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Review Article

Biomarkers of chronic urticaria: what are their role?

Biomarcadores na urticária crônica: qual o seu papel?

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ABSTRACT

Urticaria is a disease of global importance that can be debilitating for most patients. It is characterized by episodes of wheals, angioedema, or both, determined by the activation of mast cells and other inflammatory cells with the release of several mediators. The etiology is complex, involving specific phenotypes and therapies. Chronic urticaria has a recurrent and unpredictable course that can last for years. The prevalence is typically higher in females, with a peak incidence between 20 and 40 years of age. The disease can be classified by severity, impact on quality of life, and therapeutic response. A biomarker is a measurable clinical or laboratory characteristic of a biological state or condition that can influence or predict the incidence of outcome or disease. This study provides a review of the main biomarkers considered promising and with the best evidence related to duration, disease activity, and therapeutic response.

Keywords: Chronic urticaria, angioedema, biomarkers, autoimmunity.

RESUMO

A urticária é uma doença com comprometimento universal, e debilitante para a maioria dos pacientes. Caracteriza-se pela ocorrência de episódios de urticas, angioedema ou ambos, determinados pela ativação de mastócitos e outras células inflamatórias com a liberação de vários mediadores. Apresenta etiologia complexa com fenótipos e terapias bem específicas. A urticária crônica possui evolução recorrente e imprevisível, podendo estender-se por anos. Caracteristicamente possui maior prevalência no sexo feminino, com pico de ocorrência entre 20 e 40 anos. A doença pode ser diferenciada pela gravidade, impacto na qualidade de vida do paciente e resposta terapêutica. Biomarcador é uma característica clínica ou laboratorial mensurável de algum estado ou condição biológica, o qual pode influenciar ou prever a incidência de desfecho ou doença. O objetivo deste artigo é realizar uma revisão dos principais biomarcadores promissores e com melhor evidência relacionados à duração, atividade da doença e resposta terapêutica.

Descritores: Urticária crônica, angioedema, biomarcadores, autoimunidade.

Introduction

Chronic urticaria (CU) is a common skin disease with a negative impact on several aspects of patients' lives. CU is characterized by the occurrence of wheals and/or angioedema for a period of 6 weeks or longer. It can be classified as chronic spontaneous urticaria (CSU), when there is no specific trigger, or chronic inducible urticaria (CIndU), in which symptoms are induced by specific triggers.[1,2]

The lesions result from activation of mast cells and other inflammatory cells, such as basophils and eosinophils, and the subsequent release of their mediators.[3] CU has a recurrent and unpredictable

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course that can last for years, with about 20% of patients remaining symptomatic after 5 years. The prevalence is typically higher in females, with a peak incidence between 20 and 40 years of age. The disease can be classified by severity, impact on quality of life, and clinical outcome.[1,3]

Over the last decade, numerous studies have been conducted in an attempt to elucidate the mechanisms involved in the development of CU and to identify potential biomarkers.[4] A biomarker is a measurable clinical or laboratory characteristic of a biological state or condition that allows us to know, for example, the state of a disease or the response to a drug.[5]

The main difficulty in establishing biomarkers of CU lies in the heterogeneity of the clinical presentation and its complex pathogenesis. There are multiple ways of mast cell activation, with the participation of numerous cells and molecules, leading to different endotypes and phenotypes. A better understanding of these endotypes, through biomarkers, will help better understand the course of CU and find targets for new therapies.[6]

This study aimed to review the main biomarkers considered promising and with the best evidence related to disease activity, therapeutic response, and natural course of CU.

Methods

We conducted a search in Science Direct, PubMed, and Latin American and Caribbean Health Sciences Literature (LILACS) databases for original articles, reviews, guidelines, and consensus statements published in the past 20 years by using the following search terms: chronic urticaria, biomarkers, duration, prediction, prognosis, and treatment.

Biomarkers

In CU, biomarkers are useful in assessing disease severity, duration, and response to treatment.

Disease severity and duration

Several biomarkers of disease severity have been studied, including exacerbations with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), increased basophil CD203c expression, basopenia, eosinopenia, autologous serum skin test (ASST), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, mean platelet volume (MPV), vitamin D, interleukin (IL)-6, IL-18 IL-17, IL-23, tumor necrosis factor alpha (TNF-α), lipocalin (LCN2), and prothrombin fragment 1 + 2 (F1+2). However, the strongest association has been demonstrated with D-dimer, CRP, F1+2, MPV, and IL-6 3,7 (Figure 1).

Factors such as disease severity, presence of angioedema, age, NSAID-induced exacerbation, association with CIndU, presence of thyroid autoantibodies, increased IL-6 levels, basophil high-affinity IgE receptor (FcεRI) expression, and positive ASST have been evaluated as predictors of disease duration, but with conflicting results. There is weak evidence that the presence of thyroid autoantibodies is related to longer disease duration.[3-5]

Some studies have demonstrated that the coagulation cascade may be activated in patients with CSU.[8,9] Plasma markers of thrombin generation and fibrinolysis, such as D-dimer and F1+2, are elevated in patients with CSU, suggesting that, upon activation of endothelial cells, tissue factors are released with subsequent activation of the extrinsic coagulation cascade and secondary fibrinolysis. The resulting thrombin can increase vascular permeability and induce mast cell degranulation. However, there are no changes in hemostasis or a higher frequency of thrombotic events in CSU.[8,9]

F1+2 and D-dimer levels correlate with disease activity. Mean F1+2 levels were higher in patients with CSU than in controls (2.54 [SD 2.57] nmol/L *vs.* 0.87 [SD 0.26] nmol/L; $p < 0.001$), with moderate or severe disease activity in 9 of 11 (82%) and 9 of 26 (35%) patients with elevated or normal F1+2 levels, respectively ($p < 0.025$). Mean plasma D-dimer levels were higher in patients than in controls (329 [SD 188] ng/mL *vs.* 236 [SD 81] ng/mL; $p < 0.01$), with moderate or severe disease activity in 6 of 8 (75%) and 11 of 29 (38%) patients with elevated or normal plasma D-dimer levels, respectively ($p < 0.00$).[10]

In a retrospective study evaluating the relationship between D-dimer, CRP, and fibrin degradation products in 82 patients with CSU, high levels of these markers were associated with greater disease activity and, conversely, a decrease in these markers was observed in controls.[11] In a study of 141 patients with CSU, disease activity was associated with D-dimer but not with CRP, fibrinogen, MPV, or number of platelets.[12]

A retrospective Korean study evaluated whether D-dimer, CRP, and total IgE would be associated with disease activity in adult patients with CSU (n = 48) or

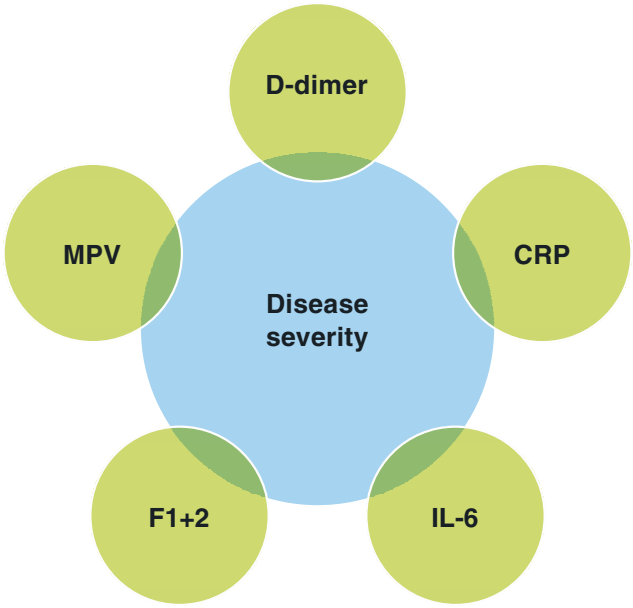

Figure 1
Biomarkers of chronic urticaria severity

CRP = C-reactive protein, MPV = mean platelet volume, IL-6 = interleukin 6, F1+2 = prothrombin fragment 1 + 2.

acute urticaria (n = 46). D-dimer levels were higher in patients with acute urticaria (1.3 g/L) than in patients with CSU (0.7 g/L) and significantly correlated with the Urticaria Activity Score (UAS) (acute urticaria r = 0.30; $p < 0.001$; CU r = 0.37; $p < 0.05$). However, there was no significant correlation between disease activity and CRP or total IgE.[13]

In an Egyptian study, plasma D-dimer and activated factor VII (FVIIa) levels were significantly higher in patients with active CSU (n = 30) than in controls (n = 30). D-dimer levels were lower in patients with grade 1 severity and higher in those with grade 4 severity. Factor VIIa levels did not differ significantly according to disease severity grades. After complete disease remission, there was a significant drop in patients' D-dimer and FVIIa levels.[14]

In Brazil, D-dimer and CRP levels and the ASST and UAS were evaluated in 55 patients with CSU. Mean D-dimer levels were 0.85 (SD 0.324) mg/L. Statistical analysis showed a strong and positive relationship between UAS and D-dimer, where serum D-dimer levels were elevated (> 0.5 mg/mL) in 22 patients; 18 of them (81.81%) were classified as having CSU with an elevated activity score. It was observed that 32.7% of patients required 3 or more medications to achieve CSU remission during follow-up.[15]

CRP is produced by the liver and is a sensitive serum marker of inflammation. It is elevated in several diseases, including infections, neoplasms, autoimmune diseases, cardiovascular diseases, and gastrointestinal diseases. Compared with ESR, CRP is a better marker of inflammation as it is less affected by other factors such as size, shape, and number of red blood cells, female sex, and pregnancy. CRP has proven useful in determining disease activity, prognosis, and treatment efficacy.[7,16]

The role of inflammation has been demonstrated in studies of patients with CU. Several inflammatory biomarkers have shown an important role in disease activity and response to CSU treatment, especially CRP. Increased CRP levels were found in patients with CU and associated with other inflammatory markers

(leukocytosis, neutrophilia, and elevated levels of IL-6, C3 and C4), greater disease severity, impaired quality of life, and positive ASST.[7,17,18]

A retrospective study was conducted in 2 centers, involving 1253 patients with CSU, with the purpose of evaluating the prevalence and relevance of elevated CRP levels. One third of the patients (n = 418) had high CRP levels, which were associated with positive ASST (p = 0.009) and hypertension (p = 0.005) but not with other possible causes or comorbidities of CSU. CRP correlated with disease activity (p < 0.001), impaired quality of life (p = 0.026), and inflammatory and coagulation markers (p < 0.001).[7]

Grzanka et al. demonstrated that IL-17 and CRP levels were significantly higher in patients with CSU than in healthy individuals. Also, there was a significant difference in IL-17 and CRP levels between patients with CSU with mild, moderate-severe symptoms and healthy individuals, with the following CRP levels, respectively (expressed as median [IQR/min-max]): 1.4 (20.92-23.55/19.28-48.60) *vs.* 9.8 (20.92-24.08/18.85-62.73) *vs.* 0.4 (0.20-0.40/0.10-0.60) mg/L (p < 0.001). CRP did not correlate significantly with IL-17.[19]

Two other studies found higher CRP levels in patients with positive ASST (5.81 [SD 4.70] and 5.31 [SD 2.74]) than in those with negative ASST (2.89 [SD 4.85] and 2.53 [SD 1.27]) and controls (2.76 [SD 4.52] and 2.34 [SD 1.38]), as well as a correlation between disease activity and CRP levels.[20,21] Magen et al. also evaluated MPV, as some studies have indicated that MPV correlates with platelet function. Large platelets are more reactive, and the presence of large platelets in the blood is an *in vivo* indicator of platelet activity. A significant positive correlation was found between CU severity score and MPV in patients with a positive ASST (r = 0.44; p = 0.001) but not in patients with a negative ASST.[21]

Among pro-inflammatory mediators, IL-6 is a promising biomarker in CSU due to its role in promoting the inflammatory response. Elevated IL-6 levels were detected in CSU, with a positive correlation with CRP levels, and also in patients with CSU in the active stage and with moderate to severe disease.[18,22,23] However, in a study evaluating IL-18 and IL-6 levels in patients with CSU and healthy controls, there was no statistically significant difference between the groups, unlike other studies that showed a correlation between higher levels of these cytokines and disease activity.[24]

ASST is a non-specific test that assesses the existence of autoreactivity, that is, the presence of endogenous pro-inflammatory or wheal-inducing factors, including autoantibodies, which are triggers for mast cell and basophil degranulation. Positive ASST is correlated with the presence of IgG anti-FcεRI and IgG anti-IgE antibodies, responsible for type IIb autoimmune CSU (aiCSU), whose diagnostic criteria are as follows: (a) a positive *in vitro* bioassay demonstrating autoantibody functionality (basophil histamine release assay [BHRA] or basophil activation marker expression, such as CD63 or CD203c by flow cytometry); (b) positive autoreactivity (a positive ASST) demonstrating the in vivo relevance of mast cell degranulation and increased capillary permeability; and (c) a positive immunoassay for autoantibodies against FcεRIα (Western blot or ELISA) demonstrating autoantibody specificity.[25]

Positive ASST has been associated with greater disease activity, longer duration, and basopenia,[15,26,27] but further studies are needed. A systematic review of parameters associated with CSU duration and severity found 8 studies demonstrating an association between positive ASST and CSU severity, and 8 studies reporting no association.[28]

Increased FcεR1α expression with upregulated CD203c expression on peripheral basophils is observed in patients with CU. Aiming to investigate whether increased basophil activation would be associated with disease activity, basophil CD203c expression was evaluated in 82 patients with CU and 21 healthy controls. Mean CD203c expression was significantly higher in patients with CU than in controls (57.5% *vs.* 11.6%, p < 0.001). Basophil CD203c expression was significantly higher in patients with severe CU than in those with non-severe CU (66.5% [SD 23.3%] *vs.* 54.0% [SD 23.3%], p = 0.033).[29]

Autoimmune thyroid disease is frequently observed in patients with CSU, as is the presence of antithyroid antibodies. Anti-TPO IgG measurements are recommended in international urticaria guidelines to assess type IIb autoimmunity.[1] The presence of anti-TPO IgG has not been related to urticaria severity, but some studies have associated it with disease duration. A retrospective study found that 12% of patients with CSU had anti-TPO IgG, and these patients had longer disease duration than those without anti-TPO IgG. However, there was no difference in disease severity. The same study also reported that 70% of patients had positive ASST and autologous plasma skin test (APST), and both tests were associated with disease

severity.[30] In 2004, Toubi et al. identified that ASST and antithyroid antibodies were positive in 28% and 12% of patients with CSU, with the disease lasting longer in these patients than in those with negative ASST and anti-TPO IgG. However, there was no association with disease severity.[31]

Response to treatment

Non-sedating antihistamines at standard or high doses are recommended as first- and second-line treatment for CSU. However, up to 50% of patients are refractory to high doses of antihistamines and require other medications, such as omalizumab and cyclosporine, to achieve complete symptom control.[1] Predicting treatment efficacy before prescribing it is essential to achieve remission, or if not possible, to improve disease control, avoiding wasting time with an ineffective therapeutic regimen. However, the validation of biomarkers for this purpose remains poorly defined. Studies have been developed using CRP, D-dimer, total IgE, basophil CD203c and FcεRI expression, IL-31, ASST, and BHRA, among others.[3]

High disease activity and high levels of weekly UAS (UAS7), CRP, and D-dimer appear to be good predictors of refractoriness to H1-antihistamines (Figure 2). Low total IgE levels are strongly related to poor or no response to omalizumab, and good response to cyclosporine is predicted by the BHRA, as demonstrated in a systematic review.[32]

Refractoriness to antihistamines

Some clinical biomarkers have been related to refractoriness to anti-H1, including the presence of comorbidities such as atopic asthma, rhinitis, rhinosinusitis, thyroid diseases, and hypertension. However, the evidence for this correlation remains weak.[33,34]

In a retrospective study of 549 patients with CU, more than 75% of patients were refractory to anti-H1, and baseline UAS7 was the only parameter able to predict refractoriness; approximately 90% of patients with UAS7 > 16 required treatment with omalizumab or cyclosporine.[35] Another retrospective study of 385

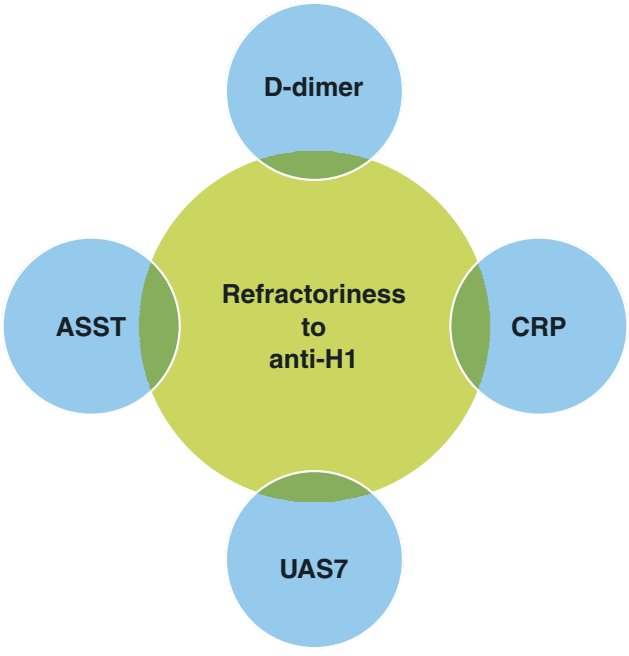

Figure 2
Biomarkers of refractoriness to antihistamines
ASST = autologous serum skin test, CRP = C-reactive protein, UAS7 = urticaria activity score 7.

patients with CSU reported that patients refractory to anti-H1 were characterized by a higher incidence of angioedema, concomitant CIndU, positive ASST, and higher baseline UAS (5.28 in the refractory group and 3.32 in anti-H1 responders). Higher CRP levels were also observed.[36] The finding was confirmed in a sample of 1253 patients with CSU, in which high CRP levels were also correlated with refractoriness to anti-H1.

When evaluating biomarkers of response to levocetirizine in 84 patients with CU, 7.1%, 9.5%, 12%, 31%, and 47.6% of responders had elevated levels of D-dimer, fibrinogen, ESR, CRP, and total IgE, respectively, as well as 54.8%, 26.2%, 35.7%, 54.8%, and 23.8% of non-responders, respectively.[37]

Montjoye et al., in a prospective study of 95 patients with CSU, found elevated CRP levels in anti-H1 non-responders ($p < 0.0001$) and in more severe diseases ($p = 0.033$). Plasma D-dimer levels were also higher in non-responders ($p = 0.008$) and in patients with concomitant autoimmune disease and/or with autoantibodies ($p = 0.016$). Blood basophil counts were lower in anti-H1 non-responders ($p = 0.023$) and in patients with more severe disease ($p = 0.023$), positive ASST ($p = 0.001$), and autoimmune disease ($p = 0.057$).[38]

Coagulation activation has been studied in the pathophysiology of CU. Tissue factor is expressed in the eosinophils present in the inflammatory infiltrate in urticaria, and thrombin is able to degranulate mast cells. Therefore, an increase in plasma levels of D-dimer, a marker of fibrinolysis, may be a potential biomarker of refractoriness to anti-H1.[37-39] Asero reported that D-dimer levels were elevated in 0 of 41 patients (0%) with an "excellent" response to cetirizine, 3 of 14 (21%) with a "good" response, 3 of 5 (60%) with a "partial" response, 18 of 23 (78%) with a "poor" response, and 7 of 8 (88%) non-responders.[39]

The role of ASST as a biomarker of anti-H1 refractoriness is still controversial. Although some studies have demonstrated this correlation,[36,40] others have not.[41] Ye et al. found that ASST can be a good marker of good response to treatment.[27] Chanprapaph et al. observed a correlation with the APST, but not with the ASST[30] (Figure 2).

Response to omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody indicated for the treatment of anti-H1-resistant CSU that has demonstrated good efficacy and safety in clinical trials and real-life studies.[1] Response to omalizumab can be classified by the time of occurrence as fast, slow, or absent after 6 months of treatment or by type as complete (UAS7: 0), good (UAS7: 1-6), partial (UAS7: 7-15), or absent (UAS7 > 16), as proposed by Arnau et al.[42] Furthermore, after discontinuing treatment, some patients experience relapse, which in the OPTIMA trial occurred in 50% of patients.[43] Determining biomarkers of initial response and relapse profiles is necessary in the discussion with patients about treatment indication and their expectations[44] (Figure 3).

Low serum total IgE levels have been associated with poorer response to omalizumab treatment. Straesser et al. evaluated serum IgE levels in patients with CSU divided into 4 quartiles. The odds ratio for response to omalizumab was 13.8 for patients 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] Marzano et al. reported similar data in a study of 470 patients in which responders had mean total IgE levels of 131.6 kUA/L and non-responders of 42.1 kUA/L ($p < 0.0001$).[46]

Baseline total IgE levels above 43.0 IU/mL that increased by 2-fold or more at week 4 of omalizumab treatment were correlated with improvement in CSU at week 12 of treatment.[47] Furthermore, baseline total IgE levels appear to correlate with time to CSU relapse after discontinuation of omalizumab treatment. Higher IgE levels were associated with shorter time to relapse of CSU symptoms after discontinuation of omalizumab.[48] Cugno et al. demonstrated that not only IgE but also baseline D-dimer levels were higher in responders than in non-responders to omalizumab in CSU.[49] Regarding D-dimer, this finding was not reported by Marzano et al.[46] Asero et al. evaluated D-dimer levels before and 3 weeks after omalizumab administration and found no difference between responders and non-responders in baseline D-dimer levels. However, responders showed a significant drop after the second dose, indicating that D-dimer may be a good marker of efficacy.[50] Other markers, such as a decrease in IL-31 and CRP levels and an increase in basophil levels, were also identified as markers of efficacy.[38,51] IL-31 is produced primarily by activated Th2 lymphocytes and skin mast cells and plays an important role in the induction of chronic skin inflammation, especially pruritus. Elevated levels were found in patients with CSU, but with no relationship to severity.[51]

Markers of type IIb autoimmunity, such as positive ASST, BHRA, and basophil activation test (BAT) and basopenia, have been associated with delayed or no response to omalizumab.[52]

ASST and BHRA are used in the diagnosis of autoimmune CU by assessing the presence of serum autoreactivity and autoantibody functionality, respectively. Positive ASST and BHRA have been associated with a slow response to omalizumab, but the evidence remains inconsistent. In the study by Gericke et al., an analysis of the profile of omalizumab responders showed that most BHRA-positive patients responded only after the second injection, with a median time to response of 29 days, whereas BHRA-negative patients had a median time to response of 2 days. Only 1 of 39 fast responders was BHRA-positive, whereas 8 of 17 slow responders were BHRA-positive ($p < 0.0001$). Regarding the ASST, 12 of 33 fast responders and 10 of 13 slow responders showed a positive ASST ($p < 0.012$).[53]

Another marker that has been the target of several studies is basophil FcεRI expression. Deza et al. described that basophil FcεRI expression levels before omalizumab treatment were significantly higher in responders than in non-responders. Also, after initiating omalizumab, there was a significant reduction of almost 90% in basophil FcεRI expression about 1 month after the first dose, with a lower reduction in non-responders than in responders, as well as speed response, which showed the same response profile.[54,55]

The expression of some receptors on the surface of basophils has been related to disease severity. Ye et al. showed that basophil CD203c expression was higher in patients with severe CSU, suggesting that the quantification of basophil activation and CD203c expression measured by flow cytometry may be used as a potential predictor of CSU severity.[29] Also investigated as a marker of response to omalizumab and disease activity, upregulation of CD203c was present in 18/41 individuals (43.9%), and omalizumab was effective in 29/41 patients with CU (71%). Of the 18 individuals demonstrating CD203c-upregulating activity, only 9 (50%) experienced clinical improvement with omalizumab. However, of the 23 without CD203c-upregulating activity, 20 (87%) had a satisfactory clinical response ($p = 0.02$). Therefore, having a negative result in the expression of these markers predicts a greater likelihood of responding to omalizumab.[56]

UAS7, a tool that assesses disease activity over 7 days, is used to assess disease severity in daily practice and in clinical studies, and also to assess response to treatment. A study evaluating UAS7 as a predictor of relapse after discontinuation of omalizumab demonstrated that patients with high baseline UAS7 and late response experienced rapid relapse[57] (Figure 3).

Response to cyclosporine

For non-responders to omalizumab, the recommended treatment is cyclosporine, an immunosuppressant that has a moderate effect on the inhibition of mediator release from mast cells. In contrast to other immunosuppressants with cytotoxic action, cyclosporine does not suppress the bone marrow and has no known risk of teratogenicity in humans. Its efficacy in combination with second-generation H1-antihistamines has been demonstrated in clinical trials, but it is used as third-line therapy due to a higher incidence of adverse effects, which, however, is lower than that with long-term use of corticosteroids.[10]

A systematic review showed strong evidence that positive BHRA and the presence of low total IgE levels are predictors of a good response to cyclosporine.[32] Grattan et al. conducted a randomized clinical trial that demonstrated a positive baseline BHRA in 72% of cyclosporine responders (*vs.* 11% of non-responders).[58] Two other studies showed that positive BHRA is a predictor of remission with cyclosporine treatment,[59,60] but ASST does not appear to be a good biomarker.[58]

Serum IgE levels were significantly lower in cyclosporine responders (43.0 IU/mL) than in non-responders (148.5 IU/mL) ($p < 0.001$), being negatively correlated with the decrease in UAS7 at 3 months of treatment.[61] Endo et al. showed that low baseline total IgE levels were associated with low UAS7 after cyclosporine treatment.[62]

Asero reported that D-dimer levels showed a highly significant negative correlation with response to cyclosporine ($p < 0.017$); with 10 of 11 (91%) patients with normal plasma D-dimer levels *vs.* 7 of 18 (39%) patients with elevated plasma D-dimer levels showing a completely successful response to treatment.[63]

It is clear that CU is a heterogeneous disease with different phenotypes, possible clinical characteristics, associated factors, and different clinical course, as well as different degrees of response to the

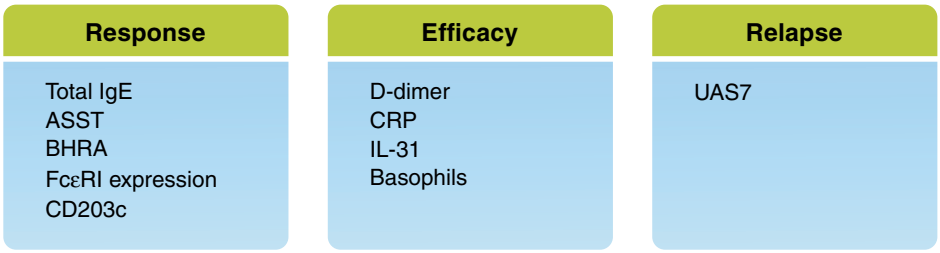

Figure 3
Biomarkers of response to omalizumab
ASST = autologous serum skin test, BHRA = basophil histamine release assay, FcεRI = high-affinity IgE receptor, CRP = C-reactive protein, IL-31 = interleukin 31, UAS7 = urticaria activity score 7.

treatments administered. It is particularly relevant to identify biomarkers able to classify patients according to their phenotype, possibly identifying underlying immunological mechanisms in order to stratify patients according to disease severity and prognosis and to identify the best responders to any therapy, especially to biological products. We highlight the importance of using accessible biomarkers in clinical practice, such as CRP, D-dimer, anti-TPO, total IgE, and UAS7. However, further prospective studies are needed to confirm these predictors and identify others.

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