Emerging Biomarkers and Therapeutic Pipelines for Chronic Spontaneous Urticaria

Gustavo Deza, MD[a,*], Peter A. Ricketti, MD[b,*], Ana M. Giménez-Arnau, MD, PhD[a,†], and Thomas B. Casale, MD[b,†]
Barcelona, Spain; and Tampa, Fla

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List of Design Committee Members: Gustavo Deza, MD, Peter A. Ricketti, MD, Ana M. Giménez-Arnau, MD, PhD, and Thomas B. Casale, MD (authors); Michael Schatz, MD, MS (editor)

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

[a]Department of Dermatology, Hospital del Mar- Institut Mar d'Investigacions Mèdiques, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
[b]Division of Allergy and Immunology, University of South Florida College of Medicine, Tampa, Fla
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Corresponding author: Ana M. Giménez-Arnau, MD, PhD, Department of Dermatology, Hospital del Mar- Institut Mar d'Investigacions Mèdiques, Universitat Autònoma de Barcelona (UAB), Passeig Marítim, 25-29, 08003 Barcelona, Spain. E-mail: anamariagimenezarnau@gmail.com or 22505aga@comb.cat.
*,† These authors contributed equally to this work.
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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. **(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