

Autoimmune chronic spontaneous urticaria



Pavel Kolkhir, MD,^{a,b,c,*} Melba Muñoz, MD, PhD,^{a,b,d,*} Riccardo Asero, MD,^e Marta Ferrer, MD, PhD,^f Emek Kocatürk, MD,^g Martin Metz, MD,^{a,b} Yi-Kui Xiang, MD,^{a,b} and Marcus Maurer, MD^{a,b}
Berlin, Germany; Moscow, Russia; Paderno Dugnano, Italy; Madrid, Spain; and Istanbul, Turkey

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: June 2022. Credit may be obtained for these courses until May 31, 2023.

Copyright Statement: Copyright © 2022-2023. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1.00 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Pavel Kolkhir, MD, Melba Muñoz, MD, PhD, Riccardo Asero, MD, Marta Ferrer, MD, PhD, Emek Kocatürk, MD, Martin Metz, MD, Yi-Kui Xiang, MD, and Marcus Maurer, MD (authors); Zuhair K. Ballas, MD (editor)

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: P. Kolkhir is or recently was a speaker for Novartis and Roche. M. Muñoz is or recently was a speaker and/or advisor for Innate Pharma and Genentech. R. Asero is or was recently a speaker and/

or advisor for Novartis, ALK, Allergy Therapeutics, HAL Allergy, Lofarma, Menarini, Malesci, Sanofi, and Thermo Fisher. M. Ferrer has received honoraria (advisory board, speaker) from Genentech, Menarini, Uriach, FAES, and MSD and has received a research grant from GlaxoSmithKline and Novartis, and advisory and speaker fees from Novartis. E. Kocatürk has received honoraria (advisory board, speaker) from Novartis, Sanofi, and Menarini. M. Metz has received honoraria (advisory board, speaker) from Amgen, ArgenX, Celldex, Moxie, Novartis, Roche, and Sanofi. Y.-K. Xiang declares no relevant conflict of interest. M. Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GlaxoSmithKline, GI Innovation, Gilead, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach. Z. K. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To distinguish clinical and laboratory findings that differentiate endotypes of chronic spontaneous urticaria (CSU).
2. To identify diagnostic criteria for type IIb autoimmune CSU.
3. To identify therapeutic agents for CSU, including new and emerging treatments.

Recognition of Commercial Support: This CME activity has not received external commercial support.

List of CME Exam Authors: Geoffrey Hall, DO, Nicole Koutlas, MD, Pooja Purswani, MD, Alex Wonnapharhown, MD, and Amy Stallings, MD

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The examination authors declare no relevant conflicts of interest.

Chronic spontaneous urticaria (CSU) is a debilitating mast cell-driven disease characterized by recurrent wheals and/or angioedema. Substantial progress has been made in dissecting the 2 main autoimmune mechanisms that drive the pathogenesis

of CSU. Type I autoimmune (autoallergic) CSU is associated with IgE antibodies against autoantigens, for example, thyroid peroxidase and IL-24. Type IIb autoimmune CSU is mediated by autoantibodies that activate mast cells, for example, via IgE

From ^athe Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, and Humboldt-Universität zu Berlin, Berlin; ^bFraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin; ^cI.M. Sechenov First Moscow State Medical University (Sechenov University), Division of Immune-Mediated Skin Diseases, Moscow; ^dClinician Scientist Program, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin; ^eAmbulatorio di Allergologia, Clinica san Carlo, Paderno Dugnano; ^fthe Department of Allergy and Clinical Immunology, Clínica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra Pamplona (IDISNA), Spain, RETIC de Asma, Reacciones Adversas y Alérgicas, Madrid (ARADYAL), Spain, Madrid; and ^gKoç University School of Medicine, Department of Dermatology, Istanbul.

*These authors contributed equally to this work.

Received for publication October 11, 2021; revised March 17, 2022; accepted for publication April 14, 2022.

Corresponding author: Marcus Maurer, MD, Charité – Universitätsmedizin Berlin, Institute of Allergology, Charitéplatz 1, 10117 Berlin, Germany. E-mail: marcus.maurer@charite.de.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2022 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2022.04.010>

and FcεRI, and is present in less than 10% of patients with CSU when strict criteria are used, that is, triple positivity of autologous serum skin test, immunoassays for IgG autoantibodies, and basophil activation tests. A subpopulation of patients with CSU has both types. Type IIb autoimmune CSU is characterized by higher disease severity, concomitant autoimmune diseases, low levels of total IgE, elevated levels of IgG-anti-thyroid peroxidase, basopenia, eosinopenia, poor response to antihistamines and to omalizumab, and a good response to cyclosporine. Novel targeted therapies for CSU are under development such as ligelizumab, an anti-IgE, fenebrutinib and remibrutinib, Bruton's tyrosine kinase inhibitors, and dupilumab, an anti-IL-4Rα. Further studies should investigate the overlap between autoallergic and type IIb autoimmune CSU, optimize the diagnosis of both autoimmune endotypes using easy-to-perform, noninvasive, and inexpensive markers, and assess differences in response to therapy. (J Allergy Clin Immunol 2022;149:1819-31.)

Key words: Chronic spontaneous urticaria, autoallergy, autoimmunity, type I, type IIb, BHRA, BAT, IgE, IgG-anti-TPO, treatment, markers

INTRODUCTION

Chronic spontaneous urticaria (CSU) manifests with the recurrent spontaneous appearance of wheals that each lasts for several hours, accompanied with intense itch, in most cases daily or almost daily for several years.¹ Most patients with CSU also develop angioedema, that is, intermittent localized and self-limiting swellings of the subcutaneous and/or submucosal tissue, which result, like wheals, from a temporary increase in vascular permeability. Up to 13% of patients with CSU exclusively experience angioedema and do not develop wheals.²

CSU is common and debilitating

About 1% of the population is affected with CSU, and this prevalence is increasing. CSU affects children and adults, with a marked female preponderance in the latter.³ CSU is associated with a substantial burden with significant impact on patients' quality of life and can be difficult to treat.⁴ Patients with CSU have reduced productivity as well as increased rates of psychological comorbidities.⁵⁻⁷ The recent Assessment of the economic and humanistic burden of chronic spontaneous/idiopathic urticaria patients (ASSURE-CSU) study demonstrated that more than 20% of patients with CSU miss more than or equal to 1 hour of work per week, and overall productivity impairment was 27%.⁴ In addition, significant health care resources and costs are incurred to treat patients with CSU. Therefore, CSU is associated with a high physical and economic burden not only for patients and their families and partners but also for health care systems. Thus, there is a high unmet need for novel and better treatment options for patients with CSU.

CSU is a mast cell-driven disease

The development of both the wheals and the angioedema in CSU is due to the activation of skin mast cells and release of mediators.¹ In addition to mast cells, the pathogenesis of CSU involves an inflammatory infiltrate with interplay of multiple

Abbreviations used

aiCSU:	Autoimmune chronic spontaneous urticaria
ASST:	Autologous serum skin test
BAT:	Basophil activation test
BHRA:	Basophil histamine release assay
c5a:	Complement 5a
c5aR:	Complement 5a receptor
CSU:	Chronic spontaneous urticaria
EP:	Eosinophil peroxidase
MRGPRX2:	Mas-related G protein-coupled receptor X2
sgAH:	Second-generation H1 antihistamine
TPO:	Thyroid peroxidase
TSLP:	Thymic stromal lymphopoietin

effector cells including T cells, basophils, and eosinophils.⁸⁻¹⁰ Many patients with CSU report exacerbation of their disease in response to triggers, such as stress, infections, foods, or the intake of nonsteroidal anti-inflammatory drugs. Although these triggers and the exacerbation of disease they induce, in many cases, are linked to increased skin mast cell activation, they are not held to be the underlying cause of CSU. Rather, they may be aggravators and disease modifiers or merely bystanders that cannot be reproduced by provocation in a controlled setting.^{1,11}

CSU is an autoimmune condition

At least 2 possible causes of CSU, 2 autoimmune endotypes, are recognized, with different types of autoantibodies that have been associated with the activation of skin mast cells.¹² These CSU endotypes have been named on the basis of Gell and Coombs classification of hypersensitivity reactions. Because type I hypersensitivity is characterized by the aberrant production of IgE antibodies, patients harboring IgE autoantibodies have been classified into the type I autoimmune endotype of CSU (type I aiCSU), also called autoallergic CSU. In contrast to classical type I hypersensitivity and allergy, which involve exogenous allergens, type I aiCSU is characterized by IgE antibodies directed to self-antigens (also called autoallergens).^{13,14} Similarly, type IIb hypersensitivity is characterized by an antibody-dependent process in which specific IgG antibodies bind to autoantigens to create pathogenic states. Therefore, patients with CSU who harbor IgG autoantibodies have been classified into the autoimmune type IIb endotype, different to type IIa that involves cytolytic destruction of targeted cells.^{12,15} An overlap between the 2 endotypes has been recently reported.¹⁶

Both of these CSU endotypes share the same phenotype, that is, the occurrence of itchy wheals, angioedema, or both, with the same mechanisms downstream of mast cell activation that lead to vasodilation, increased extravasation, activation of sensory skin nerves, and the recruitment of inflammatory cells. In this context, the released mast cell mediators exert their effects via receptors on skin-resident and recruited target cells.^{12,17} Type I aiCSU is thought to be more common than type IIb aiCSU.^{13,14,18} The 2 forms of CSU may differ in several important clinical and laboratory features, including response to treatment,^{12,13,19} though only 1 study performed simultaneous testing of both type I and IIb aiCSU so far to assess overlaps.¹⁶

Here, we review recently published findings that are relevant to our current understanding of autoimmunity as a cause of CSU.

Specifically, we discuss the pathogenesis, clinical features, and biomarkers of type I and type IIb aiCSU, we look at how patients with these types of CSU respond to treatment, and we present novel targeted treatments under development that can help to better understand both endotypes. Finally, we summarize what is already known about autoimmune urticaria and provide the most important gaps of knowledge.

TYPE I aiCSU (AUTOALLERGIC CSU)

In the last decade of last century, data emerged that pointed to a role of IgE autoantibodies in CSU.²⁰ This, together with other findings,¹⁴ led to the first randomized controlled CSU trial of omalizumab, an anti-IgE antibody, in patients with CSU with IgE autoantibodies to thyroid peroxidase (TPO), a common CSU autoallergen (the Xolair in chronic urticaria induced by serum IgE targeting endoallergens [X-CUISITE] study¹⁹). Treatment of these patients with omalizumab resulted in a fast response and a high rate of complete response, 70%, higher than in any of several subsequent studies of omalizumab in CSU. Together with further research on the prevalence, role, relevance, and targets of IgE autoantibodies in patients with CSU, the results of X-CUISITE and other omalizumab studies in CSU established the type I autoimmune CSU (type I aiCSU) endotype of CSU or autoallergic CSU.^{12-14,19}

Prevalence and pathogenesis of autoallergic CSU

In 1999, the presence of IgE autoantibodies against TPO in a patient with CSU suggested autoallergy as a relevant mechanism.²⁰ On the basis of receiver operating characteristic curve and mixed distribution analyses, Altrichter et al¹⁴ later reported elevated IgE-anti-TPO levels in 54% (259) and 61% (191) of 478 patients with CSU, respectively.¹⁴ Most other studies confirmed the presence of IgE-anti-TPO in a subpopulation of patients with CSU, albeit mostly at lower rates (0%-34%, $\geq 10\%$ in most studies,²¹ reviewed in Kolkhir et al¹²). In addition, several,^{12,21} but not all,²² studies reported significantly higher prevalence of IgE-anti-TPO in patients with CSU versus patients with autoimmune thyroid disease (0%-70%^{21,23,24}) and/or healthy controls (0%-8%^{12,21,25}). Patients with CSU with levels of IgE-anti-TPO comparable to those in healthy controls might have IgE antibodies to other autoantigens, other autoantibody types, for example, IgG, both, or have nonautoimmune CSU, which request further investigation.

Recently, Sánchez et al²¹ showed higher rates of itchy wheal-and-flare skin reactions to skin prick tested or intradermally injected TPO in patients with CSU versus patients with autoimmune thyroid disease and healthy controls.²¹ Patients with CSU with elevated IgE-anti-TPO showed significantly higher rates of positive test results than did patients with CSU with low IgE-anti-TPO. Furthermore, positive skin prick test reactions and intracutaneous test reactions to TPO were observed after passive transfer of IgE-anti-TPO from a patient with CSU to the skin of control subjects without IgE-anti-TPO.²¹ However, this evidence should be considered with caution because the presence of specific IgE to allergens was described in people without signs of clinical disease.

Very recently, IgE autoantibodies against eosinophil peroxidase (EP) and eosinophilic cationic protein were reported in CSU by Sánchez et al.²⁶ TPO inhibited 42% of IgE binding

to EP, whereas EP inhibited 59% of IgE binding to TPO, suggesting cross-reactivity between these peroxidase proteins. Cross-reactivity between TPO, which is not present in the skin, and EP might contribute to skin mast cell activation in patients with CSU, which is known to be associated with eosinophil recruitment to skin lesions.²⁶

In addition to IgE-anti-TPO and IgE-anti-EP, patients with CSU were reported to have IgE against double-stranded DNA,²⁷ IL-24 (80%),¹³ tissue factor (60%),^{16,28} eosinophil cationic protein (5%),²⁶ FcεRI,¹⁶ and thyroglobulin (87%),²⁸ and the functional relevance of IgE to some of them such as IL-24,¹³ double-stranded DNA,²⁷ and TPO^{21,29} was confirmed in *in vitro* studies. In total, patients with CSU have IgE to more than 200 autoantigens, which is more prevalent and different than seen in healthy controls.¹³ However, this point should be confirmed by further studies because some authors reported the presence of IgE autoantibodies such as IgE-anti-IL-24 in healthy controls.³⁰

Recently, IL-24 mRNA expression was reported to be increased in lesional skin of patients with CSU as compared with nonlesional skin and skin from healthy controls.³¹ Expression of autoantigens only in the skin might explain why IgE autoantibodies and their autoallergens, in patients with CSU, interact primarily in the skin and cause skin mast cell activation rather than activation of mast cells in other organs. However, there is still no other evidence of local autoallergen release at sites of wheals, and further studies are needed to investigate this.

Demographic, clinical, and laboratory features of autoallergic CSU

Little is known about the demographic, clinical, and laboratory features of patients with autoallergic CSU. Recent studies have demonstrated significantly higher total IgE levels^{29,32} and higher rate of comorbid allergic diseases³² in patients with CSU who exhibit IgE-anti-TPO compared with those without. In another study, total IgE levels did not differ significantly in sera from 7 patients with CSU and 7 healthy individuals, but the autoreactive proportion of IgE of patients with CSU was 1000-fold higher than that of healthy individuals and was of the lipophilic nature.³³ Interestingly, a recent machine-learning-based analysis of chronic urticaria subtypes, where patients were assigned to 4 clusters on the basis of their clinical and laboratory features, showed that, on average, the highest total IgE levels clustered together with the highest rate of comorbid atopic dermatitis, the lowest rate of ANA, and IgG-anti-TPO positivity.³⁴ One study showed that serum levels of IgE-anti-IL-24 correlated with CSU disease activity and basopenia.¹³

As mentioned before, patients with CSU with increased IgE-anti-TPO³² can be expected to show a fast and good response to omalizumab.¹⁹ Furthermore, in patients with severe CSU, decrease in IgE-anti-tissue factor and IgE-antithyroglobulin was induced by omalizumab treatment and paralleled the clinical response to the drug.²⁸ A recently published study including a total of 1100 Chinese Han adult patients with CSU demonstrated that IgE-anti-TPO is an independent predictor of antihistamine-refractory CSU.²⁵

Diagnosis of type I aiCSU

Diagnosing patients with type I autoimmune/autoallergic CSU requires testing for IgE autoantibodies. As of now, there are no

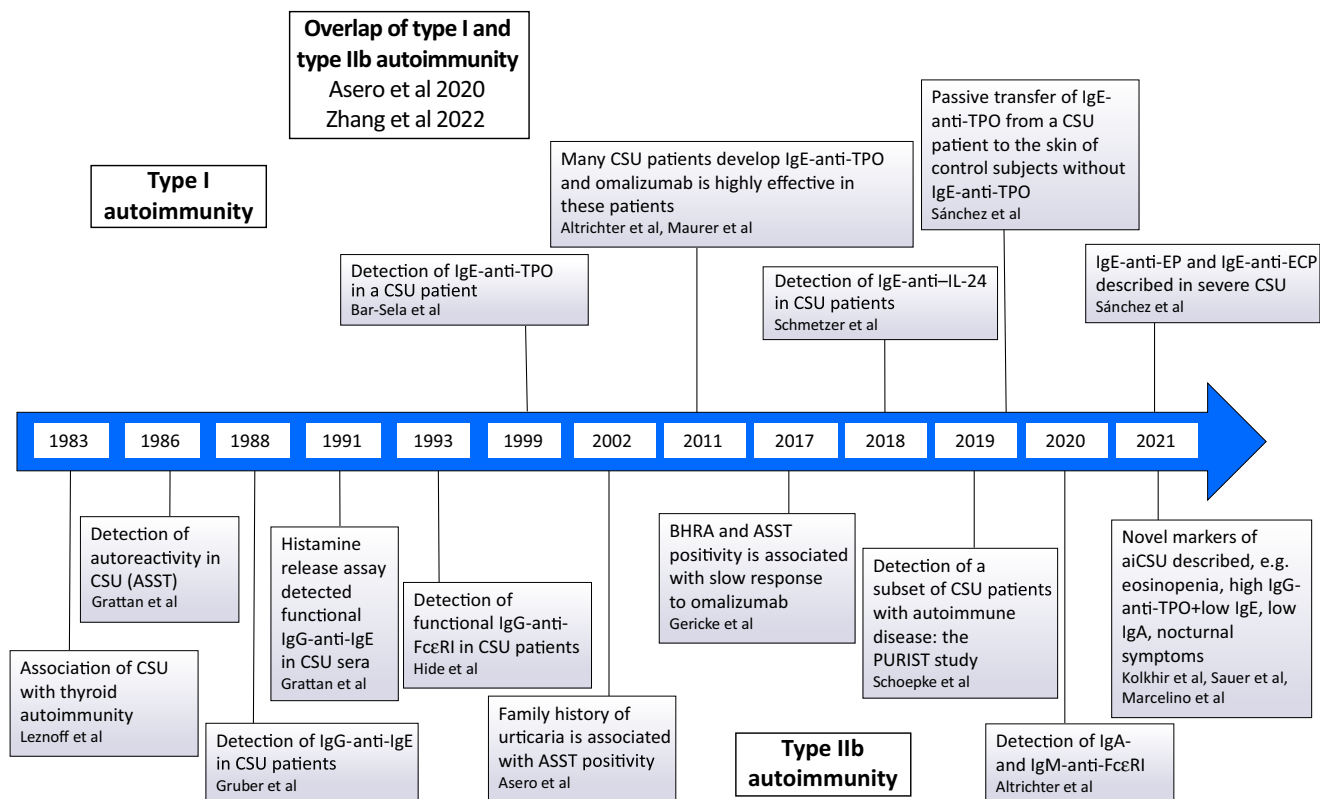


FIG 1. Timeline of advances in the research on aiCSU (data from references 13, 14, 16, 18-21, 25, 26, 38-42, 45-49, 51, 57, 59, and 138). EC, Eosinophil cationic protein; EP, eosinophil peroxidase.

standardized or commercially available tests for IgE autoantibodies. Tests for IgE autoantibodies such as IgE-anti-TPO or IgE-anti-IL-24 are established and used at some Urticaria Centers of Reference and Excellence,³⁵ but not in routine clinical practice.

The differences between the results of studies on IgE-anti-TPO in CSU are probably, at least in part, due to differences in methods used (eg, direct ELISA vs capture ELISA). Many patients with CSU with IgE-anti-TPO also have IgG-anti-TPO, which can interfere with the detection of the former and affect the rates of IgE-anti-TPO-positive patients detected with different assays and in different patient populations.^{12,36,37}

In addition to the urgent need to develop standardized and widely available tests of IgE autoantibodies that are relevant for CSU, the full spectrum of autoantigens to which patients with CSU have IgE autoantibodies needs to be characterized. IgE autoantibodies to individual autoallergens need to be investigated for their prevalence, cross-reactivity, relevance, and function including their ability to form functional circulating immune complexes. It is still unclear how the different IgE autoantibodies drive a common pathogenesis. In addition, the cellular and molecular mechanisms that underlie and drive the generation of autoreactive IgE need further investigation.

TYPE IIb aiCSU

A role of mast cell-targeted and activating IgG autoantibodies to IgE or to its high-affinity receptor FcεRI in the pathogenesis of CSU has been known for more than 30 years (Fig 1).^{38,39} It was first reported in 1988 that patients with CSU can have

histamine-releasing IgG autoantibodies against IgE,⁴⁰ and this observation was followed by the demonstration of wheal formation at the site of an intracutaneous autologous sera injection, now known as the autologous serum skin test (ASST), in a subgroup of patients with CSU.⁴¹ Subsequently, a single serum fraction (>100 kDa) capable of inducing both a positive ASST result and positive histamine release assay was identified.³⁸ Lastly, IgG-anti-FcεRI autoantibodies were shown to be an important mast cell-activating serum factor in CSU.³⁹

Today, CSU in patients who have these autoantibodies is called type IIb aiCSU. Type IIb aiCSU remained ill characterized for many years. The reasons for this include, but are not limited to, the sparse availability of immunoassays for IgG-anti-IgE and IgG-anti-FcεRI and the fact that not all IgG-anti-IgE and IgG-anti-FcεRI are functional, that is, activate mast cells and cause the release of mediators.^{42,43}

Recently, the international Profiling urticaria for the identification of subtypes (PURIST) study¹⁸ was the first to assess, in a sizable patient population with CSU, the 3 defining features of type IIb aiCSU, that is, the presence of a positive ASST result, a positive immunoassay for IgG-anti-FcεRI or IgG-anti-IgE, and a positive basophil test result (the basophil activation test, BAT, and/or basophil histamine release assay, BHRA).⁴⁴ The results of the PURIST study showed that less than 10% of patients with CSU have type IIb aiCSU and that these patients tend to have more severe disease, low levels of total IgE, and high levels of thyroid peroxidase autoantibodies.¹⁸ Other relevant recent studies showed that IgM and/or IgA autoantibodies against FcεRI might contribute to the pathogenesis of type IIb aiCSU.⁴⁵ In the last

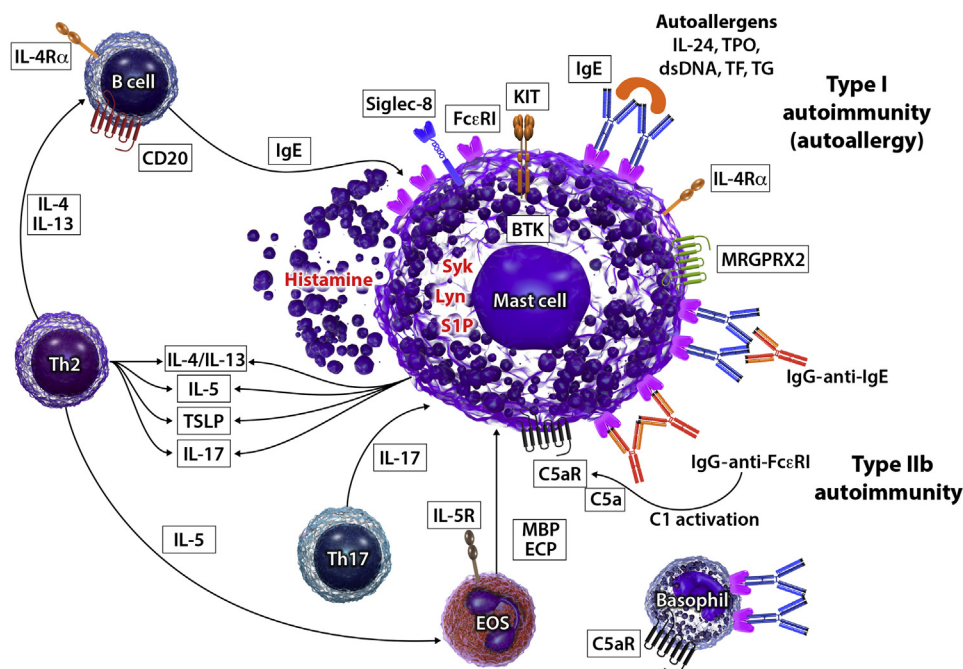


FIG 2. Pathogenesis and endotypes of CSU and possible targets for therapy. Mast cells are activated by IgE autoantibodies to autoallergens (type I autoallergy) or IgG-anti-IgE/IgG-anti-FcεRI autoantibodies (type IIb autoimmunity). Complement is activated by the binding of IgG-anti-FcεRI to FcεRI on mast cells and basophils, leading to histamine release via C5aR. Th2 cytokines such as IL-4, IL-5, and IL-13 are responsible for stimulating IgE production and the activation of mast cells, basophils, and eosinophils. Some of the current and future molecular targets for CSU treatment are framed such as IgE, IL-4Rα, Siglec-8, C5aR, KIT, MRGPRX2, CD20, IL-5R, TSLP, IL-17, IL-5, and BTK. *Btk*, Bruton tyrosin kinase; *ECP*, eosinophil cationic protein; *MBP*, major basic protein; *TF*, tissue factor; *TG*, thyroglobulin.

decade, several additional markers of type IIb aiCSU have emerged including nocturnal symptoms,⁴⁶ eosinopenia,⁴⁷ and low levels of total IgA.⁴⁸ In addition, recent advances in the characterization of type IIb aiCSU include its poor and/or slow response to conventional treatment with antihistamines and omalizumab.^{47,49-51}

Prevalence and pathogenesis of type IIb aiCSU

Type IIb aiCSU, by definition, is due to mast cell–targeted and activating autoantibodies (Fig 2). As of now, patients with CSU display IgG, IgA, and/or IgM autoantibodies to IgE or its high-affinity receptor FcεRI (also IgE-anti-FcεRI¹⁶), at different rates.^{16,44,45} Whether or not patients with CSU can have mast cell–activating autoantibodies directed at activating receptors other than FcεRI, for example, Mas-related G protein–coupled receptor X2 (MRGPRX2) or complement 5a receptor (C5aR), is currently unknown. IgG-anti-FcεRI and/or IgG-anti-IgE were reported in 0% to 69% of patients with CSU, with most studies reporting rates of more than 20% and less than 50% (reviewed in Kolikhir et al¹²). For example, in a recent study, 24%, 60%, and 57% of patients with CSU had elevated serum levels of IgG-, IgM-, and IgA-anti-FcεRI, respectively.⁴⁵ Twenty-six percent of patients with CSU had both IgG-anti-FcεRI and a positive BHRA result. Similarly, 25% and 32% of patients with CSU had a positive ASST result in combination with BHRA positivity and BHRA positivity only, respectively.⁴⁴ Although these rates are higher as compared with less than 10% in the PURIST study, definition of type IIb aiCSU in these older studies was based on 1 to 2

markers only as compared with the PURIST study (all 3 markers, ie, ASST, basophil tests, and IgG autoantibodies immunoassay). However, the strict criteria for type IIb aiCSU used in the PURIST study do not imply that the rest of the patients with just 1 positive biomarker or 2 cannot have a type IIb response.

In vitro studies with basophils and mast cells have shown that IgG autoantibodies to FcεRI or IgE from patients with CSU have been associated with their activation and release of bioactive mediators.^{39,43,52} However, 15% of patients with CSU were found to have immunoreactive anti-FcεRI autoantibodies without histamine-releasing activity.⁴³ Mast cell activation was seen only with complement-fixing IgG 1 and 3 subclasses of antibodies and to a lesser degree IgG 4 but not IgG 2.⁵³ Also, IgG autoantibodies to FcεRI and/or IgE were present in healthy control subjects and patients with diseases other than CSU.^{54,55} It is still not clear what makes these autoantibodies pathogenic in CSU. This might be linked to the low levels of IgE seen in the sera of patients with type IIb aiCSU. The reduction in serum IgE can lead to the decreased occupancy of FcεRI by IgE, and the natural anti-FcεRI autoantibodies might become pathogenic.⁵⁶

Demographic, clinical, and laboratory features of type IIb aiCSU

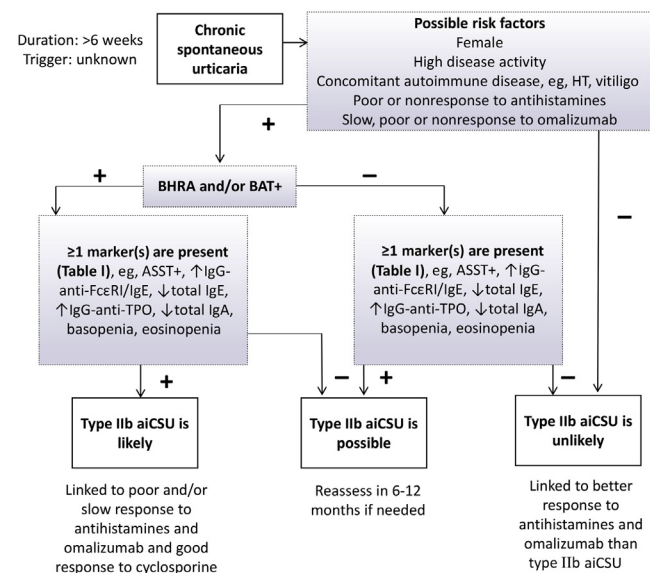
A typical patient with type IIb aiCSU is an adult female with high disease activity and concomitant autoimmune disease(s), predominantly autoimmune thyroiditis and/or vitiligo, and a family history of autoimmune disorders^{18,57} (Table I). In addition to the PURIST study, several other studies showed an association

TABLE I. Emerging demographic, clinical, and laboratory markers of type IIb aiCSU

Markers	Results	% of patients with type IIb aiCSU	How type IIb aiCSU was diagnosed	First author ^{reference}
Sex	High female rates	87%-93%	Triple positivity* or high IgG-anti-TPO plus low IgE	Kolkhir, ⁵¹ Schoepke ¹⁸
Autoimmune diseases	Present, higher risk	Mostly HT (60%) and vitiligo (7%)	Triple positivity	Kolkhir, ⁵⁷ Schoepke ¹⁸
Angioedema	Present	62%-76%	High IgG-anti-TPO plus low IgE or BAT/BHRA positivity	Kolkhir, ⁵¹ Marcelino ⁴⁶
Nocturnal symptoms	Present	70%-79%	BAT/BHRA positivity	Marcelino ⁴⁶
Symptoms for >5 d/wk	Present	92%	BAT/BHRA positivity	Marcelino ⁴⁶
Disease activity (UAS7)	High (median, 21)	—	Triple positivity or BAT/BHRA positivity	Schoepke, ¹⁸ Ye, ¹²⁴ Curto-Barredo, ¹²⁵ Marcelino ⁴⁶
Quality of life (DLQI)	Low (mean, 9-10)	—	BAT/BHRA positivity	Marcelino ⁴⁶
Total IgE	Low (<40 IU/mL or <30 IU/mL)	69%-86% or 38%-41%	Triple positivity or BAT/BHRA positivity	Kolkhir, ⁵¹ Schoepke, ¹⁸ Sauer, ⁴⁸ Marcelino ⁴⁶
IgG-anti-TPO	High (≥34 kU/L)	39%-62%	Triple positivity or BAT/BHRA positivity	Kolkhir, ⁵¹ Schoepke, ¹⁸ Marcelino ⁴⁶
IgA	Low (<1.84 g/L or <0.7 g/L)	73.5% or 9.6%	BAT positivity	Sauer ⁴⁸
Blood basophil counts	Low (<0.01 × 10 ⁹ /L)	30%	Triple positivity or BHRA positivity	Kolkhir, ⁴⁷ Schoepke ¹⁸
Blood eosinophil counts	Low (<0.05 × 10 ⁹ /L)	24%	BHRA positivity	Kolkhir ⁴⁷
Disease control (UCT)	Low (mean, 7.7-7.8)	—	BAT/BHRA positivity	Marcelino ⁴⁶
Response to sgAHs	Poor response	87%	BAT positivity	Irinyi ¹²⁶
Response to omalizumab	Slow, poor, and/or nonresponse	50%	BHRA or BAT positivity	Gericke, ⁴⁹ Palacios, ¹²⁷ Ghazanfar, ¹²⁸ Endo ¹²⁹

DLQI, Dermatology Life Quality Index; HT, Hashimoto's thyroiditis; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

*Positive result as of ASST + BAT/BHRA + immunoassay for IgG-anti-FcεRI/IgE.

**FIG 3.** Algorithm for diagnosis of type IIb aiCSU. HT, Hashimoto's thyroiditis.

between type IIb autoimmunity (assessed by CD63/203c and/or BHRA positivity) and higher disease activity (Table I). The presence of IgG-anti-TPO, a marker for autoimmune thyroid disease and type IIb aiCSU, was associated with higher CSU recurrence after disease remission.⁵⁸ Ninety-six percent of patients with urticaria with first-degree relatives who also had urticaria exhibited a positive ASST result, and were mostly females.⁵⁹ The observed high prevalence of aiCSU among female patients is also supported by an older study showing the association between female sex, positive ASST result, and thyroid autoimmunity.⁶⁰

Recently, the Component-resolved screening for autoimmune chronic spontaneous urticaria (CORSAs) study revealed several additional markers of type IIb aiCSU including angioedema, nocturnal symptoms, and symptoms for more than 5 days/wk.⁴⁶

Other emerging surrogate markers of type IIb aiCSU are low levels of total IgE and IgA,⁴⁸ basopenia, eosinopenia,⁴⁷ and a poor response to conventional treatment^{61,62} (discussed in the next sections). Interestingly, in 1 study, elevated levels of IgM-anti-FcεRI but not IgG- or IgA-anti-FcεRI (IgE-anti-FcεRI were not measured) were linked to low blood basophil and eosinophil counts.⁴⁵

Diagnosis of type IIb aiCSU

Since 2013, the “criterion standard” for the diagnosis of type IIb aiCSU is a positive ASST result, together with a positive result of a functional bioassay, that is, basophil test (BHRA and BAT), and demonstration of IgG-anti-FcεRI, IgG-anti-IgE, or both by an immunoassay.⁴⁴ Immunoassays for IgG/IgM/IgA-anti-FcεRI/IgE autoantibodies are not usually available for routine clinical practice.¹⁸ Basophil tests are considered the best single tests for diagnosing type IIb aiCSU and showed better correlation with other markers of type IIb aiCSU and response to treatment than the ASST or immunoassays for autoantibodies (Fig 3).^{18,46,51} For example, patients with CSU with type IIb aiCSU and patients with CSU with a positive basophil test result both had markedly lower levels of total IgE, higher levels of IgG-anti-TPO, or both, as compared with patients with CSU with a positive ASST result or IgG-anti-FcεRI/IgE autoantibodies only.^{18,51}

The ASST is a poor predictor of a positive basophil test result,^{46,63} and ASST positivity had low predictive values (27%) for type IIb aiCSU against non-type IIb aiCSU in the PURIST study.¹⁸ A recent review of studies on the ASST concluded that

all BHRA-positive patients scored positive on ASST, whereas most ASST-positive patients with CSU did not demonstrate functionally active circulating histamine-releasing autoantibodies.⁶⁴ Indeed, virtually all (91%) of BAT/BHRA-positive patients were also ASST-positive in the PURIST study, whereas only 39% of ASST-positive patients were also positive for basophil tests.¹⁸ This suggests that autoreactivity shown by positive ASST in some patients may be linked to circulating histamine-releasing serum factors other than autoantibodies, for example, coagulation factors or MRGPRX2 agonists. Recently, coagulation factors were demonstrated to induce mediator release from human skin mast cells and basophils via production of complement 5a (C5a) acting on the C5aR.⁶⁵ Furthermore, in patients with CSU, a positive ASST result was linked to elevated levels of IgM against FcεRIα, but not IgG-anti-FcεRI or IgA-anti-FcεRI.⁴⁵ This might explain the low predictive values of ASST in the PURIST study, where IgG autoantibodies but not IgM autoantibodies were measured and a large discrepancy between positive ASST result and sera positive for IgG-anti-FcεRI/IgE detected by ELISA was seen.¹⁸

Healthy individuals (17%-55%) and patients with other allergic and nonallergic diseases can also show ASST positivity.⁶⁶ The use of the ASST is also limited by possible false-positive results due to concomitant symptomatic dermographism or formation of vasoactive mediators during serum preparation. However, the ASST appears to be a good screening test for type IIb aiCSU when combined with other clinical and laboratory markers. For example, the probability of a positive BAT or BHRA result was 86.4%, 90.0%, and 100% if ASST positivity was used in combination with the presence of angioedema, increased levels of thyroid autoantibodies, and low total IgE levels, respectively.⁴⁶ This may be useful in everyday clinical practice to select patients for basophil testing. However, ASST had a high negative predictive value, ranging from 59% to 100%, for different positivity criteria. Therefore, a negative ASST result was recommended as a reliable clinical tool to exclude the presence of functional circulating autoantibodies detectable by BHRA.⁶³

Although Hashimoto's thyroiditis is frequently associated with type IIb aiCSU,^{18,57} thyroid autoimmunity is very common among other CSU subsets as well.⁶⁷ Thus, the detection of IgG-anti-TPO antibodies alone is not sufficiently specific to diagnose patients with type IIb aiCSU.⁵¹ A useful diagnostic marker for type IIb aiCSU that can be used in clinical practice is, however, the combination of high IgG-anti-TPO and low total IgE levels (Table 1). This combination has been shown to be associated with positive ASST result, positive BAT result, and other markers of type IIb aiCSU.^{18,46,51,68} A patient with CSU with elevated IgG-anti-TPO and low total IgE has a more than 3 times higher risk of having a positive BAT result as compared with one without.⁵¹ The most current revision and update of the international EAACI/GA²LEN/EuroGuiDerm/APAAACI urticaria guideline recommends assessing patients with CSU for total IgE and IgG-anti-TPO.¹ Importantly, total IgE levels should be assessed before starting the treatment with omalizumab.

OVERLAP OF TYPE I AND TYPE IIb aiCSU

It is likely that not all patients with CSU can be strictly allocated either to an autoallergic or to a type IIb autoimmune endotype on the basis of presence of IgE or IgG/IgM/IgA autoantibodies directed to self-antigens, respectively. The real

overlap rates are still unknown because the PURIST, CORSA, and some other studies of type IIb aiCSU did not exclude patients with type I aiCSU and did not assess the coexpression of IgE and other types of autoantibodies in the same patients.

A recent report by Asero et al¹⁶ tested the co-occurrence of IgE and IgG autoantibodies to high- and low-affinity IgE receptors (FcεRI and FcεRII), tissue factor, and thyroglobulin. More than 50% of patients had IgE and IgG to 1 or more of these autoantigens, and 25% of patients had levels of IgE-anti-FcεRI.¹⁶ Also, markers of type IIb aiCSU, for example, basophil tests, and markers of autoallergic CSU, for example, IgE-anti-IL-24, have been shown to correlate with disease activity and basopenia,^{13,18} and IgE-anti-TPO and IgG-anti-TPO, in several studies, have been reported to be coexpressed by patients with CSU.^{14,22,25,48} The correlation between IgG and IgE autoantibodies was seen in other autoimmune diseases, for example, systemic lupus erythematosus.⁶⁹ In some studies,¹⁴ no correlation between total IgE and IgE-anti-TPO was seen, suggesting that some patients with low total IgE, a marker for type IIb CSU, might also have IgE autoantibodies. Moreover, in recent studies, patients with elevated IgE-anti-TPO levels had significantly lower IgA and/or IgE levels.^{25,48} Finally, late responders to omalizumab showed higher levels of both anti-tissue factor IgE and IgG than early responders.¹⁶

Further studies should explore the rate and relevance of coexistence of autoallergic and autoimmune drivers of CSU and the possibility that secondary autoimmune mechanisms may develop in some patients with autoallergic CSU and vice versa, that is, that IgE autoantibodies appear first followed by IgG, IgM, and/or IgA autoantibodies over the course of the disease. Overlap of IgE and IgG class autoantibodies must be expected to have an impact on the efficacy of currently available and future treatment options.

THE TREATMENT OF PATIENTS WITH aiCSU

In the next 2 sections, we review the treatment options that already exist and novel treatments that are under development⁷⁰ and how patients with type I and type IIb aiCSU can be expected to differ in their response.

Available treatments

Treatment of patients with CSU adopts a step-wise approach that targets mast cell mediators, for example, histamine or the mast cell itself.^{70,71} The first steps of standard treatment involve second-generation H1-antihistamines (sgAHs) followed by dose escalation up to 4-fold of the same sgAH in case of no or partial response. In antihistamine-refractory cases, omalizumab—a humanized IgG-type anti-IgE antibody—is the recommended treatment option.¹ Despite omalizumab's high efficacy, a significant proportion of patients require third-line treatment, which, at present, is limited to cyclosporine, an immunosuppressant that interferes with signal transduction and activation of mast cells, T cells, and basophils.⁷²

Although histamine is the major mediator released on mast cell activation and H1 antihistamines constitute the basis for urticaria treatment, a recent meta-analysis showed a response rate of only 38.6% at standard doses.⁷³ Type IIb aiCSU has been suggested to be more refractory to antihistamines,^{46,47,62} and several clinical and laboratory markers of type IIb aiCSU are linked to poor

TABLE II. Emerging autoimmunity-related markers of response to treatments in patients with CSU

Markers	Results	Response to treatment*		
		H ₁ antihistamines	Omalizumab	Cyclosporine
Sex	Female	Not a good marker ⁸⁶	Not a good marker ⁸⁶	Not a good marker ⁸⁶
Disease activity (UAS7)	↑	Poor ⁸⁶	Inconsistent evidence ⁸⁶	Probably good ^{130,131}
BHRA and/or BAT	+	Poor ¹²⁶	Poor, ¹²⁹ slow ⁴⁹	Good ^{85,86}
ASST	+	Inconsistent evidence ⁸⁶	Inconsistent evidence, ⁸⁶ slow ⁴⁹	Inconsistent evidence ⁸⁶
Eosinopenia	+	Poor ⁴⁷	Poor ⁴⁷	Unclear ¹³²
Basopenia	+	Poor ⁴⁷	Poor ^{47,133}	Unclear ¹³⁰
ANA	+	Inconsistent evidence, ⁸⁶ probably poor response to updosings ¹³⁴	Poor ^{57,135}	Inconsistent evidence ⁸⁶
IgG-anti-TPO	↑	Inconsistent evidence, ⁸⁶ probably poor ²⁵	Probably poor ⁵⁷	Probably not a good marker ⁸⁶
IgG-anti-TG	↑	Probably poor ²⁵	—	—
IgE-anti-TPO	↑	Probably poor ²⁵	—	—
Total IgE	↓	Inconsistent evidence, ⁸⁶ probably poor ²⁵	Poor ⁸⁶	Good ^{85,86}
IgG anti-TPO + total IgE	↑ + ↓	Poor ⁵¹	—	—
Ratio of IgG-anti-TPO to total IgE	↑	Poor ⁵¹	Poor ⁷⁹	—
Ratio of w4IgE/bIgE	↓	—	Poor ⁵⁰	—
C-reactive protein	↑	Poor ⁸⁶	Inconsistent evidence ⁸⁶	Unclear ¹³¹
D-dimer	↑	Poor ⁸⁶	Unclear ^{86,136}	Unclear ¹³⁷

↑, High/elevated; +, positive/present; ↓, low/decreased; —, no evidence; ANA, antinuclear antibody; bIgE, baseline levels of total IgE; TG, thyroglobulin; UAS7, Urticaria Activity Score over 7 days; w4IgE, levels of total IgE 4 wk after treatment with omalizumab.

*Based on the results of systematic reviews and meta-analyses where available, otherwise on the findings of key original studies.

response to sgAHs including high disease activity, positive BHRA and/or BAT result, eosinopenia, basopenia, low total IgE, and elevated IgG-anti-TPO levels (Table II). In particular, only 30% of patients with both elevated IgG-anti-TPO and low total IgE levels responded to sgAHs.⁵¹ Low blood basophil counts were associated with nonresponse to antihistamines and a positive ASST result.^{47,74}

Omalizumab inhibits the interaction between IgE and its high-affinity receptor FcεRI and thereby prevents mast cell and basophil activation, and it also blocks IgE binding to its low-affinity receptor (CD23) on B cells and antigen-presenting cells.⁷⁵ Omalizumab can also dissociate prebound IgE from mast cells and basophils, resulting in a reduction of proximal signaling events and decrease in mast cell mediator release.⁷⁶

In patients with IgE autoantibodies against autoallergens such as TPO and double-stranded DNA, the inhibition of IgE binding to FcεRI by omalizumab and the downregulation of FcεRI would represent a central mechanism of action. In addition, accumulation of omalizumab-IgE immune complexes might sequester endogenous autoantigens that potentially react with IgE.⁷⁷ In a randomized controlled trial, 70% patients with antihistamine-resistant CSU and IgE-anti-TPO showed complete protection from wheal development versus 4.5% patients in the placebo group.¹⁹

In subjects with IgG autoantibodies against IgE or FcεRI, the efficacy of omalizumab is probably linked to the downregulation of FcεRI on mast cells and basophils as a result of reduced IgE.⁷⁸ Poor response and/or nonresponse to omalizumab was associated with BHRA/BAT positivity, low total IgE levels,⁶⁷ high IgG-anti-TPO, their combination and ratio as well as eosinopenia and basopenia, all of which are markers of type IIb aiCSU (Table II). In particular, Chen et al⁷⁹ reported a higher median ratio of IgG-anti-TPO to IgE, a marker for type aiCSU, in omalizumab nonresponders as compared with responders.

In the clinical setting, omalizumab shows 2 response patterns: early responders (often in week 1, always before week 4) and late responders who show delayed onset of response after week 4 and up to week 24.⁸⁰ The rapid reduction of free IgE by omalizumab in patients with autoallergic CSU may lead to a rapid depletion of

IgE autoantibodies, thus a rapid response to treatment, which supports that these IgE autoantibodies play a role in the pathogenesis of CSU.⁸¹ Late response can be explained by receptor downregulation on skin mast cells, which is a slow continuous process.⁸² These late responders were associated with a higher incidence of BHRA positivity, and BHRA-positive patients responded with a median time of response of 29 days, whereas BHRA-negative patients had a median time of response of only 2 days.⁴⁹ Similarly, Nettis et al⁸³ identified a significant association between ASST positivity and slower response to omalizumab in patients with CSU.

Cyclosporine is an immunosuppressive agent that showed overall response rates of 54% to 73%, with 6% to 57% of patients experiencing 1 or more adverse event on very low to moderate doses.⁸⁴ As of yet, low total IgE and positive basophil test results are considered to be the best markers linked to good response to cyclosporine in CSU (Table II).^{85,86} This is in line with the notion that type IIb aiCSU responds better to cyclosporine than non-type IIb aiCSU. In fact, ASST and basophil test results became negative after cyclosporine treatment, in line with the clinical response.^{87,88} These effects of cyclosporine can be explained by an inhibition of histamine release from human skin mast cells, basophils,⁷² and leukocytes preincubated with cyclosporine after stimulation with sera and purified IgG from these sera from patients with CSU.⁸⁹ Furthermore, cyclosporine can inhibit T-cell and B-cell proliferation,⁹⁰ which might downregulate the activators of mast cells in patients with type IIb aiCSU, that is, the IgG autoantibodies. In contrast to omalizumab, treatment with cyclosporine in patients with features of type IIb aiCSU, for example, low total IgE, ASST positivity, and/or antithyroid antibodies, might be associated with longer remission after drug tapering/withdrawal.^{91,92} Further studies should evaluate this and whether markers of poor response to antihistamines and/or omalizumab such as a high baseline urticaria activity score over 7 days and a combination of elevated IgG-anti-TPO and low total IgE can also predict good response to cyclosporine treatment.

Case reports of patients with antihistamine-resistant CSU and positive markers for autoimmunity, for example, positive ASST

and/or basophil test results, suggested efficacy of plasmapheresis, rituximab (anti-CD20), IVIG, methotrexate, cyclophosphamide,⁹³ and mycophenolate mofetil (reviewed in Holm et al⁹⁴ and Combalia et al⁹⁵).

Novel treatments under development

Most novel therapies under development are expected to work for both endotypes, type I and type IIb, although some can be expected to work better in one than the other. Furthermore, these novel treatments, with their different modes of action, can help to understand known endotypes and possibly help to identify additional ones.

Ligelizumab is a promising humanized monoclonal anti-IgE antibody that has shown a 40-fold to 50-fold greater affinity to IgE and higher efficacy controlling CSU symptoms as compared to omalizumab.^{96,97} In a phase 2b dose-finding trial, a higher number of patients reached complete control of symptoms of CSU with ligelizumab therapy of 72 mg or 240 mg than with omalizumab or placebo.⁹⁷ Ligelizumab is less potent than omalizumab in inhibiting IgE-CD23 interactions,⁷⁶ which might explain its lack of higher efficacy than omalizumab in asthma studies.⁹⁸ Similarly to omalizumab, it is expected to be effective in both aiCSU endotypes, with probably higher response rates and faster response in type I aiCSU.

Complement factors, particularly C5a, are essential to induce mast cell and basophil mediator release driven by IgG autoantibodies.⁹⁹ C5a is thought to be generated following binding of IgG-anti-FcεRI to FcεRI on mast cells and is able to activate mast cells via C5aR.¹⁰⁰ *In vitro*, an antibody against C5aR inhibited histamine release induced by sera from patients with CSU.¹⁰¹ Because C5a can also be activated by the coagulation pathway,⁶⁵ anti-C5 and anti-C5aR are expected to also be beneficial for patients with a type I CSU. Therefore, it is to be expected that anti-C5 and anti-C5aR therapies will work across all CSU endotypes, but should be especially effective in type IIb aiCSU, and future studies will test this.

BTK regulates FcεRI signaling in human mast cells and basophils, via FcεRI, as well as in B cells, via the B-cell receptor. Treatment with BTK inhibitors blocks IgE-mediated activation of mast cells and basophils.^{102,103} Fenebrutinib, a highly selective, reversible, oral BTK inhibitor, improved disease control in patients with CSU within the first week when used in doses of 50 mg every day, 150 mg every day, and 200 mg twice a day. Furthermore, fenebrutinib, at lower doses, demonstrated greater benefit in patients with type IIb autoimmunity than without and reduced circulating anti-FcεRI autoantibodies, indicating that patients with type IIb aiCSU may be more sensitive to BTK inhibition (NCT03137069). Fenebrutinib was generally well tolerated, with reversible grade 3 liver enzymes abnormalities reported in the 150 mg every day and 200 mg twice a day patient groups.¹⁰⁴ Although the follow-up study of fenebrutinib was discontinued (NCT03693625), there are other BTK inhibitors under investigation in antihistamine-refractory CSU such as rilzabrutinib (NCT05107115) and remibrutinib (NCT03926611, NCT04109313).¹⁰⁵ In a phase I trial, remibrutinib showed a favorable safety profile and promising pharmacodynamics, supporting its further development for CSU.¹⁰⁶ In a phase IIb dose-finding study, remibrutinib demonstrated a dose-response with significant improvements in UAS7 from baseline to week 4 and week 12 versus placebo, as well as

a fast onset of action, and a favorable safety profile across the entire dose range.¹⁰⁵

Several lines of evidence indicate that IL-17 and IL-23 might play a role in CSU pathogenesis and are promising targets for therapy. First, mast cells are thought to produce or take up IL-17A and store it in intracellular granules.¹⁰⁷ Second, serum levels of IL-17 and IL-23 were markedly higher in patients with CSU as compared with healthy control subjects.¹⁰⁸ Furthermore, the number of IL-17A-expressing cells, CD4⁺ T cells, and mast cells was increased in CSU lesional skin.¹⁰⁹ Lastly, both IL-17 and IL-23 serum levels correlated with CSU activity and were associated with ASST-positivity, suggesting that anti-IL-17 and anti-IL-23 treatment might be more effective in type IIb aiCSU.¹⁰⁸ Secukinumab, an anti-IL-17A antibody, has recently been shown to be effective in patients with CSU though its response onset was slow.¹⁰⁹ As of now, it is unclear whether patients with type IIb aiCSU will show higher rates of response to anti-IL-17 as compared to those with type I aiCSU, but the expectation is that they do.

T_H2 cytokines such as IL-4, IL-5, and IL-13 are responsible for stimulating IgE production and can contribute to the activation of mast cells, basophils, and eosinophils.¹¹⁰ In addition, IL-4 upregulates the expression of the IgE receptor. Preliminary reports demonstrated efficacy of dupilumab, an mAb that targets both IL-4 and IL-13 via IL-4Rα blockade, in patients with CSU.¹¹¹ This points to a role of type 2 inflammation in these patients and suggests that anti-IL-4Rα therapy might be more effective in type I aiCSU. According to a recent press release, dupilumab significantly reduced itch and hives in omalizumab-naïve patients (138 patients aged 6 years and older) when used as add-on to antihistamines, compared with those treated with antihistamines alone (placebo) in the phase III LIBERTY CUPID trial (NCT04180488). Further studies will evaluate dupilumab in patients with CSU who are omalizumab intolerant or incomplete responders to omalizumab. There are no studies, as of now, on differences in the response to dupilumab treatment between patients with type I and type IIb aiCSU. These are needed and may be predicted to show a better response in the former.

Other novel therapies might also have a beneficial effect in both endotypes of aiCSU. For example, lircatelimab, an anti-Siglec-8 mAb, is being evaluated in antihistamine-resistant patients with CSU (NCT03436797). The antibody acts on mast cells and eosinophils, cells that express Siglec-8, showing combined effects.¹¹² In a recent phase 2 study, 13 omalizumab-naïve and 11 omalizumab-refractory patients with CSU showed a disease activity drop of −73% and −47%, respectively.¹¹³ CDX-0159, an anti-KIT mAb, is being tested in CSU and chronic inducible urticaria in phase I studies (NCT04538794, NCT04548869). Almost all patients (95%) with antihistamine-refractory cold urticaria and symptomatic dermographism experienced complete response after a single dose of CDX-0159, and serum tryptase and skin mast cell depletion mirrored clinical activity.¹¹⁴ Future studies will compare patients with type I and type IIb aiCSU for their response to lircatelimab and CDX-0159.

Novel treatments will teach us about differences in the role of certain mechanisms/factors related to different endotypes, such as eosinophils. Eosinophils may have an important role in CSU¹⁰ due to their ability to activate mast cells through major basic protein and eosinophil cationic protein.^{115,116} The presence of both eosinophils and eosinophil granules was demonstrated in CSU lesions.¹¹⁷ In this regard, a possible mechanism of blood

TABLE III. Summary of features of type I and type IIb aiCSU (modified from Maurer et al⁶²)

Features	Type I	Type IIb	Overlap issues
Defining criteria	Presence of IgE to self	ASST+, IgG-anti-FcεRI/IgE+, and BAT/BHRA+ ⁴⁴	IgA, IgM, and IgE autoantibodies were shown in some patients with IgG autoantibodies ^{16,45}
Disease activity	Increased in patients with IgE-anti-IL-24 ¹³	Increased ¹⁸	Both types can show increased disease activity
Rates of allergic diseases	Might be higher in patients with IgE-anti-TPO ^{25,32}	Unknown	—
Rates of autoimmune diseases	Rates of autoimmune thyroiditis might be increased in patients with high IgE-anti-TPO levels ²⁵	Increased ⁵⁷	IgG-anti-TPO correlated with IgE-anti-TPO ²⁵
Total IgE levels	Low in patients with increased IgE-anti-TPO ²⁵	Low ¹⁸	Increased IgE-anti-TPO levels were associated with low total IgA ⁴⁸ and total IgE levels ²⁵ (both markers of type IIb aiCSU)
IgG-anti-TPO levels	Might be high in patients with high IgE-anti-TPO levels ²⁵	High ¹⁸	IgG-anti-TPO correlated with IgE-anti-TPO ²⁵
Basopenia rates	Might be increased in patients with elevated IgE-anti-IL-24 ¹³	High ¹⁸	Increased IgE-anti-IL-24 levels were associated with basopenia ¹³
Eosinopenia rates	Unknown	High ⁴⁷	—
Response to sgAHs	Might be poor in IgE-anti-TPO–positive cases ²⁵	Poor ⁵¹	Positive IgE-anti-TPO, positive IgG-anti-TPO, and total IgE <40 IU/mL were independent predictors of antihistamine-refractory CSU ²⁵
Response to omalizumab	Expected to be fast and good in patients with IgE-anti-TPO ¹⁹	Poor, slow ⁴⁹	Late responders to omalizumab showed higher levels of both anti–tissue factor IgE and IgG than early responders ¹⁶
Response to cyclosporine	Unknown	Good ^{85,86}	—
Response to fenebrutinib	Unknown, might be good	Good	Fenebrutinib diminished disease activity in patients with antihistamine-refractory CSU, including more patients with refractory type IIb autoimmunity ¹⁰⁴

eosinopenia and basopenia in type IIb CSU is the migration of both cell types from the blood into the lesional skin of patients with CSU. Furthermore, IgG-anti-FcεRII were described in patients with CSU and were able to induce histamine release via eosinophil activation.¹¹⁵ In addition, an antibody targeting the IL-5 receptor, benralizumab, showed significant symptom reduction in patients with CSU.¹¹⁸ Further studies evaluating the efficacy of benralizumab (NCT04612725) and of the anti-IL-5 drug mepolizumab (NCT03494881) in antihistamine-resistant CSU are ongoing.

Finally, there are other treatments in development that may teach us about new endotypes, for example, therapy that targets MRGPRX2 and alarmins such as thymic stromal lymphopoietin (TSLP). MRGPRX2 is responsible for an IgE-independent pathway of mast cell, basophil, and eosinophil activation.^{116,119} Patients with severe CSU showed increased numbers of MRGPRX2-expressing mast cells in lesional skin.¹¹⁶ Several MRGPRX2 antagonists are in preclinical stage development.^{120,121} TSLP together with other alarmins, IL-33 and IL-25, are type 2 cytokines that initiate the release of a broad array of cytokines involved in atopy. Increased expression of T_H2-initiating cytokines including TSLP in the lesional skin of patients with CSU¹²² indicates the need for investigation of corresponding drugs such as tezepelumab, an anti-TSLP mAb, in CSU.

OPEN QUESTIONS AND UNMET NEEDS

Although it is very clear that patients with CSU with functional autoantibodies do not show signs of anaphylaxis, it is still unclear

why this is so. As for basophil activation in patients with CSU and these autoantibodies, this is very hard to assess. Many patients have low basophil numbers. Also, these patients exhibit nonresponder basophil populations. It is possible that circulating basophils that express functional FcεRI on their surface respond differently than those recruited to the lesional skin, because their degranulation might need tissue-specific cofactors. In addition, different types of basophils may play a role in the type of response to TPO, and serum factors may prevent activation, at least partially. For example, basophils of patients with CSU incubated with IgE-anti-TPO from control subjects showed lower expression of CD203c than after incubation with patients' autologous IgE-anti-TPO serum or with IgE-anti-TPO serum from another patient with CSU.²¹ Finally, basophil activation in the blood by CSU autoantibodies may not suffice to produce anaphylaxis.

Patients with type I and type IIb aiCSU can experience wheals, angioedema, or both (Table III). Whether the rates of these 3 phenotypes may be different in patients with type I and type IIb aiCSU is currently unknown. Recent work suggests that this may be the case, demonstrating that patients with CSU who exclusively develop angioedema but no wheals are less likely to have type IIb aiCSU than those patients who only or also develop wheals.³⁰ This may explain the very high rate of omalizumab complete responders in standalone angioedema patients with CSU.¹²³

Emerging features and markers of type IIb aiCSU, for example, basopenia and low total IgE, need to be validated across centers/studies, and the strength of the association between them and aiCSU-defining tests, and the predictive

values, sensitivity, and specificity of the former to predict the latter have to be better assessed in further studies. Accordingly, type IIb aiCSU diagnosis criteria might be revised in the future on the basis of results of these studies and will include new markers in addition or instead of the ones that were suggested in 2013.⁴⁴

What do we know?

- Type I and type IIb autoimmunity are the 2 proposed causes of CSU.
- Patients with CSU can have type I aiCSU, type IIb aiCSU, or both.
- On a patient level, type I and type IIb aiCSU share the same phenotype.
- As endotypes, type I and type IIb aiCSU may differ in disease course, clinical features, and response to treatment.
- Novel and endotype-targeted treatments are under development.

What is still unknown?

- The precise cellular and molecular mechanisms of type I and type IIb aiCSU remain to be characterized.
- The drivers and mechanisms of onset and spontaneous remission of type I and type IIb aiCSU need to be identified and characterized.
- The exact rate of patients with CSU with type I aiCSU, type IIb aiCSU, both, or nonautoimmune CSU is unknown.
- Better tests for type I and type IIb aiCSU need to be developed and made available.
- Additional causes of CSU need to be identified and characterized.
- The role, relevance, and mechanisms of triggers of exacerbation and disease modifiers need to be elucidated.

REFERENCES

- Zuberbier T, Latiff AHA, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. *Allergy* 2022;77:734-66.
- Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011;66:317-30.
- Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. *Allergy* 2020;75:423-32.
- Maurer M, Abuzakouk M, Berard F, Canonica W, Oude Elberink H, Gimenez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy* 2017;72:2005-16.
- Balp M-M, Vietri J, Tian H, Isherwood G. The impact of chronic urticaria from the patient's perspective: a survey in five European countries. *Patient* 2015;8:551-8.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997;136:197-201.
- Mendelson MH, Bernstein JA, Gabriel S, Balp M-M, Tian H, Vietri J, et al. Patient-reported impact of chronic urticaria compared with psoriasis in the United States. *J Dermatolog Treat* 2017;28:229-36.
- Natbony SF, Phillips ME, Elias JM, Godfrey HP, Kaplan AP. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983;71:177-83.
- Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. *J Allergy Clin Immunol* 1986;78:914-8.
- Altrichter S, Frischbutter S, Fok JS, Kolkhir P, Jiao Q, Skov PS, et al. The role of eosinophils in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2020;145:1510-6.
- Zuberbier T, Pfrommer C, Specht K, Vieths S, Bastl-Borrmann R, Worm M, et al. Aromatic components of food as novel eliciting factors of pseudoallergic reactions in chronic urticaria. *J Allergy Clin Immunol* 2002;109:343-8.
- Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017;139:1772-1778.e1.
- Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2018;142:876-82.
- Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase—a novel pathomechanism of chronic spontaneous urticaria? *PLoS One* 2011;6:e14794.
- Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M Reply. *J Allergy Clin Immunol* 2018;141:1166-7.
- Asero R, Marzano AV, Ferrucci S, Lorini M, Carbonelli V, Cugno M. Co-occurrence of IgE and IgG autoantibodies in patients with chronic spontaneous urticaria. *Clin Exp Immunol* 2020;200:242-9.
- Bracken SJ, Abraham S, MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. *Front Immunol* 2019;10:627.
- Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, Grattan CEH, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: results of the PURIST study. *Allergy* 2019;74:2427-36.
- Maurer M, Altrichter S, Bieber T, Biedermann T, Brautigam M, Seyfried S, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011;128:202-9.e5.
- Bar-Sela S, Reshef T, Mekori YA. IgE antithyroid microsomal antibodies in a patient with chronic urticaria. *J Allergy Clin Immunol* 1999;103:1216-7.
- Sánchez J, Sánchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. *Allergy Asthma Immunol Res* 2019;11:29-42.
- Çildag S, Yenisey Ç, Ünübol M, Şentürk T. Comparison of immunoglobulin E anti-thyroid peroxidase antibodies in patients with Hashimoto thyroiditis and chronic spontaneous urticaria. *Med Pharm Rep* 2021;94:53-7.
- Guo J, Rapoport B, McLachlan SM. Thyroid peroxidase autoantibodies of IgE class in thyroid autoimmunity. *Clin Immunol Immunopathol* 1997;82:157-62.
- Concha LB, Chang CC, Szema AM, Dattwyler RJ, Carlson HE. IgE antithyroid antibodies in patients with Hashimoto's disease and chronic urticaria. *Allergy Asthma Proc* 2004;25:293-6.
- Zhang L, Qiu L, Wu J, Qi Y, Wang H, Qi R, et al. IgE and IgG anti-thyroid autoantibodies in Chinese patients with chronic spontaneous urticaria and a literature review. *Allergy Asthma Immunol Res* 2022;14:131-42.
- Sánchez J, Sánchez A, Munera M, Garcia E, Lopez J-F, Velásquez-Lopera M, et al. Presence of IgE autoantibodies against eosinophil peroxidase and eosinophil cationic protein in severe chronic spontaneous urticaria and atopic dermatitis. *Allergy Asthma Immunol Res* 2021;13:746-61.
- Hatada Y, Kashiwakura J, Hayama K, Fujisawa D, Sasaki-Sakamoto T, Terui T, et al. Significantly high levels of anti-dsDNA immunoglobulin E in sera and the ability of dsDNA to induce the degranulation of basophils from chronic urticaria patients. *Int Arch Allergy Immunol* 2013;161:154-8.
- Cugno M, Asero R, Ferrucci S, Lorini M, Carbonelli V, Tedeschi A, et al. Elevated IgE to tissue factor and thyroglobulin are abated by omalizumab in chronic spontaneous urticaria. *Allergy* 2018;73:2408-11.
- Shin YS, Suh D-H, Yang E-M, Ye Y-M, Park H-S. Serum specific IgE to thyroid peroxidase activates basophils in aspirin intolerant urticaria. *J Korean Med Sci* 2015;30:705-9.
- Sabaté-Brescó M, Rodríguez-Garjón N, Azofra J, Baeza ML, Donado CD, Gaig P, et al. A comparative study of sex distribution, autoimmunity, blood, and inflammatory parameters in chronic spontaneous urticaria with angioedema and chronic histaminergic angioedema. *J Allergy Clin Immunol Pract* 2021;9:2284-92.
- de Montjoye L, Herman A, Hendrickx E, Chéou P, Blanchetot C, Hofman E, et al. Increased expression of IL-24 in chronic spontaneous urticaria. *Allergy* 2019;74:1811-3.
- Sánchez J, Sánchez A, Cardona R. Clinical characterization of patients with chronic spontaneous urticaria according to anti-TPO IgE levels. *J Immunol Res* 2019;2019:4202145.
- Lakin E, Church MK, Maurer M, Schmetzer O. On the lipophilic nature of auto-reactive IgE in chronic spontaneous urticaria. *Theranostics* 2019;9:829-36.
- Türk M, Ertaş R, Zeydan E, Türk Y, Atasoy M, Gutsche A, et al. Identification of chronic urticaria subtypes using machine learning algorithms. *Allergy* 2021;77:323-6.
- Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. *Allergy* 2016;71:1210-8.
- Sanz ML, Prieto I, Garcia BE, Oehling A. Diagnostic reliability considerations of specific IgE determination. *J Investig Allergol Clin Immunol* 1996;6:152-61.
- Kadooka Y, Idota T, Gunji H, Shimatani M, Kawakami H, Dosako S, et al. A method for measuring specific IgE in sera by direct ELISA without interference by IgG competition or IgG autoantibodies to IgE. *Int Arch Allergy Immunol* 2000;122:264-9.
- Grattan CE, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991;21:695-704.
- Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;328:1599-604.

40. Gruber BL, Baeza ML, Marchese MJ, Agnello V, Kaplan AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988;90:213-7.
41. Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. *Br J Dermatol* 1986;114:583-90.
42. Asero R, Tedeschi A, Lorini M, Salimbeni R, Zanoletti T, Miadonna A. Chronic urticaria: novel clinical and serological aspects. *Clin Exp Allergy* 2001;31:1105-10.
43. Sabroe RA, Fiebiger E, Francis DM, Maurer D, Seed PT, CEh Grattan, et al. Classification of anti-FcεpsilonRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. *J Allergy Clin Immunol* 2002;110:492-9.
44. Konstantinou GN, Asero R, Ferrer M, Knol EF, Maurer M, Raap U, et al. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. *Allergy* 2013;68:27-36.
45. Altrichter S, Zampeli V, Ellrich A, Zhang K, Church MK, Maurer M. IgM and IgA in addition to IgG autoantibodies against FcεRIα are frequent and associated with disease markers of chronic spontaneous urticaria. *Allergy* 2020;75:3208-15.
46. Marcelino J, Baumann K, Skov PS, Pereira Santos MC, Wysocki I, Scheffel J, et al. What basophil testing tells us about CSU patients – results of the CORSA study. *Front Immunol* 2021;12:742470.
47. Kolkhir P, Church MK, Altrichter S, Skov PS, Hawro T, Frischbutter S, et al. Eosinopenia, in chronic spontaneous urticaria, is associated with high disease activity, autoimmunity, and poor response to treatment. *J Allergy Clin Immunol Pract* 2020;8:318-25.
48. Sauer M, Scheffel J, Frischbutter S, Kolkhir P, Xiang Y-K, Siebenhaar F, et al. Lower IgA levels in chronic spontaneous urticaria are associated with lower IgE levels and autoimmunity. *Front Immunol* 2021;12:657211.
49. Gericke J, Metz M, Ohanian T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;139:1059-61.e1.
50. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy* 2018;73:705-12.
51. Kolkhir P, Kovalkova E, Chernov A, Danilycheva I, Krause K, Sauer M, et al. Autoimmune chronic spontaneous urticaria detection with IgG anti-TPO and total IgE. *J Allergy Clin Immunol Pract* 2021;9:4138-46.e8.
52. Grattan CE, Boon AP, Eady RA, Winkelmann RK. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. *Int Arch Allergy Appl Immunol* 1990;93:198-204.
53. Soundararajan S, Kikuchi Y, Joseph K, Kaplan AP. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol* 2005;115:815-21.
54. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FcεpsilonRIα autoantibodies in autoimmune-mediated disorders. Identification of a structure-function relationship. *J Clin Invest* 1998;101:243-51.
55. Chan Y-C, Ramadani F, Santos AF, Pillai P, Ohm-Laursen L, Harper CE, et al. "Auto-anti-IgE": naturally occurring IgG anti-IgE antibodies may inhibit allergen-induced basophil activation. *J Allergy Clin Immunol* 2014;134:1394-401.e4.
56. Miescher SM, Horn MP, Pachlupnik JM, Baldi L, Vogel M, Stadler BM. Natural anti-FcεpsilonRIα autoantibodies isolated from healthy donors and chronic idiopathic urticaria patients reveal a restricted repertoire and autoreactivity on human basophils. *Hum Antibodies* 2001;10:119-26.
57. Kolkhir P, Altrichter S, Asero R, Daschner A, Ferrer M, Giménez-Arnau A, et al. Autoimmune diseases are linked to type IIb autoimmune chronic spontaneous urticaria. *Allergy Asthma Immunol Res* 2021;13:545-59.
58. Toubi E, Vadasz Z. Predictive features associated with chronic spontaneous urticaria recurrence. *J Dermatol* 2021;48:1786-8.
59. Asero R. Chronic idiopathic urticaria: a family study. *Ann Allergy Asthma Immunol* 2002;89:195-6.
60. Asero R. Sex differences in the pathogenesis of chronic urticaria. *J Allergy Clin Immunol* 2003;111:425-6.
61. Asero R, Cugno M. Biomarkers of chronic spontaneous urticaria and their clinical implications. *Expert Rev Clin Immunol* 2021;17:247-54.
62. Maurer M, Eyerich K, Eyerich S, Ferrer M, Guterthuth J, Hartmann K, et al. Urticaria: Collegium Internationale Allergologicum (CIA) Update 2020. *Int Arch Allergy Immunol* 2020;181:321-33.
63. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA(2)LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy* 2009;64:1256-68.
64. Asero R, Pinter E, Tedeschi A. 35 years of autologous serum skin test in chronic spontaneous urticaria: what we know and what we do not know [published online ahead of print December 14, 2021]. *Eur Ann Allergy Clin Immunol*. <https://doi.org/10.23822/EurAnnACI.1764-1489.238>.
65. Yanase Y, Matsuo Y, Takahagi S, Kawaguchi T, Uchida K, Ishii K, et al. Coagulation factors induce human skin mast cell and basophil degranulation via activation of complement 5 and the C5a receptor. *J Allergy Clin Immunol* 2021;147:1101-4.e7.
66. Taskapan O, Kutlu A, Karabudak O. Evaluation of autologous serum skin test results in patients with chronic idiopathic urticaria, allergic/non-allergic asthma or rhinitis and healthy people. *Clin Exp Dermatol* 2008;33:754-8.
67. Asero R. Clinical variables of severe chronic spontaneous urticaria from total IgE standpoint: a retrospective study. *Eur Ann Allergy Clin Immunol* 2021;54:30-3.
68. Attar MHZ, Merk HF, Kotliar K, Wurpts G, Röseler S, Moll-Slodowsky S, et al. The CD63 basophil activation test as a diagnostic tool for assessing autoimmunity in patients with chronic spontaneous urticaria. *Eur J Dermatol* 2019;29:614-8.
69. Henault J, Riggs JM, Karnell JL, Liarski VM, Li J, Shirinian L, et al. Self-reactive IgE exacerbates interferon responses associated with autoimmunity. *Nat Immunol* 2016;17:196-203.
70. Kolkhir P, Elieh Ali Komi D, Metz M, Siebenhaar F, Maurer M. Understanding human mast cells: lesson from therapies for allergic and non-allergic diseases [published online ahead of print October 5, 2021]. *Nat Rev Immunol*. <https://doi.org/10.1038/s41577-021-00622-y>.
71. Khan DA, Kocatürk E, Bauer A, Aygören-Pürsün E. What's new in the treatment of urticaria and angioedema. *J Allergy Clin Immunol Pract* 2021;9:2170-84.
72. Stellato C, de Paulis A, Ciccarelli A, Cirillo R, Patella V, Casolaro V, et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. *J Invest Dermatol* 1992;98:800-4.
73. Guillen-Aguinaga S, Jauregui Presa I, Aguinaga-Ontoso E, Guillen-Grima F, Ferrer M. Updosing non-sedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br J Dermatol* 2016;175:1153-65.
74. de Montjoye L, Darrigade AS, Gimenez-Arnau A, Herman A, Dumoutier L, Baeck M. Correlations between disease activity, autoimmunity and biological parameters in patients with chronic spontaneous urticaria. *Eur Ann Allergy Clin Immunol* 2020;53:55-66.
75. Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;164:S6-11.
76. Gasser P, Tarchevskaya SS, Guntern P, Brigger D, Ruppli R, Zbären N, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun* 2020;11:165.
77. Chang TW. The pharmacological basis of anti-IgE therapy. *Nat Biotechnol* 2000;18:157-62.
78. Chang TW, Chen C, Lin C-J, Metz M, Church MK, Maurer M. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015;135:337-42.
79. Chen Y, Yu M, Huang X, Tu P, Shi P, Maurer M, et al. Omalizumab treatment and outcomes in Chinese patients with chronic spontaneous urticaria, chronic inducible urticaria, or both. *World Allergy Organ J* 2021;14:100501.
80. Kaplan A, Ferrer M, Bernstein JA, Antonova E, Trzaskoma B, Raimundo K, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol* 2016;137:474-81.
81. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-mediated autoimmunity. *Front Immunol* 2018;9:689.
82. Maurer M, Khan DA, Komi DEA, Kaplan AP. Biologics for the use in chronic spontaneous urticaria: when and which. *J Allergy Clin Immunol Pract* 2021;9:1067-78.
83. Nettis E, Cegolon L, Di Leo E, Lodi Rizzini F, Detoraki A, Canonica GW. Omalizumab chronic spontaneous urticaria: efficacy, safety, predictors of treatment outcome, and time to response. *Ann Allergy Asthma Immunol* 2018;121:474-8.
84. Kulthanan K, Chawekulrat P, Komoltri C, Hunnangkul S, Tuchinda P, Chularojanamontri L, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol Pract* 2018;6:586-99.
85. Kulthanan K, Subchookul C, Hunnangkul S, Chularojanamontri L, Tuchinda P. Factors predicting the response to cyclosporin treatment in patients with chronic spontaneous urticaria: a systematic review. *Allergy Asthma Immunol Res* 2019;11:736-55.
86. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. *Allergy* 2021;76:2965-81.
87. Grattan CEH, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000;143:365-72.
88. Frezzolini A, Proveni A, Teofoli P, Pomponi D, De Pittà O. Serum-induced basophil CD63 expression by means of a tricolour flow cytometric method for the in vitro diagnosis of chronic urticaria. *Allergy* 2006;61:1071-7.
89. Marsland AM, Soundararajan S, Joseph K, Kaplan AP. Effects of calcineurin inhibitors on an in vitro assay for chronic urticaria. *Clin Exp Allergy* 2005;35:554-9.
90. Hannam-Harris AC, Taylor DS, Nowell PC. Cyclosporin A directly inhibits human B-cell proliferation by more than a single mechanism. *J Leukoc Biol* 1985;38:231-9.
91. Santiago L, Ferreira B, Ramos L, Gonçalves M. IgE levels are negatively correlated with clinical response to cyclosporin in chronic spontaneous urticaria. *Br J Dermatol* 2019;180:199-200.

92. Kolkhir P, Pogorelov D, Kochergin N. Chronic spontaneous urticaria associated with vitiligo and thyroiditis (autoimmune polyglandular syndrome IIIC): case series. *Int J Dermatol* 2017;56:e89-90.
93. Bernstein JA, Garramone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. *Ann Allergy Asthma Immunol* 2002;89:212-4.
94. Holm JG, Ivyskiy I, Thomsen SF. Use of nonbiologic treatments in antihistamine-refractory chronic urticaria: a review of published evidence. *J Dermatol Treat* 2018;29:80-97.
95. Combalia A, Losno RA, Prieto-González S, Mascaró JM. Rituximab in refractory chronic spontaneous urticaria: an encouraging therapeutic approach. *Skin Pharmacol Physiol* 2018;31:184-7.
96. Arm JP, Bottoli I, Skerjanec A, Floch D, Groenewegen A, Maahs S, et al. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. *Clin Exp Allergy* 2014;44:1371-85.
97. Maurer M, Gimenez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med* 2019;381:1321-32.
98. Trischler J, Bottoli I, Janocha R, Heusser C, Jaumont X, Lowe P, et al. Ligelizumab treatment for severe asthma: learnings from the clinical development programme. *Clin Transl Immunol* 2021;10:e1255.
99. Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 1999;104:169-72.
100. Ferrer M. Immunological events in chronic spontaneous urticaria. *Clin Transl Allergy* 2015;5:30.
101. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. *J Allergy Clin Immunol* 2002;109:114-8.
102. Iyer AS, Morales JL, Huang W, Ojo F, Ning G, Wills E, et al. Absence of Tec family kinases interleukin-2 inducible T cell kinase (Itk) and Bruton's tyrosine kinase (Btk) severely impairs Fc epsilonRI-dependent mast cell responses. *J Biol Chem* 2011;286:9503-13.
103. MacGlashan D Jr, Honigberg LA, Smith A, Buggy J, Schroeder JT. Inhibition of IgE-mediated secretion from human basophils with a highly selective Bruton's tyrosine kinase, Btk, inhibitor. *Int Immunopharmacol* 2011;11:475-9.
104. Metz M, Sussman G, Gagnon R, Staubach P, Tanus T, Yang W, et al. Fenebutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, in H1-antihistamine-refractory chronic spontaneous urticaria: a randomized clinical trial. *Nat Med* 2021;27:1961-9.
105. Maurer M, Berger W, Gimenez-Arnau A, Hayama K, Jain V, Reich A, et al. The Bruton's tyrosine kinase inhibitor remibrutinib (LOU064) in chronic spontaneous urticaria: top line results of a phase 2b dose-finding study. Presented at: the 30th European Academy of Dermatology and Venereology Virtual Congress, 29th September – 2nd October 2021.
106. Kaul M, End P, Cabanski M, Schuhler C, Jakab A, Kistowska M, et al. Remibrutinib (LOU064): a selective potent oral BTK inhibitor with promising clinical safety and pharmacodynamics in a randomized phase I trial. *Clin Transl Sci* 2021;14:1756-68.
107. Noordenbos T, Blijdorp I, Chen S, Stap J, Mul E, Cañete JD, et al. Human mast cells capture, store, and release bioactive, exogenous IL-17A. *J Leukocyte Biol* 2016;100:453-62.
108. Atwa MA, Emara AS, Youssef N, Bayoumy NM. Serum concentration of IL-17, IL-23 and TNF- α among patients with chronic spontaneous urticaria: association with disease activity and autologous serum skin test. *J Eur Acad Dermatol Venereol* 2014;28:469-74.
109. Sabag DA, Matanes L, Bejar J, Sheffer H, Barzilai A, Church MK, et al. Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. *Clin Exp Allergy* 2020;50:799-804.
110. Akdis CA, Arkwright PD, Bruggen MC, Busse W, Gadina M, Guttman-Yassky E, et al. Type 2 immunity in the skin and lungs. *Allergy* 2020;75:1582-605.
111. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *J Allergy Clin Immunol Pract* 2019;7:1659-61.e1.
112. Dellon ES, Peterson KA, Murray JA, Falk GW, Gonsalves N, Chehade M, et al. Anti-Siglec-8 antibody for eosinophilic gastritis and duodenitis. *N Engl J Med* 2020;383:1624-34.
113. Altrichter S, Staubach P, Pasha M, Singh B, Chang AT, Bernstein JA, et al. An open-label, proof-of-concept study of lirenlimab for antihistamine-resistant chronic spontaneous and inducible urticaria. *J Allergy Clin Immunol* 2022;149:1683-90.e7.
114. Hawro T, Terhorst-Molawi D, Grekowitz E, Kiefer L, Metz M, Alvarado D, et al. CDX-0159, an anti-KIT antibody, demonstrates rapid and sustained clinical response and improved quality of life in patients with chronic inducible urticaria. Presented at: the 30th European Academy of Dermatology and Venereology Virtual Congress, 29th September – 2nd October 2021.
115. Puccetti A, Bason C, Simeoni S, Millo E, Tinazzi E, Beri R, et al. In chronic idiopathic urticaria autoantibodies against Fc epsilonRII/CD23 induce histamine release via eosinophil activation. *Clin Exp Allergy* 2005;35:1599-607.
116. Fujisawa D, Kashiwakura J-I, Kita H, Kikukawa Y, Fujitani Y, Sasaki-Sakamoto T, et al. Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. *J Allergy Clin Immunol* 2014;134:622-33.e9.
117. Toyoda M, Maruyama T, Morohashi M, Bhawan J. Free eosinophil granules in urticaria: a correlation with the duration of wheals. *Am J Dermatopathol* 1996;18:49-57.
118. Bernstein JA, Singh U, Rao MB, Berendts K, Zhang X, Mutasim D. Benralizumab for chronic spontaneous urticaria. *N Engl J Med* 2020;383:1389-91.
119. Wedi B, Gehring M, Kapp A. The pseudoallergen receptor MRGPRX2 on peripheral blood basophils and eosinophils: expression and function. *Allergy* 2020;75:2229-42.
120. Ogasawara H, Furuno M, Edamura K, Noguchi M. Novel MRGPRX2 antagonists inhibit IgE-independent activation of human umbilical cord blood-derived mast cells. *J Leukocyte Biol* 2019;106:1069-77.
121. Suzuki Y, Liu S, Ogasawara T, Sawasaki T, Takasaki Y, Yorozuya T, et al. A novel MRGPRX2-targeting antagonistic DNA aptamer inhibits histamine release and prevents mast cell-mediated anaphylaxis. *Eur J Pharmacol* 2020;878:173104.
122. Kay AB, Clark P, Maurer M, Ying S. Elevations in T-helper-2-initiating cytokines (interleukin-33, interleukin-25 and thymic stromal lymphopoietin) in lesional skin from chronic spontaneous ('idiopathic') urticaria. *Br J Dermatol* 2015;172:1294-302.
123. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgerit T, Maurer M. How to treat patients with chronic spontaneous urticaria with omalizumab: questions and answers. *J Allergy Clin Immunol Pract* 2020;8:113-24.
124. Ye Y-M, Yang E-M, Yoo H-S, Shin Y-S, Kim S-H, Park H-S. Increased level of basophil CD203c expression predicts severe chronic urticaria. *J Korean Med Sci* 2014;29:43-7.
125. Curto-Barredo L, Yelamos J, Gimeno R, Mojal S, Pujol RM, Gimenez-Arnau A. Basophil activation test identifies the patients with chronic spontaneous urticaria suffering the most active disease. *Immun Inflamm Dis* 2016;4:441-5.
126. Irinyi B, Széles G, Gyimesi E, Tumpek J, Herédi E, Dimitrios G, et al. Clinical and laboratory examinations in the subgroups of chronic urticaria. *Int Arch Allergy Immunol* 2007;144:217-25.
127. Palacios T, Stillman L, Borish L, Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. *J Allergy Clin Immunol Pract* 2016;4:529-30.
128. Ghazanfar MN, Sand C, Thomsen SF. Effectiveness and safety of omalizumab in chronic spontaneous or inducible urticaria: evaluation of 154 patients. *Br J Dermatol* 2016;175:404-6.
129. Endo T, Toyoshima S, Hayama K, Tagui M, Niwa Y, Ito M, et al. Relationship between changes in the 7-day urticaria activity score after treatment with omalizumab and the responsiveness of basophils to Fc ϵ RI stimulation in patients with chronic spontaneous urticaria. *Asia Pac Allergy* 2020;10:e12.
130. Curto-Barredo L, Archilla LR, Vives GR, Pujol RM, Gimenez-Arnau AM. Clinical features of chronic spontaneous urticaria that predict disease prognosis and refractoriness to standard treatment. *Acta Derm Venereol* 2018;98:641-7.
131. Endo T, Toyoshima S, Kanegae K, Izaki S, Nishimori N, Ito M, et al. Identification of biomarkers for predicting the response to cyclosporin A therapy in patients with chronic spontaneous urticaria. *Allergol Int* 2019;68:270-3.
132. Loria MP, Dambra PP, D'Oronzio L, Nettis E, Pannofino A, Cavallo E, et al. Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol* 2001;23:205-13.
133. Rijavec M, Košnik M, Koren A, Kopač P, Šelb J, Vantur R, et al. A very low number of circulating basophils is predictive of a poor response to omalizumab in chronic spontaneous urticaria. *Allergy* 2021;76:1254-7.
134. Magen E, Waitman D-A, Dickstein Y, Davidovich Y, Kahan NR. Clinical-laboratory characteristics of ANA-positive chronic idiopathic urticaria. *Allergy Asthma Proc* 2015;36:138-44.
135. Ertas R, Hawro T, Altrichter S, Ozyurt K, Erol K, Ketenci Ertas S, et al. Antinuclear antibodies are common and linked to poor response to omalizumab treatment in patients with CSU. *Allergy* 2020;75:468-70.
136. Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. *Int Arch Allergy Immunol* 2017;172:40-4.
137. Asero R. Plasma D-dimer levels and clinical response to cyclosporin in severe chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015;135:1401-3.
138. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983;119:636-40.