [1]. A thorough understanding of its mechanisms allows us to offer the best treatment approach for

each patient, considering the disease duration and severity, as well as the response to each potential treatment, in order to improve their quality of life. In this article, we review the most recent findings in urticaria physiopathology along with potential clinical and laboratory biomarkers.

URTICARIA PHYSIOPATHOLOGY

Mast cells play a central role in CSU physiopathology and can be activated by different pathways. On the other hand, increasing interest in basophils has emerged as peripheral basophil's number is decreased in CSU and functional impairment has been observed. After basophil stimulation with anti-FcεRI antibodies, two different groups of patients were described: a reactive (67%) and a

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KEY POINTS

- Urticaria mechanisms are still not totally understood.
- The development of new therapies for urticaria is based on new insights on its mechanisms.
- Biomarkers may be useful to predict disease duration, severity and response to treatment.

nonreactive group. Among the nonreactors, there is a subgroup of patients with marked basopenia. This group has a reduced surface expression of FcεRI and FcγRII, decreased binding of IgE and IgG, increased serum reactivity and auto-antibodies against thyroid peroxidase, suggesting a possible auto-immune-associated mechanism [7].

Chronic spontaneous urticaria and its association with autoimmune diseases is well documented. Immunoglobulin-G (IgG) autoantibodies to IgE or the IgE receptor (FcεRI) and IgE antibodies against thyroid peroxidase have already been reported [8]. Two recent studies helped to corroborate those data showing that 25–52% of CSU patients had IgG auto-antibodies to FcεRIα. This association was more frequent in patients with a positive autologous serum skin test (ASST) and autologous plasma skin test (APST). No association was found with clinical response to antihistamines [9,10].

In order to identify possible autoallergens as targets for IgE in patients with CSU, Schmetzer *et al.* evaluated sera of 1062 patients and compared with 482 healthy controls. Thirty-one auto-antigens were detected in more than 70% of patients. Eight were soluble or membrane-bound and potentially expressed on the skin, but only IgE against IL-24 was present in all CSU patients. Interestingly, IL-24 induced degranulation in mast cells preincubated with IgE from CSU patients but not from healthy controls, showing its functionality in CSU. Moreover, IgE-anti-IL-24 levels were associated with disease activity. Despite the presence of IgE anti-IL-24 in some healthy donors, its concentration was markedly lower in this group. New assays might help to better explain the role of this cytokine in CSU [11¹¹].

To explore the role of other cytokines in CSU physiopathology, Chen *et al.* selected IL-35, a suppressor of Th1 and Th17 cells, that play an essential role in many autoimmune diseases. Serum levels of IL-35 were investigated in CSU patients and compared with atopic dermatitis patients and healthy controls, as well as IL-35 levels before and after antihistamine treatment. CSU patients showed significantly lower levels of IL-35 when compared with the other groups, but increased levels after

treatment, suggesting that this cytokine may play a role in CSU pathogenesis [12]. Other cytokines usually involved in immune responses as IL-17, IL-31 and IL-33 were also found in higher plasma levels in CSU patients when compared with controls [13].

Heat shock proteins (Hsp) are molecules that play a role in inflammation and immune system function. The 70 kDa Hsp (Hsp70) has been associated with many auto-immune diseases. Circulating Hsp70 and anti-Hsp70 antibodies were evaluated in patients with CSU and compared with controls. Both plasma Hsp70 and serum anti-Hsp70 levels were increased in CSU patients. Anti-Hsp70 antibodies levels were correlated with the grade of inflammation and CRP concentration. Although not clear if Hsp70 and its circulating antibodies have a role in CSU or it is just an epiphenomenon, they can be an attractive target for further studies [14].

Virus infection can be an important trigger in acute urticaria or CSU exacerbation [15]. However, there is no general agreement on the role of other infections in CSU. Immunoglobulin-E antibodies to *Staphylococcus* spp. have been demonstrated and may play a role in diseases as atopic dermatitis and allergic rhinitis. A retrospective study of sera from 49 CSU patients was performed to address the presence and functionality of these immunoglobulins in CSU patients. Levels of IgE against staphylococcal enterotoxin were higher but not statistically significant in CSU patients than in healthy controls, including staphylococcal enterotoxin B (SEB). SEB could induce basophil histamine release in CSU patients and be clinically correlated with disease duration. These findings suggest that IgE against staphylococcal antigens could trigger and perpetuate inflammation in a subgroup of CSU patients, but more studies are necessary to clarify the role of *Staphylococcus* spp. and other infections in this disease [16].

BIOMARKERS FOR DISEASE ACTIVITY, SEVERITY AND DURATION

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathogenic process or pharmacologic responses to a therapeutic intervention. They can be useful in CSU to distinguish it from other diseases, evaluate disease activity, severity and duration and predict response to treatment [17]. The potential biomarkers reviewed in this article are summarized in Tables 1 and 2.

Auto-immune thyroid disease patients have a higher rate of CSU as well as antithyroid antibodies prevalence is higher in CSU patients. In a retrospective analysis of outpatient CSU patients, around

Table 1. Biomarkers for disease duration, severity, activity and time to remission

Anti-TPO +
Longer duration of disease
No association with severity
ASST and APST+
More severe disease
No association with time to remission
IL-17, IL-31 and IL-33 levels
High levels associated with a more severe disease
High levels of IL-31 associated with severe pruritus
CRP levels
High levels associated with shorter duration of disease
High levels associated with disease activity

12% had antibodies against thyroid peroxidase (anti-TPO). These patients had a more prolonged disease when compared with negative anti-TPO patients. However, no differences were observed regarding disease severity when comparing patients with a positive or negative anti-TPO. ASST and APTS were also performed in these patients to assess autoreactivity, with positive results in 70%. Both tests were associated with disease severity (attacks >4 days/week). No differences in time to remission were observed in patients with positive skin tests when compared with those with negative results [18].

Inflammatory cytokines can be potential biomarkers for disease severity in CSU. In a study with 51 CSU patients and 20 controls, patients with a severe disease (based on UAS7) had higher IL-17 and IL-33 levels when compared with those with mild disease. Pruritus severity was also associated with higher levels of IL-31. A better understanding of the role of these cytokines in urticaria may provide the rational for new treatment strategies [13].

C-reactive protein (CRP) is a sensitive marker of inflammation. Data from 1253 patients were

analyzed showing that one-third of patients had elevated levels of CRP. These patients showed a shorter duration of disease and higher disease activity based on the UAS7. CRP levels were also associated with ASST positivity and D-dimer levels, confirming it as a useful biomarker for disease activity to monitor CSU patients [19].

Inflammatory conditions, such as metabolic syndrome may contribute to the development of CSU. Obesity and overweight were evaluated in patients with CSU. A significant association was demonstrated between heavyweight and older age to disease onset. A trend to longer disease duration was also observed in patients with higher BMI values. Obesity must be assessed and treated in CSU patients, like in any other disease, but further studies are necessary to consider it an excellent clinical biomarker for disease duration [20].

BIOMARKERS FOR RESPONSE TO TREATMENT

Considering the significant role of mast cells in urticaria physiopathology, reducing mast cells activation, as well as its mediators (e.g. histamine) effects in target organs, have been the suggested approach to treat CSU. Nonsedating modern H1-antihistamines in standard or high doses are recommended as first and second line treatment for CSU [1]. However, up to 50% of patients are refractory to high doses of antihistamines and require other drugs to achieve complete symptom control [21]. Positivity to APST and high levels of CRP are related with an inadequate response to antihistamines [18,19]. On the other hand, anti-TPO levels were not associated with response to treatment [18].

Omalizumab is an anti-IgE monoclonal antibody that reduces the levels of free IgE and down-regulates FcεRI expression on basophils and mast cells, showing efficacy and safety in refractory CSU treatment. Potential mechanisms include reducing the activity of IgG autoantibodies against IgE or its high-affinity receptor in mast cells and basophils and reducing IgE activity against autoantigens. However, its mechanism of action in urticaria is not entirely understood, as omalizumab is effective despite the presence of autoreactive antibodies [21].

In order to investigate the ability of omalizumab in inhibiting mast cell and basophil degranulation induced by sera from CSU patients, Serrano-Candelas *et al.* selected CSU sera able to induce expression of CD63 in mast cells and basophils from healthy donors and treated them with different concentrations of omalizumab or human IgG as a control. Despite its effect in preventing IgE binding to its receptor, omalizumab was unable to inhibit CSU

Table 2. Biomarkers for response to treatment

Antihistamines
APST+ associated with nonresponse
CRP high levels associated with nonresponse
Omalizumab
Anti-TPO not associated with response to treatment
IgE lower levels in nonresponders
IgE not associated with time to response
FcεRI expression in basophils increased in responders and predict fast response
Cyclosporine
IgE lower levels predict better response
ASST+ associated with a better response

patient sera-dependent cell degranulation. The impact of in-vivo administration of omalizumab on the activating capacity of sera was then evaluated in patients participating in a placebo-controlled randomized clinical trial. No changes in the activating capacity of sera on mast cells or basophils were observed, and the clinical outcomes were similar independently on the serum ability in cell activation. These data suggest that omalizumab efficacy cannot be explained by the inhibition of sera activity in mast cells and basophils. Moreover, the capacity of CSU sera to activate basophils and mast cells is not a good marker for predicting clinical response to omalizumab [22].

On the other hand, there is increasing evidence that total serum IgE can be used as a biomarker for omalizumab response in CSU. Three recent studies analyzed baseline IgE levels and response to omalizumab. It is noteworthy that the three studies considered a response to treatment based on the urticaria activity score in 7 days (UAS7), as suggested by an expert panel review [23]. In all studies, it was clear that baseline IgE levels were lower in nonresponders [24–26]. However, no differences were observed when comparing IgE baseline levels in complete (UAS7 of 0) and partial responders (minimum 30% in UAS7 reduction) [25]. When stratifying patient's baseline IgE levels in quartiles, clinical response to omalizumab differed significantly in another multicenter retrospective study. Patients with a serum IgE higher than 168 IU/ml have an odds ratio of 13.81 for a response when compared with patients with levels of IgE below 15.2 IU/ml, suggesting that higher IgE baseline levels predict a better response to omalizumab [27]. Interestingly, no differences in time to response was observed when comparing patients with normal or elevated IgE levels in a prospective study with 93 CSU patients [28].

Baseline IgE levels and relapse after stopping omalizumab were also analyzed. Nevertheless, here the results are at odds. Marzano *et al.* in their retrospective study showed no correlation on IgE levels and relapses within 2 months after drug withdrawal and 3 months following drug withdrawal after a second course of treatment. Differently, Ertas *et al.* [28] showed that in complete responders (UAS 0), the time to relapse was significantly shorter in patients with IgE greater than 100 IU/ml when compared with those who have normal IgE levels.

Omalizumab prevents circulating IgE to bind on its high-affinity receptors (FcεRI) in mast cells and basophils. Deza *et al.* demonstrated that baseline expression of FcεRI in CSU patient's basophils was higher than in healthy controls. Interesting, the expression in omalizumab nonresponders was lower than in responders. Moreover, clinical improvement

during therapy was associated with a reduction in the FcεRI expression and a positive correlation between IgE levels and basophil FcεRI expression was observed. Lastly, these data suggest that baseline FcεRI expression in basophils could be used as a predictor to treatment response in CSU patients, with a 100% of sensitivity and 73.2% of specificity [29]. In addition, data from the same group showed a higher baseline basophil expression of FcεRI in patients that had an UAS7 6 or less during the first 4 weeks of treatment. Thus, FcεRI expression in basophils can be also a predictor of time to omalizumab response in CSU [30].

In a proof-of-concept study, a group of seven antihistamines refractory CSU patients had their basophil proteome examined. Results show that all patient's basophils are under stress, but the response to stress is different accordingly to the response to omalizumab. Responders overexpressed intermediate filament proteins whereas nonresponders overexpressed proteins associated with catabolic processes, oxidative stress and unfolded protein pathways. With these results, the authors interrogate about possible differences in urticaria mechanisms when comparing responders and nonresponders [31].

Regardless of its well known effects on total and free IgE, there was a lack of data on the impact of omalizumab treatment in other immunoglobulins and inflammatory cells. Total baseline levels of IgE, IgG, IgM and IgA, as well as blood eosinophil, neutrophil, lymphocytes and platelets counts, were compared with levels after a prospective 12-week-treatment of CSU patients with omalizumab or retrospectively in patients treated for a minimum of 3 months. No differences on immunoglobulin levels were observed after omalizumab treatment, as well as differences between complete or nonresponders. Different groups reported a significant reduction in neutrophils but different effects on eosinophil and platelet numbers. Currently, neither of these parameters (immunoglobulin levels or blood cells count) can be used to predict response to treatment [32,33].

The coagulation cascade is activated in CSU and increased D-dimer levels are associated with disease severity [34]. Omalizumab is effective in severe refractory CSU, but whether D-dimer is a reliable biomarker to response to treatment is still under discussion, with recent studies showing divergent results. Cugno *et al.* [25] observed that pretreatment D-dimer levels were lower in nonresponders when compared with partial and complete responders. In opposition, Marzano *et al.* [24] reported no correlation of D-dimer levels and clinical response to omalizumab, as well as any relation with relapse after discontinuing the drug.

Cyclosporine (CsA) is recommended for CSU treatment when omalizumab fail or is contraindicated. Response to CsA is associated with lower IgE levels, and the response is more effective (UAS ≤ 6) in patients with a positive ASST. Both ASST and IgE levels can be useful biomarkers to predict response to CsA [35,36].

CONCLUSION

Urticaria mechanism is still not totally understood. However, with the current knowledge is already possible to suggest some useful biomarkers for disease activity, severity, duration and response to treatment. With new insights into urticaria mechanisms, other potential biomarkers will come out to be used in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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The article describes an autoallergen (IL-24) that helps to validate the type I autoimmunity mechanism in CSU.