



Chronic Urticaria: Advances in Understanding of the Disease and Clinical Management

Liting He¹ · Wanyu Yi¹ · Xin Huang¹ · Hai Long¹ · Qianjin Lu^{1,2}

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Abstract

Chronic urticaria (CU) is a common skin condition characterized by the recurrence of wheals, with or without angioedema, which lasts for at least 6 weeks. Owing to its pruritus and incurability, this disease adversely affects the patients' physical and mental health and diminishes the quality of life. CU is generally classified into two subtypes based on the relevance of eliciting factors: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), the latter of which is further divided into several subtypes. To improve the understanding and clinical management of this highly heterogeneous disorder, the EAACI/GA²LEN/EDF/WAO guideline was developed and published in 2018 based on evidence and expert consensus. The diagnostic and treatment algorithms proposed by the guideline have largely facilitated dermatologists in clinical practice. However, several questions remained unsolved and have been widely investigated in the recent years. First, a better understanding of the association between chronic urticaria and its potential underlying causes or eliciting factors such as autoimmunity, infections, coagulation aberrance, and vitamin D deficiency is warranted. This would lead to updates in the diagnostic and treatment procedures of different subtypes of chronic urticaria. Secondly, treatment for recalcitrant cases, especially those resistant to or intolerant of second-generation antihistamines and (or) omalizumab, calls for novel therapeutic measures or strategies. In the present review, we summarized recent advances in the understanding and management of both CSU and CIndU, with special emphasis on their underlying causes or eliciting factors, pathogenic mechanisms, potential targets for intervention, and advances in treatment strategies.

Keywords Chronic spontaneous urticaria · Chronic inducible urticaria · Refractory urticaria · Pathogenesis · Differential diagnosis · Treatment · Omalizumab

Introduction

Chronic urticaria (CU), one of the most common dermatological diseases, has high rates of lifetime prevalence and affects nearly 1.4% population [1]. The pathogenesis of CU remains elusive, and its classification into chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIndU) depends on whether there is an eliciting factor or not [2]. As

a chronic disease, CU annoys people dramatically due to its repeated attacks and chronic course of months to years. It is estimated that more than 47% of cases last over 1 year and 11% still persist after 5 years [3]. CU affects patients both physically and mentally, and may cause even greater impact to patients' quality of life than ischemic heart disease does, although it is self-limited and confined to the skin [4].

Guidelines and consensus on the diagnosis and treatment of CU have largely facilitated the clinical practice in the management of this disease [2]; however, several questions remain unsolved. First, a thorough understanding of the association between chronic urticaria and its potential underlying causes or eliciting factors is in great need to further improve the management strategies of this disease. Secondly, treatment for recalcitrant cases, especially those resistant to or intolerant of second-generation antihistamines or omalizumab, calls for novel therapeutic measures. Here

✉ Hai Long
dr.hailong@csu.edu.cn

¹ Department of Dermatology, Hunan Key Laboratory of Medical Epigenomics, The Second Xiangya Hospital of Central South University, 139 Middle Renmin Road, Hunan 410011 Changsha, China

² Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing 210042, Jiangsu, China

we summarized recent advances in the understanding and management of both CSU and CIndU, with special emphasis on their underlying causes or eliciting factors, pathogenic mechanisms, potential targets for intervention, and advances in treatment strategies.

CSU

CSU is diagnosed based on typical manifestations of chronic urticaria and the absence of identifiable eliciting factors. It is estimated that CSU accounts for 2/3 of patients with CU [5]. The etiology and pathogenesis of CSU are largely uncovered in spite of the consensus that skin mast cell (MC) is the main player in the pathophysiology [6]. A few mechanisms have been proposed these years to contribute to the occurrence of CSU, including autoimmunity, infections, coagulation cascade, vitamin D deficiency, and genetic factors [7]. In the midst of these potential mechanisms, autoimmunity is considered to be the most frequent (50–60%) [8]. For the treatment of CSU, second-generation H1-antihistamines (sgAH) and omalizumab still rank the first and second on the choice list, respectively [2]. However, the real-life circumstances are far more complicated than a cluster of alternative drugs other than sgAH and omalizumab are taken into consideration for recalcitrant cases. Besides, novel therapeutic measures or strategies are in demand considering the side effects and powerlessness of alternative drugs. To decipher this sophisticated disease better, it is of eminent importance to summarize advances on the understanding of potential underlying causes or eliciting factors of CSU and potential treatment options.

Updated Understanding of the Pathogenesis of CSU

CSU is recognized as a chronic inflammatory condition characterized by the abnormal activation and degranulation of MCs and basophils [9]. Though numerous cells (MC, basophil, eosinophil, T cell, B cell, endothelial cell, and so on) and mediators are postulated to play a role in the pathogenesis of CSU, skin MC is the well-acknowledged dominating effector cell followed by basophil [6, 7]. Nevertheless, mechanisms involved in the activation and degranulation of MCs are still poorly understood. It is proved that different mechanisms can lead to different patterns of cytoplasmic granule secretion from MCs, and these distinct degranulation dynamics and granule features account for diverse patterns of MC-dependent inflammation [10]. Over the past few years, several mechanisms were widely investigated and indicated as important participants in the pathophysiology of CSU, which might be roughly divided into autoimmunity-related (Fig. 1) and non-autoimmunity-related mechanisms (Fig. 2).

Autoimmunity

The role of autoimmunity in CSU has been widely investigated since autologous serum skin test (ASST) preliminarily implicated the participation of immunological factors in the pathogenesis of CSU [11]. It is generally believed now that two types of autoimmunity (type I and type II) contribute to the pathogenesis of CSU, which are mediated by IgE autoantibodies and IgG autoantibodies, respectively.

Type I autoimmunity, also known as autoallergy, is based on the successful detection of IgE targeting autoantigens in patients with CSU. More than 20 years ago, IgE anti-thyroid peroxidase (TPO) was discovered as an antibody targeting autoantigen in a proportion of patients with CSU [12]. Since then, IgE anti-TPO and IgE anti-dsDNA in CSU were noted and their connections with the pathogenesis of CSU were investigated [13, 14]. Schmetzer et al. [15] further performed a screening of these IgE-form autoantibodies in serum of patients with CSU using protein microarray analysis. They screened out more than 200 IgE anti-autoantigens and identified IgE anti-IL-24 as a specific and functional biomarker in patients with CSU, which is associated with disease activity. Soon afterwards, another study found an increased expression of IL-24 in peripheral blood mononuclear cells (PBMCs) and in local urticarial wheals in a subset of CSU patients, yet no correlation between IL-24 expression and autoimmune status was indicated [16]. Furthermore, reduction of sera IgE anti-IL-24 was suggested as partly contributing to the therapeutic effect of autologous serum therapy [17]. In addition to direct detection of IgE autoantibodies and confirmation by functional tests, the good therapeutic effect of omalizumab in moderate-to-severe CSU indirectly validated the role of IgE in CSU to some extent [18]. IgE autoantibodies bonded to the high-affinity IgE receptors (FcεRI) on MCs result in cross-linking of FcεRI-bound IgE autoantibodies and corresponding autoantigens, which triggers a series of biochemical events that culminate in MC degranulation. Siglec-8, an inhibitory receptor expressed on MCs and eosinophils, has been shown to suppress IgE-mediated MC responses and mitigate non-allergic inflammation upon ligation with a monoclonal antibody [19]. Interestingly, a soluble isoform of FcεRI was discovered recently, which could act as an endogenous inhibitor of IgE-mediated MC activation, an effect opposite to that of membrane FcεRI [20].

Type II autoimmunity is featured by the appearance of IgG autoantibodies, especially the IgG-anti-FcεRIα and IgG-anti-IgE. IgG-anti-FcεRIα/IgE is present in approximately 45% of patients with CSU, as reported in most studies, even though a recent study revealed a lower-than-expected incidence (7%), of which the difference greatly owes to the constraints added to the analyses [21]. FcεRI, a high-affinity membrane receptor of IgE, together with receptor of complement anaphylatoxin C5a (C5aR, also called CD88), both of whom expressed on MCs

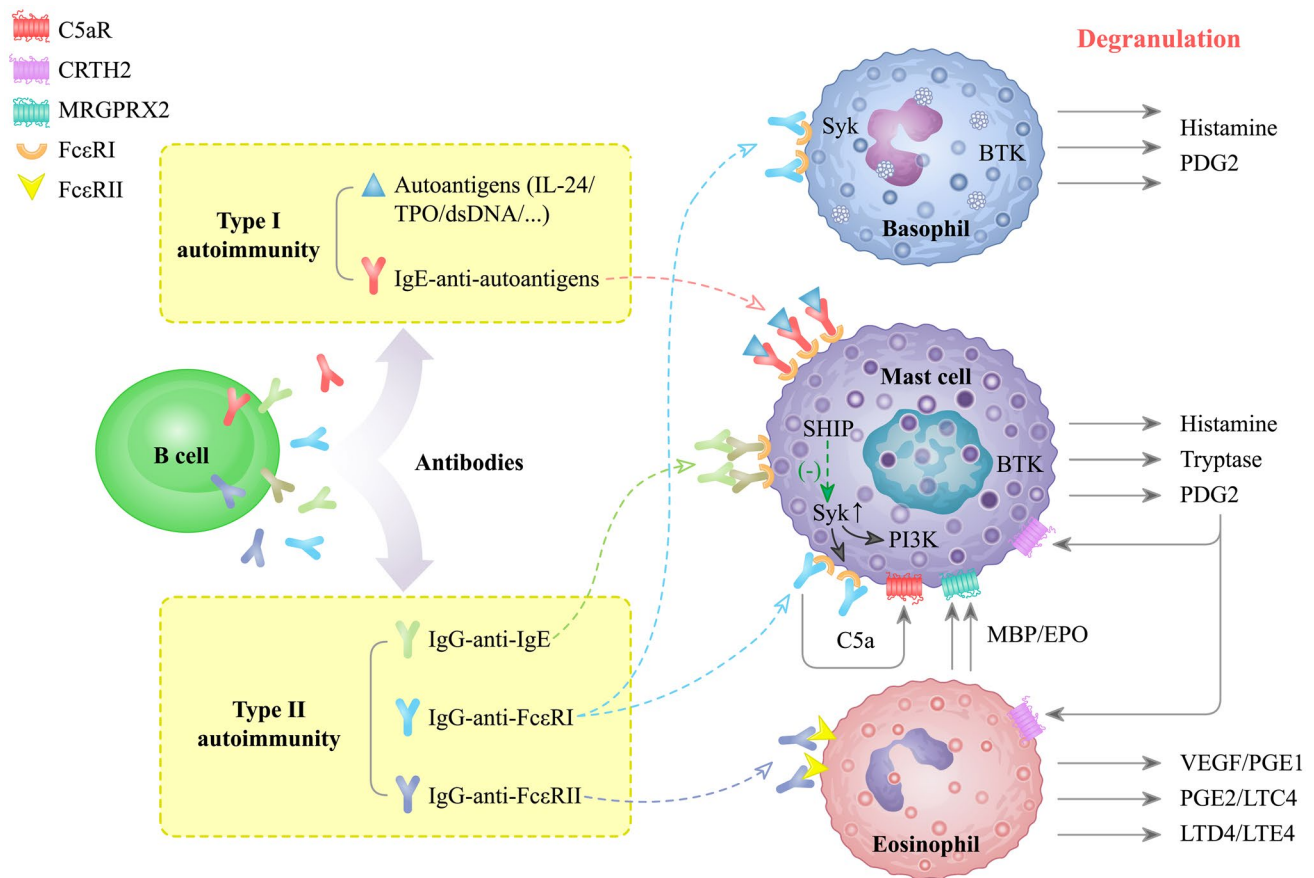


Fig. 1 A schematic model of the autoimmune pathogenesis of CSU. TPO thyroid peroxidase, IL interleukin, TF tissue factor, Syk spleen tyrosine kinase, BTK Bruton's tyrosine kinase, FcεRI high-affinity IgE receptor, FcεRII low-affinity IgE receptor, SHIP Src homology 2-containing inositol phosphatases, PI3K phosphoinositide 3-kinases, PGD2 prostaglandin D2, C5a complement 5a, C5aR complement

and basophils, was confirmed to play a role in IgG-anti-FcεRI-mediated degranulation [22]. It is recognized that IgG autoantibodies targeting FcεRI or FcεRI-bound IgE might activate effector cells and induce the subsequent degranulation in a direct way. Beyond that, IgG-anti-FcεRI was supposed to augment the degranulation via activation of C5 and the integration of C5a and C5aR [23, 24]. There was also a clue that eosinophils could undergo a similar activation by IgG against the low-affinity IgE receptor (FcεRII) expressed on eosinophils. These eosinophils activated by anti-FcεRII autoantibodies are endowed with the ability to release their major basic protein (MBP) and eosinophil peroxidase (EPO), which in turn can cause MC degranulation via Mas-related G protein-coupled receptor-X2 (MRGPRX2) on MCs [25, 26]. Furthermore, a most recent study including 35 CSU patients found that the serum level of IgM- or IgA-anti-FcεRIα was commonly increased in patients with CSU, and that elevated IgM-anti-FcεRIα was more frequently present in ASST-positive patients and was linked to basopenia and eosinopenia [27].

5a receptor, EPO eosinophil peroxidase, MBP major basic protein, VEGF vascular endothelial growth factor, PGE prostaglandin E, LTC4 leukotriene C4, LTD4 leukotriene D4, LTE4 leukotriene E4, CRTH2 chemoattractant receptor-homologous molecule expressed on T helper type 2, MRGPRX2 Mas-related G protein-coupled receptor-X2

Apart from the aforementioned findings, autoreactive CD4+ T cells that target FcεRIα were detected in most CSU patients in a study, with a cytokine secretion profile more typical of a Th1-cell response [28]. Clinical observations have also reported a higher prevalence of comorbidities with other autoimmune diseases such as Graves' disease (>2%), vitiligo (>3%), pernicious anemia (the end-stage disease resulting from autoimmune attack of the gastric mucosa), and Hashimoto's thyroiditis (>5%) in patients with CSU, as well as a noticeable percentage of family history of autoimmune diseases (>15%) in these patients, providing a further supporting evidence for the role of autoimmunity in the pathogenesis of CSU [29].

The downstream mechanisms after activation of MC or basophil in an autoimmune way which lead to degranulation have also been investigated. One of the mechanisms is the FcεRI-dependent signaling pathway consisting of Src family kinases (Lyn and Fyn), spleen tyrosine kinase (Syk), and a line of downstream pathway molecules [30].

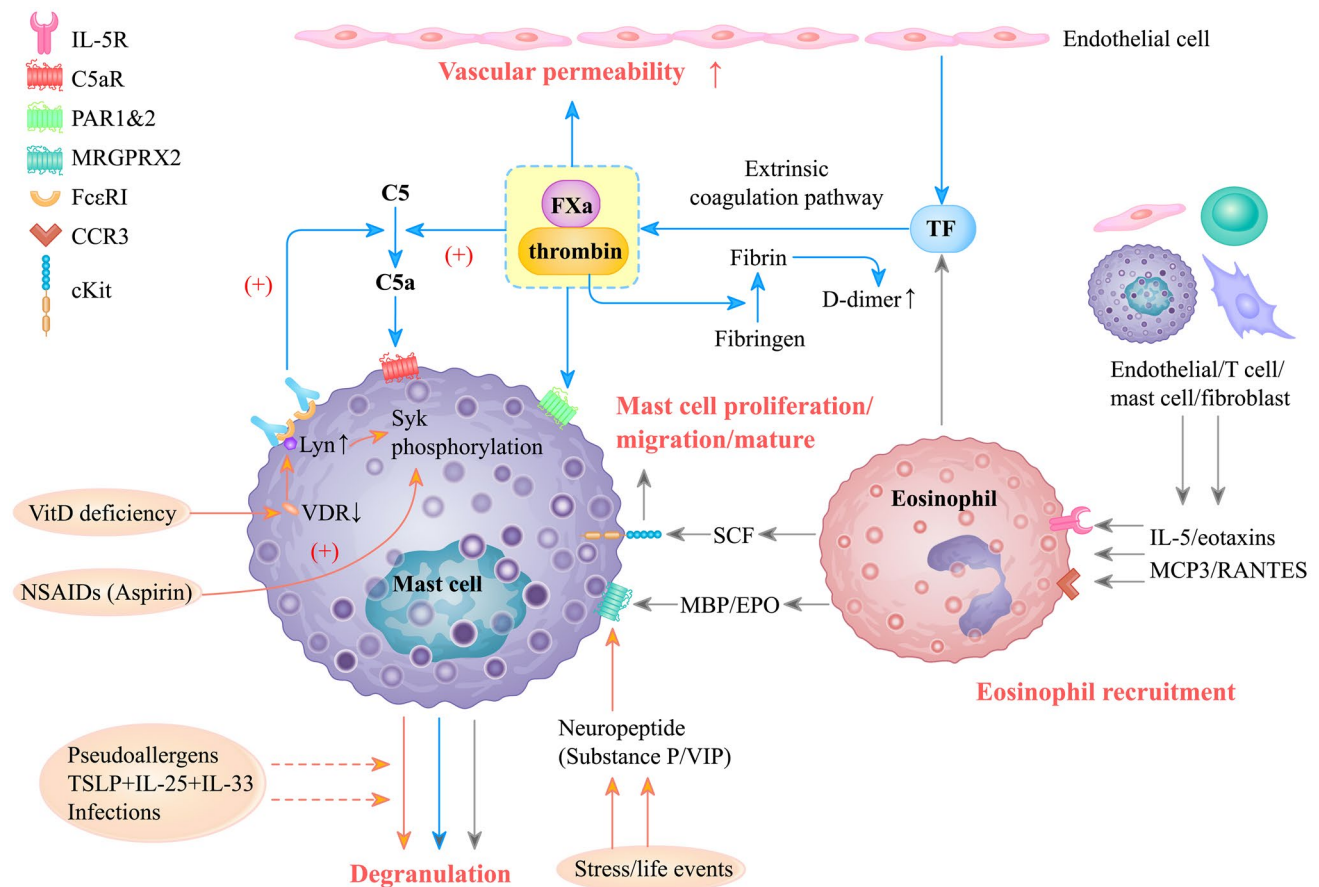


Fig. 2 An illustration of the current understanding of non-autoimmune mechanisms of CSU. Eosinophils interact with mast cells by secreting stem cell factor that plays a role in the proliferation, migration, and maturation of mast cells. Extrinsic coagulation pathway contributes to the degranulation of mast cells by interacting with PAR1, PAR2, and C5a receptors expressed on these cells. Stress and life events, vitamin D deficiency, and aspirin may also lead to mast cell degranulation via different molecular pathways. Besides, TSLP combined with IL-25 and IL-33, pseudoallergens, as well as infections, are suggested to be causing factors to stimulate mast cell degranulation in the pathogenic

process of CSU, albeit the exact mechanisms remain unclear, C5a complement 5a, C5aR complement 5a receptor, FXa activated factor X, TF tissue factor, FcεRI high-affinity IgE receptor, Syk spleen tyrosine kinase, PAR protease-activated receptor, VitD vitamin D, NSAIDs non-steroidal anti-inflammatory drugs, VDR vitamin D receptor, SCF stem cell factor, MRGPRX2 Mas-related G protein-coupled receptor-X2, EPO eosinophil peroxidase, MBP major basic protein, IL interleukin 5, IL-5R interleukin 5 receptor, MCP3 monocyte chemotactic protein-3, TSLP thymic stromal lymphopoietin, VIP vasoactive intestinal peptide

Once FcεRI aggregation happens, Lyn and Fyn transphosphorylate the immunoreceptor tyrosine-based activating motif (ITAM) within FcεRI β- and γ-subunits, subsequently promoting the activation and recruitment of Syk to ITAM, and then propagating the signals through recruitment of downstream secondary molecules including those involved in the phosphoinositide-3 kinase (PI3K) pathway. This process finally results in the mobilization of intracellular calcium and degranulation [31]. Bruton's tyrosine kinase (BTK), a downstream signal transduction molecule, was found to further upregulate the signaling pathways [32]. Oppositely, Src homology 2-containing inositol phosphatases, SHIP-1 and SHIP-2, were recruited to the phosphorylated FcεRIβ upon stimulation, serving as downregulators of this process [33]. In about half of

patients with CSU, mast cells isolated from peripheral blood can spontaneously degranulate and release histamine upon FcεRI-mediated IgE sensitization, and a corresponding higher level of Syk and lower level of SHIP was found in these CSU patients [9, 34].

To sum up, it has been generally accepted that there are at least 2 distinct pathways, type I and type II autoimmunity, involved in the pathogenesis of CSU. Several comprehensive reviews summarized the role of autoimmunity in CSU and came to a concordant conclusion on this [9, 35].

Non-autoimmunity

Whereas autoantibodies are present in only a proportion of patients with CSU, mechanisms other than autoimmunity

were proposed to be involved in the pathogenesis of the other CSU patients.

Coagulation cascade was postulated to take part in the pathogenesis of CSU. This was partly supported by the observation of a higher positive rate of autologous plasma skin test (APST) than ASST (86% vs. 53%) in patients with CSU [36]. Furthermore, elevation of several coagulation biomarkers, such as plasma prothrombin fragment F1 + 2, activated factor VII (FVIIa), and D-dimer, was indicated to be associated with active cases or severe exacerbation of CSU in a line of studies [37, 38]. Results derived from these studies showed an association of this disease with coagulation cascade and fibrinolysis, at least in the phase of activation and exacerbation. Besides, an observation that plasma levels of D-dimer turned out to be normal during CSU remission further confirmed the role of clotting process in CSU [39]. Further attentions were drawn to the extrinsic coagulation pathway, for which tissue factor (TF) is an initial activator, because of the detection of FVIIa, a product of extrinsic coagulation cascade, other than factors initiating the intrinsic coagulation pathway such as activated factor XII (FXIIa), in CSU patients [40]. In CSU, eosinophils were suggested as the primary source of TF [41]. Once TF derived from eosinophils activates the extrinsic coagulation pathway, activated coagulation factors (e.g., thrombin and Xa) generated during the cascade subsequently increase the vascular permeability either directly by working on endothelial cells or indirectly by inducing the degranulation of MCs via bonding to protease-activated receptors (PAR-1 and PAR-2) on MCs or promoting the generation of C5a by their serine protease properties [37]. The indirect functioning way of generating C5a was well-confirmed in vitro in a recent study [42]. Recent studies have evaluated the efficacy of anticoagulant therapy (e.g., heparin, warfarin) and antifibrinolytic therapy (e.g., tranexamic acid), respectively, in refractory CU, reflecting a potentially important role of the coagulation cascade in CSU [43, 44].

The relation between vitamin D deficiency and the pathogenesis of CSU has been reported over the past 30 years [45]. Vitamin D is proved to be endowed with immunoregulatory and anti-inflammatory properties [46]. In CSU, noteworthy lower serum vitamin D levels were reported in most studies [47]. Vitamin D supplementation in a high dosage for 4–12 weeks was suggested to be useful to alleviate disease activity in some CSU patients [48]. The underlying mechanism of vitamin D's role in CSU remains unclear. Nevertheless, vitamin D receptor (VDR) expressed by MCs, which forms complexes with Lyn to inhibit the binding of Lyn to FcεRI β chain and myeloid differentiation primary response 88 (MyD88), was demonstrated as a major molecule in this process. Briefly, vitamin D downregulates the phosphorylation of Syk and inhibits MyD88-dependent signaling pathway by kidnapping Lyn through VDRs, thus maintaining MC

stabilization. VDRs were also found to repress the expression of tumor necrosis factor-α (TNF-α) in MCs [49]. In addition, a latest research indicated that 25-hydroxyvitamin D could suppress the generation of vascular endothelial growth factor (VEGF) by MCs in an IgE-dependent way via inhibiting the PI3K/Akt/p38 MAPK/HIF-1α axis [50].

Regardless of acute or chronic urticaria, infections have been postulated to be pathogenic factors. Among various pathogens, chronic infection of *Helicobacter pylori* (Hp) has been well-studied; however, its potential correlation with CSU remains an ambiguous and contradictory causative property [51, 52]. A recent meta-analysis enrolling 22 studies concluded that Hp might have a relationship with the occurrence and persistence of CSU, and Hp eradication therapy could partly resolve CSU symptoms [53]. An 21–35 kDa Hp-associated protein component was regarded as the potential pathogenic factor devoting to the association between chronic Hp infection and CSU [54]. Most recently, nevertheless, a population-based cohort study showed that peptic ulcer disease was associated with an increased risk of CSU independent of Hp infection [55]. The association between CSU and other pathogenic species such as *Staphylococcus aureus* [56], toxocara [57], and hepatitis virus [58] was also analyzed, but only weak evidence was revealed. For example, serum levels of functional IgE against *Staphylococcus aureus* enterotoxins (SE-IgE) were significantly higher in CSU patients than in healthy controls, and were shown to be strongly correlated with disease activity in CSU patients [56].

Emotional factors may contribute to the onset and exacerbation of CSU in part of patients. A series of early observations that stress could exacerbate allergic skin wheal responses in patients with atopic dermatitis encouraged following researches [6]. MRGPRX2, featured by selective expression on MCs, plays a role in drug-induced anaphylactoid reactions, neurogenic inflammation, pain, itch, and chronic inflammatory diseases [59]. As the receptor for MBP, EPO, and neuropeptides, MRGPRX2 displays a significant higher expression on skin MCs from CSU patients compared with those from healthy controls [60]. Growing evidence has shown that stress exacerbates the symptoms of CSU by releasing neuropeptides such as substance P that function through MRGPRX2 expressed on skin MCs [61]. A complex neuro-immune-cutaneous model was proposed to explain the underlying pathophysiological mechanisms involved in the connection of CSU and psychological stress [62].

Non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, may exacerbate allergic symptoms in patients with CSU. A recent study suggested that aspirin might promote the phosphorylation of Syk when FcεRI-dependent signaling pathway was activated, and patients with CU tended to be more sensitive to aspirin compared with healthy controls [63].

Except for all the mechanisms mentioned above, type I allergy [64], pseudoallergens [65], genetic factors [66], T helper 2 (Th2) cell-initiating cytokine environment (thymic stromal lymphopoietin (TSLP), IL-33, IL-25, etc.) [67], stem cell factor (SCF) produced by eosinophils, fibroblasts and endothelial cells [68], prostaglandin D2 (PGD2), and chemoattractant receptor-homologous molecule expressed on T helper type 2 (CRTH2) [69] were also speculated to take part in the etiology and pathogenesis of certain subsets of patients with CSU.

Diagnosis and Assessment of CSU

According to the guidelines, information collected when making the diagnosis needs to cover three major aspects: differential diagnosis, disease status (activity, impact, and control status), and triggers of exacerbation or underlying causes [2]. As for differential diagnosis, there are different considerations for patients with different symptoms (Fig. 3). For patients who merely develop wheals, urticarial vasculitis, auto-inflammatory disorders (e.g., cryopyrin-associated periodic syndromes (CAPS)), and Schnitzler syndrome should be considered differential diagnosis. In patients who only suffer from angioedema, without hives, bradykinin-mediated angioedemas—such as angiotensin-converting enzyme inhibitor (ACEI)—induced

angioedema and hereditary angioedema (HAE)—are major differential diagnoses. For the moment, urticaria activity score (UAS) and/or angioedema activity score (AAS), CU quality of life questionnaire (CU-Q2oL) and/or angioedema quality of life questionnaire (AE-QoL), and urticaria control test (UCT) are recommended for baseline assessment of disease activity, quality of life, and disease control, respectively. To find out triggers of exacerbation or underlying eliciting factors of CSU aforementioned, a thorough history and physical examinations are supposed to be the first step followed by selective further diagnostic tests. With respect to diagnostic tests, it is recommended that no extra screening programs (except for CRP, and/or ESR, differential blood count) should be performed unless there are relative indications [2]. With the application of omalizumab and accumulating studies on CSU biomarkers, it is noteworthy that some indicators may be of certain value for projecting disease activity, treatment response (Fig. 4), and underlying causes. Among these indicators, D-dimer is supposed to be associated with disease activity [39], and baseline total IgE level may be helpful in predicting treatment response before initial usage of omalizumab [70]. In addition, ASST, basophil histamine release assay (BHRA), and basophil activation test (BAT) may be performed to help screen out autoimmune CSU (aiCSU) [8].

Fig. 3 Differential diagnoses of CSU and corresponding diagnostic workup. C3 complement 3, C4 complement 4, C1q complement 1q, DIF direct immunofluorescence, ACE angiotensin-converting enzyme, C1-INH: C1 inhibitor

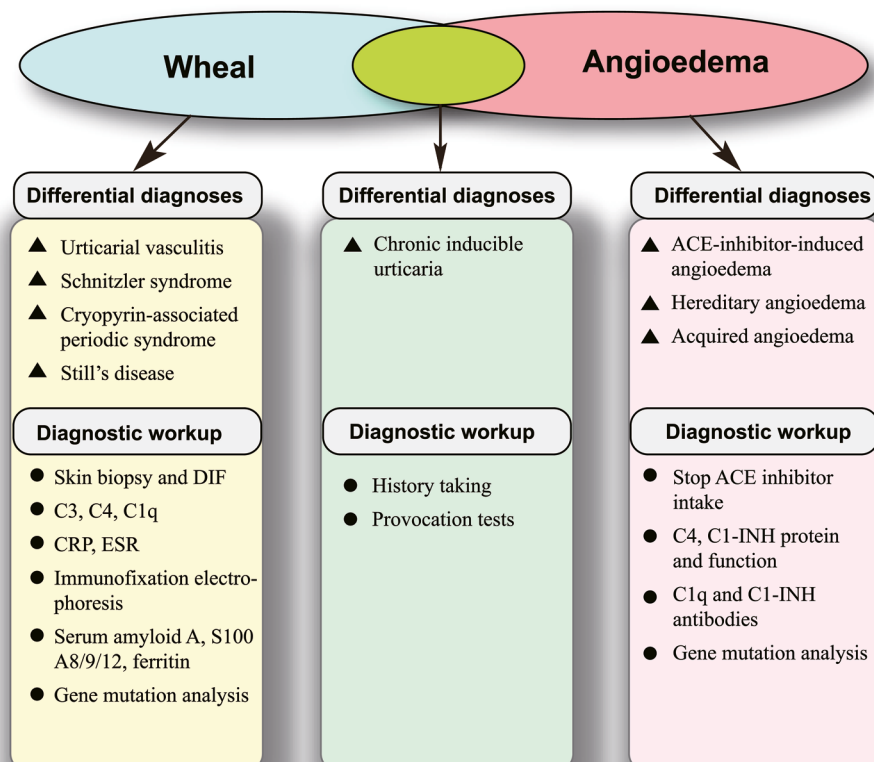
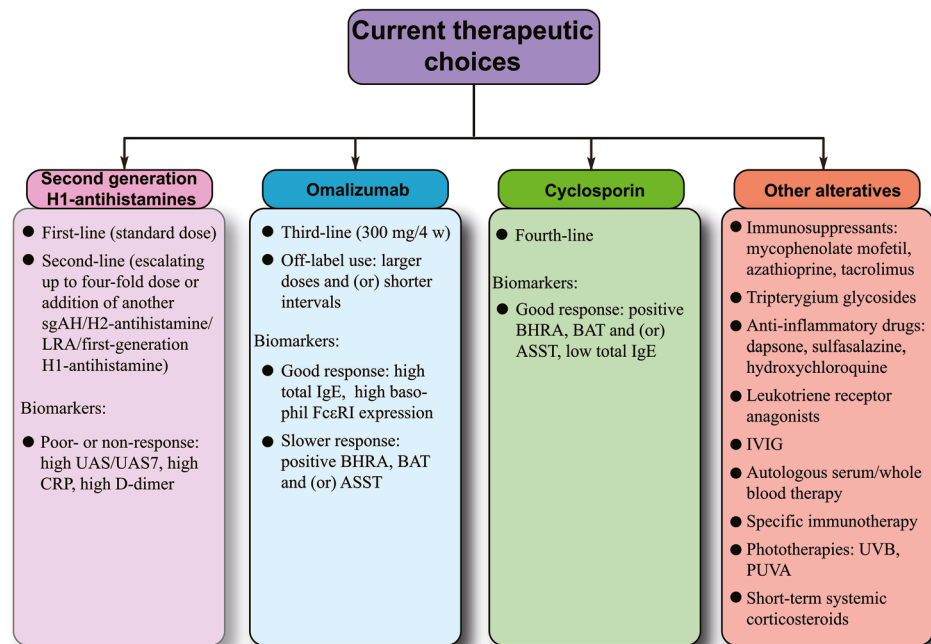


Fig. 4 Therapeutic choices for CSU and potential biomarkers associated with treatment response. UAS urticaria activity score, CRP C-reactive protein, BHRA basophil histamine release assay, BAT basophil activation test, ASST autologous serum skin test, IVIG intravenous immunoglobulin, UVB ultraviolet B, PUVA psoralen plus ultraviolet A



Advances in Treatment for CSU

Current Therapeutic Strategies

Second-Generation H1-Antihistamines It has been 40 years since sgAHs were introduced for clinical use, which has gradually replaced the usage of first-generation H1-antihistamines in CU owing to their much lower penetration through the blood–brain barrier and less side effects. According to the current guidelines, licensed dose of sgAH is the first-line treatment for all types of CU. As the second-line therapy, escalating up to quadruple dose of sgAH is recommended by the EAACI/GA²LEN/EDF/WAO guideline, and dose advancement of sgAH or the addition of another sgAH or an H2-antihistamine/leukotriene receptor antagonist (LRA)/first-generation H1-antihistamine is recommended by the American guideline [2, 71].

As recommended in the guidelines, beyond-label dosage gradually prevails in clinical practice. It is estimated that 63.2% of patients refractory to licensed dose achieved complete remission when the dosage was increased by two to four times [72]. And a growing body of evidence has shown desirable efficacy and safety profiles in both the short-term and long-term application of high-dose sgAHs [73, 74]. Nonetheless, there is still a subgroup of CSU patients who do not respond to H1-antihistamines even at a fourfold standard dose. Thus, factors that could predict refractoriness to treatment with H1-antihistamines were investigated. It is indicated that higher baseline UAS7 scores

[75], elevated plasma levels of D-dimer and CRP [39, 76], higher serum platelet activating factor (PAF) [77], eosinopenia [78], elevated ESR values [79], single-nucleotide polymorphism (SNPs) of specific genes (e.g., ORAI1, CACNA1C, CRP) [80–82], and concomitant CIndU [75] might be potentially predictive for refractoriness to treatment with sgAHs, although further assessment is needed to validate these hypotheses.

Special attention needs to be paid to evidence supporting the treatment with sgAHs in pediatric patients and in pregnant or lactating female patients with CSU. For children, the long-term safety of licensed dosage of nearly 10 sgAHs (cetirizine, desloratadine, fexofenadine, levocetirizine, rupatadine, bilastine, and loratadine included) has been confirmed [2]. However, the efficacy and safety regarding high-dose sgAHs in pediatric patients with recalcitrant CSU was seldom investigated. Recently, a cohort study of 175 pediatric CU patients (144 with CSU) revealed that the disease could be well-controlled by up dosing sgAHs to fourfolds in most cases [83]. However, a retrospective research involving 66 CSU pediatric patients, published also in 2020, showed that the enhancement of efficacy of sgAHs in children was restricted to twice the standard dosage, albeit good safety profiles of higher dosage (up to fourfolds) were observed [84]. For treatment choice during pregnancy or lactation periods, no substantial progress has been made due to the unavailability of clinical trials in this special group of patients. Even though, different attempts were made in clinical practice. The 2018 EAACI/GA²LEN/EDF/WAO guideline made a recommendation that loratadine could be considered the first choice according to weak evidence

available [2]. Studies demonstrating successful experience about the use of ebastine during pregnancy and lactation were presented in a case report [85].

Omalizumab Omalizumab, a recombinant humanized monoclonal antibody that selectively binds to free IgE at the C3 domain of its heavy chains and inhibits the binding of IgE to FcεRI on basophils and MCs, can subsequently reduce the number of free IgE, downregulate the expression of FcεRI on these cells, and thus prevent the activation of basophils and MCs [86]. The usage of omalizumab is ever-increasing and becomes the mainstay of therapy for chronic urticaria since licensed by FDA in 2014 for patients (older than 12 years old) with CSU refractory to high-dose sgAHs.

The standard dosage, 300 mg/4 weeks, of omalizumab is effective for a substantial proportion of patients with CSU, though a subgroup of patients will not respond or only partially respond to it [87]. For these patients, choices are either to continue therapy with omalizumab with beyond-label dosages or to turn to alternative drugs. According to data from the real-world studies, most patients with CSU who remain symptomatic to standard dosage of omalizumab may respond to a higher dose of up to 600 mg every 4 or even 2 weeks without compromising its safety profile defined by clinical trials with approved dosage [88, 89]. Shortening dosing interval and using a higher single dose are two options of dose advancement [90]. For patients who benefit from omalizumab, the time and ways to withdrawal as well as the safety of long-term application should then be taken into consideration. In view of the property of spontaneous remission, it has been proposed that patients being treated with omalizumab could try withdrawal periodically as soon as the complete control is achieved. Instead of abrupt stop, prolonging the interval between two doses before discontinuation of omalizumab may help dampen the disease relapse [91]. Likewise, the safety of long-term use of omalizumab up to 48 weeks was confirmed in the XTEND-CIU study [92]. Furthermore, personalized, long-term use of omalizumab (up to 6 years) was reported in several retrospective and observational studies and proved safe and effective [89]. Overall, individualized therapy should be taken as the principle when considering the dosage of omalizumab, giving the medication “as much as needed and as little as possible,” as recommended by the 2018 EAACI/GA2LEN/EDF/WAO guideline. Alternatively, for patients with partial response to omalizumab, combination therapy with other drugs such as cyclosporine could be considered [93].

Generally, omalizumab is well-tolerated and its adverse reactions are infrequent [87]. Nonetheless, anaphylaxis may occur occasionally after its injection. In a case–control study involving 118 patients with asthma who were omalizumab users, the comparison between the 30 cases with an

adjudicated history of anaphylaxis to omalizumab and the 88 controls who had been receiving omalizumab treatment without anaphylaxis to it has revealed that the risk of anaphylaxis associated with omalizumab administration significantly increased in individuals who had a prior history of anaphylaxis to food, medication, or other causes [94]. Furthermore, a study enrolling a larger sample size concluded that anaphylaxis reactions occurred mostly within the first 3 doses (72%) and within 1 h (64%) after dosing, and respiratory symptoms were most frequently reported (95%) [95]. Thus, it is recommended that patients must be supervised for 2 h after omalizumab injection in the first 3 doses, and 30 min after injection in subsequent doses [96]. The exact mechanisms underlying the anaphylactic reactions associated with omalizumab administration remain unclear. It is assumed that anaphylaxis may be triggered by the excipients that form the commercial product of this monoclonal antibody [97]. Another study has suggested that immune complexes formed by omalizumab and IgE can induce anaphylaxis and skin inflammation by engaging IgG receptors (FcγRs) in FcγR-humanized mice, implicating that Fc-engineered versions of omalizumab could be a potential strategy to reduce such adverse reactions [98]. More researches are needed to make it clear how these side effects happen, how to predict the subgroup of patients who are intolerant to omalizumab, and what should be done to avoid the relevant risk.

Along with the ever-accumulating researches on omalizumab, the heterogeneity of efficacy and response rate was noticed. Accordingly, factors that could help predict the response to omalizumab have been investigated. The baseline blood level of IgE, the direct target of omalizumab, has been proposed as a predictor for responder and non-responder [70, 99]. Patients with higher IgE levels at baseline tends to have a quicker response to omalizumab, but relapse sooner after withdrawal of this treatment [100]. Likewise, the expression of FcεRI on the surface of basophils and MCs has been verified as another potential biomarker to predict the efficacy of omalizumab with a 100% sensitivity and 73.2% specificity [101]. The correlation between D-dimer and therapeutic response was also studied, but results turned out to be contradictory, although the connection between a high serum level of D-dimer and a higher disease activity was confirmed [39, 102]. Factors that can help predict the initiating time of response have also been studied. Patients with positive BHRA, BAT, and (or) ASST are more likely to display a slower reaction pattern after administration of omalizumab [8, 103]. It is supposed that this is at least partly due to the type II autoimmunity characteristics of these patients who are positive in BHRA, BAT, and (or) ASST, in whom the downregulation of FcεRI expression on basophil and mast cell surface by omalizumab takes a relative longer time [104]. In addition to biomarkers mentioned

above, ANA [105], CD203c responsiveness [106], serum transglutaminase 2 [107], IL-31 [108], extracellular vesicle microRNAs [109], and some clinical predictors such as obesity [110], baseline UAS7 score and course of disease [99] were also reported as potential factors that may predict response before omalizumab treatment or predict relapse after its withdrawal.

While omalizumab has been approved for patients with CSU aged 12 years or older, the off-label use in patients with refractory CSU younger than 12 years old has also been studied. A latest systematic review enrolling a series of cases and retrospective studies concluded that a 150–300-mg monthly dose of omalizumab achieved a complete response in 81%, a partial response in 19%, and adverse effects related to omalizumab in none of pediatric patients with antihistamine-resistant CU, indicating an acceptable efficacy and safety profile [111]. Consistently, a recent real-world study in China came to a similar conclusion, in which 67% patients achieved well-or-complete control of CU (defined as a UCT score ≥ 12) after the first administration of omalizumab and no adverse events were observed [112]. The safety of omalizumab for pregnant or lactating women and their infants was preliminarily analyzed in an observational study in pregnant women with asthma, the Xolair Pregnancy Registry (EXPECT), which enrolled 250 patients exposed to omalizumab during the first trimester of pregnancy. The data of this study showed no increase in the rate of adverse events compared to the rate reported by previous studies on other treatments (except for omalizumab) in pregnant women with asthma [113]. Recently, a study which compared the EXPECT outcomes with those from a disease-matched comparator external cohort of pregnant women not treated with omalizumab ($n = 1153$) provided a further confirmation for its safety profile [114]. For the application of omalizumab in the treatment for pregnant women with CSU, there have been some successful cases and case series with good therapeutic effects reported, in which no apparent side effects were observed in both mothers and their infants [115, 116]. Although it is still insufficient to support the recommendation of omalizumab in this patient group due to the low potency of evidence, experience up to present has provided a favorable reference for this application.

Other Alternative Drugs Besides histamine and omalizumab, lots of alternative drugs mentioned but not preferentially recommended in the guidelines provide further therapeutic choices for refractory cases of CSU.

Cyclosporine is verified as an efficacious add-on therapy in combination with either antihistamine or omalizumab owing to its immunosuppressive effects on major effector cells (T cells, MCs, eosinophils, and basophils) [117]. Given the well-known toxicities (e.g., renal dysfunction, hypertension), its application is restricted to

severe antihistamine- and/or omalizumab-refractory CSU patients and viewed as an off-label use [2]. Although used in CSU treatment for a long time, its dosage in routine application has not been normalized (Table 1). Recently, a systematic review and meta-analysis enrolling two RCTs suggested that cyclosporine at 1–5 mg/kg/day was efficient for recalcitrant CSU and that its adverse reactions were dose-dependent. Among the patients treated with moderate (4–5 mg/kg/day), low (2–4 mg/kg/day), and very low (< 2 mg/kg/day) doses of cyclosporine, 57%, 23%, and 6% had experienced one or more side effects, respectively. Eventually, 3 mg/kg/day was proposed as the initial dose of cyclosporine for most patients [118]. Some factors have been proposed to be of value in predicting the potential of response to cyclosporine. For instance, a systematic review concluded that lower total IgE levels in the serum was associated with a better response to cyclosporine [119]. Meanwhile, patients with positive ASST, BHRA, and (or) BAT were indicated as more likely to present a faster and better response to cyclosporine [120]. Considering that patients with positive ASST, BHRA, and (or) BAT and low serum level of total IgE are more likely to have a type II autoimmunity in pathogenesis of CSU, it is suspected that individuals with a fast and favorable response to immunosuppressive therapies may pertain to the type II aiCSU [104, 119].

Some other immunosuppressants are also tried in treatment for recalcitrant CSU albeit most of them have non-negligible side effects and low level of evidence for use in CSU [121]. Methotrexate (MTX), an immunosuppressive drug widely used in autoimmune diseases and cancers, has been proved useful in individual cases of CSU, probably due to its immunomodulatory and anti-inflammatory properties that inhibit the production of autoantibodies in CSU [122]. However, RCTs published all failed to achieve a difference between the efficacy of MTX and that of placebo as an add-on therapy to H1-antihistamine. Meanwhile, adverse reactions such as hepatic dysfunction and pneumonia have been reported, although all of them were described as well-tolerated [123, 124]. In view of the poor contribution to efficacy and debatable safety profile, MTX is at least not a prior option for CSU. Mycophenolate mofetil, 1000–6000 mg/day, was also tried in patients with aiCSU who failed to response to the treatment with antihistamines or other therapeutic agents and demonstrated as a useful and well-tolerated optional therapy [125, 126]. With regard to azathioprine and tacrolimus, two other immunosuppressants, limited information are available for their usage in treatment for CSU [127, 128].

Montelukast, an inhibitor of the leukotriene-D4-receptor, has been studied in treatment for CSU since over a decade ago. The beneficial effect of its combination with sgAH in mild CU was confirmed in a RCT study including 81

Table 1 Alternative drugs evaluated for CSU treatment

Drugs	Usage and dosage	Side effects	Clinical evidence	References
Cyclosporine	p.o 1–5 mg/kg/day	Increased creatinine levels, hypertension, diarrhea, gastrointestinal disturbances, hirsutism, infections, paresthesia, peripheral neuropathy, etc	RCTs	[118, 184–187]
Tacrolimus	p.o 2–6 mg/day	Gastrointestinal symptoms, hypertension, elevated serum creatinine, headache, paresthesia, lower extremity edema, etc	Retrospective studies	[128, 146]
Azathioprine	p.o 50 mg/day or 150 mg/day	Vomiting, abdominal pain, loose stool, etc	RCTs	[127, 187, 188]
Methotrexate	p.o 10–20 mg/week 0.2–0.25 mg/kg/week	Nausea, vomiting, fatigue, elevated liver enzymes, gastrointestinal discomfort, <i>Pneumocystis jirovecii</i> pneumonia, etc	RCTs	[122–124]
Mycophenolate mofetil	p.o 1000–6000 mg/day	Gastrointestinal intolerance, viral gastroenteritis, etc	Retrospective study; prospective study	[125, 126]
Tripterygium glycosides	p.o 20 mg, thrice a day	Elevated liver enzymes, amenorrhoea, reproductive toxicity, etc	Meta-analysis of RCTs	[139]
Dapsone	p.o 20–200 mg/day	Decreased hemoglobin level, leukopenia, DRESS, mild nausea, mild neuropathy, etc	RCTs	[132–134]
Sulfasalazine	p.o 2000–4000 mg/day	Drug-induced leukopenia, gastrointestinal discomfort, elevated liver enzymes, rhabdomyolysis, etc	Retrospective studies	[189, 190]
Montelukast	p.o 5–20 mg/day	Sleeplessness, drowsiness, tiredness, aphtha, etc	RCTs	[129, 130, 191, 192]
IVIG	i.v. drip 400 mg/kg/day (for consecutive 3–5 days every 4–6 weeks)	Anaphylaxis in patients with IgA deficiency, acute renal failure, thrombosis, aseptic meningitis, etc	Case series	[140, 193, 194]
Phototherapy	e.i	Tanning, xerosis, nausea, gastrointestinal adverse effects, erythema, etc	RCTs	[145, 195]
Specific immunotherapy	Sublingual or i.h	Sleepiness, fatigue, dry mouth, headache, etc	Meta-analysis	[64]
Autologous serum/ whole blood therapy	i.m	Injection site reactions	RCTs	[17, 43, 142, 143, 196]

p.o. oral administration (per os), i.v. intravenous, e.i. external irradiation, i.h. subcutaneous injection, i.m. intramuscular injection

patients [129]. However, its efficacy in patients with moderate CSU was denied in another comparative RCT study [130]. Considering its safety and efficacy in mild CU, it is recommended in the 2014 version of American guideline as an add-on therapy in the step-two treatment of CSU for those resistant to licensed dose of sgAHs [71]. A systematic review performed recently concerning leukotriene receptor antagonists for CU provided evidence in favor of its positive effects in the treatment of CSU [131].

Dapsone is an anti-inflammatory drug that has been tried in treatment for recalcitrant CSU. A small sample double-blind placebo-controlled trial observed a remission in patients with refractory CSU after treatment with dapsone, among which nearly 10% achieved complete remission [132]. Similar results were observed in a previous randomized non-blinded clinical

trial [133]. A retrospective medical record review conducted by the tertiary-care academic medical center at the New York University School of Medicine recently reported that among their 79 patients with CSU treated with dapsone, 37% achieved a complete response and dapsone displayed a placebo-like safety profile, which verified the effectiveness and well-tolerance of dapsone again [134]. Nonetheless, severe side effects such as anemia and dapsone syndrome related to this drug deserve attention before its clinical application. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at increased risk of acute hemolytic reaction [135], and individuals carrying the HLA-B*13:01 alleles are associated with a severe and even life-threatening side effect, dapsone syndrome [136]. It is estimated that 80% of patients may experience a drop of hemoglobin level by at least 1 g/dL after taking dapsone at a dosage

of 50 mg per day or greater [137]. In order to avoid these severe side reactions, examination of G6PD and the HLA-B*13:01 alleles should be required prior to initiation of treatment with dapsone.

Other therapeutic agents or methods that have been proposed and tried for treating CSU include hydroxychloroquine [138], sulfasalazine [54], tripterygium glycosides [139], intravenous immunoglobulin (IVIG) [140], systemic corticosteroids [141], autologous serum/whole blood therapy [142, 143], specific immunotherapy (SIT) [64], and phototherapies like ultraviolet B (UVB) and psoralen plus ultraviolet A (PUVA) [144, 145]. All of them may be valuable in some cases of CSU in spite of the absence of high-level evidence, lack of universal efficacy, and/or excellent safety profiles [146]. Among them, autologous serum/blood therapy displays therapeutic effect in ASST-positive patients, and short-term systemic corticosteroids can be used for severe acute attacks of urticaria [2, 17].

Novel Drugs

Though therapeutic strategies aforementioned (Fig. 4) can mitigate or control symptoms of CSU to a large extent, none of them can cure CSU, either alone or in combination. Moreover, some of them have definite adverse reactions and need close monitoring during the treatment process [121]. With the progress of our understanding of the pathogenesis of CU (Fig. 1), dozens of new biologics and drugs targeting different key molecules or immune components have been under development and hold the potential to improve the treatment strategy in the future (Table 2). In the mildest of these treatments, some are novel targeted drugs for CSU (e.g., ligelizumab, UB-221, AK002, AZD1981, GSK2646264) and others are of off-label use (e.g., dupilumab, mepolizumab, benralizumab, rituximab).

Novel Monoclonal Antibodies Targeting IgE Ligelizumab, a promising humanized monoclonal anti-IgE antibody, shows a 40-fold to 50-fold higher binding affinity to IgE than omalizumab, with an extra potent to suppress IgE binding to FcεRI and basophil activation [147]. In a recently completed phase 2b clinical trial, CSU patients treated with either 72 mg or 240 mg of ligelizumab subcutaneously every 4 weeks achieved higher rates of complete symptom control (UAS = 0) at week 12 than those treated with 300 mg of omalizumab or placebo every 4 weeks (44%, 40%, 26%, and 0%, respectively), with no adverse effects related to ligelizumab or omalizumab documented [148]. This was followed by the initiation of several phase 3 multicenter RCTs (NCT03580356, NCT03580369, NCT03437278, NCT04210843) further evaluating the efficacy and safety profiles of ligelizumab. UB-221, another humanized anti-IgE monoclonal antibody with an eightfold higher affinity to free IgE than omalizumab,

which can neutralize free IgE and downregulate IgE synthesis, is currently tested in a phase 1 trial (NCT03632291).

Monoclonal Antibodies Targeting IL-5 or Its Receptor It has been suggested that eosinophil infiltration contributes to the pathogenesis of CSU, in which eosinophils may be recruited to urticaria lesions by mast cells via releasing IL-5 and other chemotactic mediators. Accordingly, mepolizumab and reslizumab, humanized anti-IL-5 mAbs, as well as benralizumab, an anti-IL-5 receptor mAb, which were initially approved for the treatment of patients with severe eosinophilic asthma, have been tried in the treatment of patients with CU and effectively reduced the symptoms of patients with either CSU or CIndU. Recently, three monthly subcutaneous injections of benralizumab (30 mg) were indicated as a useful treatment in improving the symptoms of sgAH-refractory CSU patients in a single-center, single-blind study [149]. In addition, an ongoing phase 2b study (NCT04612725) on the application of benralizumab in the treatment of CSU is designed to evaluate induction and maintenance dosing regimens. Currently, mepolizumab is under a phase 1 study (NCT03494881), in which 100 mg of mepolizumab is given to patients with CSU subcutaneously at weeks 0, 2, 4, 6, and 8, respectively.

Monoclonal Antibodies Targeting IL-4/13Rα Dupilumab, which was approved for moderate-to-severe atopic dermatitis (AD) as a mAb against IL-4/13Rα, is another repurposing drug for CSU. Considering the key pathogenic role of mast cells and IgE in both CSU and AD, it is reasonable to expect dupilumab as a viable treatment option for CSU. The efficacy of dupilumab in the treatment of CSU was preliminarily confirmed in cases wherein omalizumab at 600 mg monthly has failed [150]. It is suggested that the therapeutic mechanisms may attribute to the pathological role of IL-4 and IL-13 in the development of CSU as well. Subsequently, two randomized, double-blind, placebo-controlled, multicenter studies (NCT03749135, NCT04180488) of dupilumab in antihistamine-resistant CSU patients were initiated successfully, making dupilumab a promising therapy for patients with CSU in the future.

Drugs Targeting Surface Molecules or Signaling Pathways Anti-Siglec-8 antibody (AK002), topical Syk inhibitor (GSK2646264), BTK inhibitors (GDC-0853, LOU064), and CRTh2 antagonist (AZD1981) are novel targeted therapies for CSU other than anti-IgE mAbs. As aforementioned, these targets are either molecules of intracellular signaling pathways or surface molecules of pathogenic cells and participate in the pathogenesis of CSU without exception. All these treatments are currently under clinical trials for CSU at different stages and have completed at least one registered trial up to present according to the information on clinicaltrials.gov.

Table 2 Potential therapeutic targets of novel drugs/treatments for CSU and their status in the development process

Targets	Functions in pathogenesis of CSU	Drugs	NCT number of registered clinical trials	Start date of clinical trials
IgE	Binding to FcεRI on MCs and basophils, or FcεRII on eosinophils, inducing degranulation of these cells	Ligelizumab	NCT04513548	2020.08.05
			NCT04210843	2020.01.08
			NCT03907878	2019.04.13
			NCT03580369	2018.11.17
			NCT03580356	2018.10.20
			NCT03437278	2018.08.01
			NCT02649218	2016.05.24
			NCT02477332	2015.07.15
		UB-221	NCT04175704	2021.12.30
IL-4Rα	A shared subunit of receptors to IL-4 and IL-13, crucial in Th2 immune response and IgE class-switching	Dupilumab	NCT04180488	2019.12.11
			NCT03749135	2018.11.12
IL-5	Crucial for eosinophil differentiation, activation, and chemotaxis	Mepolizumab	NCT03494881	2019.07.30
IL-5R	Crucial for eosinophil differentiation, activation, and chemotaxis	Benralizumab	NCT04612725	2020.10.27
			NCT03183024	2017.09.12
Siglec-8	Inducing apoptosis in eosinophils and inhibiting FcεRI-dependent mediator release from MCs	AK002 (antolimab)	NCT03436797	2018.01.23
CRTH2	Receptor of PGD2 expressed on eosinophils and basophils, inducing chemotaxis of eosinophils and basophils	AZD1981 (a selective CRTH2 antagonist)	NCT02031679	2014.01
Syk	A signal molecule in the FcεRI pathway promoting the degranulation of MCs	GSK2646264 (a topical cream)	NCT02424799	2014.11.17
BTK	Participating in MC activation by transducing the signal downstream of FcεRI, and mediating the maturation and function of B cells by transducing the signal of B-cell receptors	Remibrutinib (LOU064)	NCT04109313	2019.10.24
		Fenebrutinib (GDC-0853)	NCT03926611	2019.06.06
			NCT03693625	2018.09.27
CD20	Essential for the differentiation and maturation of B cells	Rituximab	NCT00216762	2006.01
IL-1	A proinflammatory cytokine	Canakinumab	NCT01635127	2012.06
Stage of clinical trials	Location of clinical trials	Number of participants enrolled	Age of patients enrolled	State of clinical trials
Phase 1	Germany	68	18–79	Recruiting
Phase 3	Worldwide	1713	≥ 12	Recruiting
Phase 3	Japan	66	≥ 18	Active, not recruiting
Phase 3	Worldwide	1050	≥ 12	Recruiting
Phase 3	Worldwide	1078	≥ 12	Active, not recruiting
Phase 2	Worldwide	49	12–18	Completed
Phase 2	Worldwide	227	18–75	Completed
Phase 2	Worldwide	382	18–75	Completed
Phase 1	-	32	≥ 18	Not yet recruiting
Phase 1	Taiwan	15	20–75	Completed
Phase 3	Worldwide	234	6–80	Recruiting
Phase 2a	Worldwide	72	18–75	Recruiting
Early phase 1	USA	20	≥ 18	Recruiting

Table 2 (continued)

Stage of clinical trials	Location of clinical trials	Number of participants enrolled	Age of patients enrolled	State of clinical trials
Phase 2	World wide	160	18–130	Recruiting
Phase 4	USA	12	19–70	Completed
Phase 2a	USA, Germany	47	18–85	Completed
Phase 2a	USA	38	18–65	Completed
Phase 1	Germany, UK	34	18–70	Completed
Phase 2	Worldwide	191	18–99	Active, not recruiting
Phase 2a	Worldwide	311	18–99	Active, not recruiting
Phase 2	USA, Canada, Germany	31	18–75	Terminated
Phase 2a	USA, Canada, Germany	134	18–75	Completed
Phase 1&2	USA	15	18–70	Terminated
Phase 2	Switzerland	20	18–70	Unknown

IL-4Rα interleukin-4 receptor subunit α , *Th2* T helper type 2, *CRT2* chemoattractant receptor-homologous molecule expressed on T helper type 2 cells, *PGD2* prostaglandin D2, *MC* mast cell, *BTk* Bruton's tyrosine kinase

Other Monoclonal Antibodies Rituximab (RTX) and canakinumab are mAbs against CD20 and IL-1, respectively. Both of them have been tried in the treatment of CSU and proved as effective alternatives for severe, treatment-resistant patients. However, apart from a phase I/II open-label trial (NCT00216762) of RTX that was terminated due to safety concerns and a phase II randomized double-blind placebo-controlled study of canakinumab whose results are not available yet, there is currently no other clinical trials available for either of these two drugs.

CIndU

CIndU, another type of CU, occurs merely after exposure to specific triggers. It is classified into two types according to different properties of eliciting factors. Patients who come across urticaria symptoms closely related to the exposure to physical factors are categorized as physical CIndU, which includes symptomatic dermographism, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory urticaria. Patients whose onset of symptoms is intimately associated with nonphysical factors are categorized as nonphysical CIndU, which includes aquagenic urticaria, contact urticaria, and cholinergic urticaria [151]. It is estimated that 0.5% of the population may be affected by at least one type of CIndU [152], among which symptomatic dermographism occurs most frequently followed by cold urticaria [59]. Besides, CIndU may clinically present with CSU in a same individual. It is reported that approximately 36.3% patients with CSU could be accompanied by CIndU, especially the symptomatic dermographism [153]. Sometimes, patients with CIndU may not develop typical dermatological signs but systemic symptoms, among which anaphylaxis is supposed to be the most severe pattern [154, 155]. For

patients with CIndU, the quality of life is largely discounted due to the long disease duration and consecutive avoidance of triggering factors or activities [152]. Recent studies have advanced our understanding of the underlying etiopathogenesis and management of CIndU. Nonetheless, the underlying mechanisms are as of yet largely unknown, which results in a lack of targeted treatment options for CIndU except for the anti-IgE therapy. To figure out what can be done in the future, it is of help to summarize the updated understanding of the pathogenesis and treatment options.

Advances in the Pathogenic Mechanisms of CIndU

For cholinergic urticaria, atopic predisposition confirmed by the Erlangen Atopy Score was found in 57% of cases and suggested of clinical relevance to more serious disease activities and poorer quality of life [156]. IgE-dependent activation of MCs may play a pivotal role in the pathogenesis of cholinergic urticaria, which is evidenced by the clinical effectiveness of omalizumab treatment in these patients [157]. Sweat allergy, a type I hypersensitivity against the contents of sweats, was noticed in patients with cholinergic urticaria from early on [158]. Furthermore, MGL-1304, produced by *Malassezia (M.) globose*, has been identified as a major antigen in sweats due to the successful detection of specific anti-MGL-1304 IgE in patients' serum [159].

For cold urticaria, autoimmune and neurogenic mechanisms have been suggested to be implicated in the etiopathogenesis. Though no specific autoantigens have been found directly, it is hypothesized that exposure to cold may lead to de novo synthesis of autoantigens, which was supported by indirect evidence such as an elevated serum total IgE level in patients with cold urticaria and a good response of omalizumab in refractory cases [160, 161]. Transient receptor

potential melastatin-8 (TRPM8) channels, as vascular sensors of cold in the cutaneous microvasculature, used to be supposed as involved in the pathogenesis of cold urticaria [162], whereas this assumption was denied in subsequent studies [163].

In a recent study, a photo-allergen was detected in the serum of patients with solar urticaria by basophil activation test. In response to this serum photo-allergen, basophils from a patient with solar urticaria can be activated by an IgE-mediated mechanism [164].

Autoimmunity has been indicated to play an important role in the pathophysiology of symptomatic dermographism, which is partly supported by the detection of anti-FcεRIα autoantibodies in patients' serum and the preeminent therapeutic effect of anti-IgE drugs (omalizumab) [165, 166]. Interestingly, a symptomatic dermographism model was successfully established in monkey as early as in 1987 by intradermal injection of the serum isolated from patients with severe symptomatic dermographism to these monkeys [167].

With the successful off-label application of omalizumab in patients with different types of CIndU, the role of autoimmunity in the etiopathology of CIndU has been taken into consideration and explored in spite of the absence of sufficient evidence up to present [168]. Beyond that, other underlying mechanisms responsible for the inducing and exacerbation of CIndU may also play a role. To uncover this mysterious field, more researches of high quality are needed.

Diagnosis of CIndU

The diagnosis of CIndU depends on a thorough history and provocative tests specifically designed for each type (Table 3). When collecting history, questions like "Can you make your wheals come?" and "if yes, how can you bring out your wheals?" are suggested to be involved to preliminarily figure out the eliciting factor [152]. Once the inducement is confirmed, corresponding provocation test which aims to verify the diagnosis is supposed to be conducted. To keep the tests dependable, patients should be off the antihistamines and corticoids for at least 3 and 7 days, respectively [2]. The existing well-established protocols of provocation tests make the diagnosis credible and the data comparable. Nonetheless, a possible separation from history to test should not be ignored. It is reported that approximately 38% of patients with a positive history turned out negative in the corresponding provocative test, and more than one-fourth of patients turned positive when the test was repeated [169]. Therefore, repeated tests should be performed for these patients who display a suspicious history. After the diagnosis is verified, threshold tests are proposed for assessing the disease severity and evaluating the therapeutic effects. Physicians

and nurses should be cautious about the risk of anaphylaxis throughout the executing process of these tests and make sure that necessary preparations for an emergent rescue of anaphylactic shock, including but not limited to epinephrine, are always ready.

Advances in Treatment of CIndU

Over the past few years, progresses have been made both in the understanding of CIndU and the treatment for it. However, cohort study, RCT, and other well-designed studies are still limited, and thus clinical evidence supporting different treatment choices for CIndU are relatively limited.

The avoidance of eliciting factors is a primary preventive measure for patients with CIndU. In addition, desensitization is also a specific treatment targeting the triggers of CIndU. As of now, it has been successfully applied in cold urticaria [170], solar urticaria [171], cholinergic urticaria [172], and heat urticaria [173]. However, desensitization has not yet been routinely applied in clinical practice due to the risk of triggering severe anaphylaxis.

Besides the prevention and desensitization of eliciting factors, management of symptoms is equally valuable, and sometimes indispensable to patients whose quality of life is dramatically diminished. According to the 2018 guideline, the recommended stepwise therapy for CIndU is the same as that for CSU, which includes standard dose of sgAHs and escalated dose (up to fourfolds) of sgAHs and omalizumab as the first-, second-, and third-line treatment option, respectively [2]. However, high-quality evidence and clinical studies evaluating the efficacy of these treatment agents for CIndU are still limited. In a systemic review on treatments for CIndU, which was published in 2018, the authors have enrolled a total of 30 studies, yet no studies on aquagenic urticaria, contact urticaria, heat urticaria, or vibratory urticaria were eligible to be enrolled [174]. In other words, the overall stepwise therapy recommendation for CIndU in the current guideline was made partly based on the limited evidence available and partly based on consensus of experts and extrapolation from the treatments for CSU.

As for the sgAHs in CIndU, conclusions drawn by the latest systemic reviews on treatment options of cold urticaria, delayed pressure urticaria, and symptomatic dermographism were in line with the ones recommended by the current guidelines. According to these systemic reviews, standard dosage of antihistamines was widely proved as effective in CIndU. For cases resistant to standard dosage of antihistamines, up dosing of antihistamines can largely improve the response rate in patients with cold urticaria, whereas no similar studies were carried out in patients with delayed pressure urticaria or symptomatic dermographism [175–177]. A prospective parallel group-controlled study which included 70 CIndU and 66 CSU patients aiming to evaluate the efficacy

Table 3 Classification of CIndU and the recommended diagnostic workup for different types of CIndU

Classification of CIndU	Triggering factors	Provocation tests	Threshold tests	Assessment instruments
Cold urticaria	Cold exposure and rewarming of the skin	1) <i>Site</i>: volar forearm 2) <i>Test</i>: 4°C, 5 minutes 3) <i>Instruments</i>: TempTest® tools 4) <i>Reading time</i>: 10 minutes after test 5) <i>Positive reactions</i>: the test site develops palpable and clearly visible wheals and a flare-type skin reaction within 10 minutes of skin rewarming	1. <i>Time threshold</i>: 1) <i>Definition</i>: the shortest time duration of cold exposure to induce urticaria symptoms 2) <i>Instruments</i>: an ice cube or TempTest® tools 3) <i>Test time</i>: 5 minutes 2. <i>Temperature threshold</i>: 1) <i>Definition</i>: the highest temperature that induces a wheal 2) <i>Instruments</i>: TempTest® tools 3) <i>Test time</i>: 5 minutes	1. Disease activity: CholUAS7 [156] for cholinergic urticaria, whereas UAS7 and AAS for all other types of CIndU 2. Quality of life: CholU-QoL [197] questionnaire for cholinergic urticaria, whereas CU-QoL for the other subtypes of CIndU 3. Control test: UCT for all subtypes of CIndU
Heat urticaria	Heat exposure of the skin	1) <i>Site</i>: volar forearm 2) <i>Test</i>: 44°C, 5 minutes 3) <i>Instruments</i>: TempTest® tools 4) <i>Reading time</i>: 10 minutes after test 5) <i>Positive reactions</i>: the test site shows a palpable and clearly visible wheal and a flare-type skin reaction	1. <i>Time threshold</i>: 1) <i>Definition</i>: the shortest time duration of heat exposure to induce urticaria symptoms 2) <i>Instruments</i>: TempTest® tools 3) <i>Test</i>: 5 minutes 2. <i>Temperature threshold</i>: 1) <i>Definition</i>: the lowest temperature that induces a wheal 2) <i>Instruments</i>: TempTest® tools3) <i>Test time</i>: 5 minutes	
Delayed pressure urticaria (pressure urticaria)	Sustained mechanical pressure to the skin	1) <i>Site</i>: upper back, thighs, or volar forearm 2) <i>Test</i>: A. dermatographic tester (HTZ dermographometer): pressing against the back with an applied force of 100 g/mm² for 70 seconds B. weighted rods: pressing against the skin with weighted rods sized 1.5 cm in diameter and weighted 2.5 kg for 20 minutes, or weighted rods sized 6.5 cm in diameter and weighted 5 kg for 15 minutes 3) <i>Reading time</i>: 6 hours after test 4) <i>Positive reaction</i>: a delayed, red, palpable deep swelling occurs at the test site, with burning or painful sensations	1) <i>Definition</i>: the lowest pressure that results in a delayed angioedema or red palpable deep swelling 2) <i>Instruments</i>: DPU test device, 6.5 cm in diameter30 3) <i>Test time</i>: 15 minutes	

Table 3 (continued)

Classification of ChIdU	Triggering factors	Provocation tests	Threshold tests	Assessment instruments
Symptomatic dermographism (urticaria factitia)	Friction exerted on the skin	1) <i>Site</i> : volar forearm 2) <i>Test</i> : stroking the skin with the tip(s) of a dermatographometer 3) <i>Instruments</i> : FricTest® dermatographometer (with 4 tips of varying length) or HTZ dermatographometer (with one tip) 4) <i>Reading time</i> : 10 minutes after test5) <i>Positive reaction</i> : pruritic palpable wheals appear within 10 minutes of provocation	1) <i>Definition</i> : the lowest strength that can trigger wheals and itch 2) <i>Instruments</i> : FricTest® or HTZ dermatographometer 3) <i>Positive reactions</i> : A pruritic palpable wheal of ≥ 3 mm width	
Vibratory urticaria (vibratory angioedema)	Exposure to vibration	1) <i>Site</i> : volar forearm 2) <i>Test</i> : direct contact with a vortex vibrator at a speed of 1000 rpm for 5 minutes 3) <i>Reading time</i> : 10 minutes after test 4) <i>Positive reaction</i> : wheals or angioedema appearing at the test site	N/A	
Solar urticaria	Sunlight (UV and/or visible light) exposure	1) <i>Site</i> : buttocks 2) <i>Test</i> : irradiation with UVA 6 J/cm ² , UVB 60 mJ/cm ² and visible light, respectively 3) <i>Reading time</i> : 10 minutes after test 4) <i>Instruments</i> : UVA/UVB simulator 5) <i>Positive reaction</i> : a palpable and clearly visible wheal and a flare reaction appear at the test site	1) <i>Definition</i> : the lowest dose of irradiation that results in wheals 2) <i>Instruments</i> : UVA/UVB simulator	
Cholinergic urticaria	Heat and sweating resulting from hot baths, exercising, mental stress or anxiety	1) <i>Test</i> A. exercise with a bicycle trainer or treadmill: exercising sufficiently to cause sweating, or exercising for 30 minutes with pulse rate increased by 3 beats every minute. If positive, wait > 24 hours and perform the next step (42°C bath test). B. 42 °C bath: immersion in bath water at 42°C. After body temperature has increased by ≥ 1 °C over baseline, continue bath for 15 min. 2) <i>Reading time</i> : during test, immediately after the end of test and 10 minutes later 3) <i>Positive reaction</i> : onset of small (2–5 mm in diameter) monomorphic wheals on the trunk and proximal extremities	N/A	

Table 3 (continued)

Classification of ChnU	Triggering factors	Provocation tests	Threshold tests	Assessment instruments
Aquagenic urticaria	Skin contact with water	1) <i>Site</i> : trunk 2) <i>Test</i> : applying wet compress on the skin using 35–37°C water or physiological saline, and then checking the results after 40 minutes or earlier 3) <i>Positive reaction</i> : urticarial lesions develop inside the contact area within 10 minutes after taking off the wet compress.	N/A	
Contact urticaria	Skin contact with eliciting agents	1) <i>Test</i> : no tests are necessary when the eliciting agents are apparent; in case of need, open controlled application test, skin prick test, or closed patch tests for 20 minutes can be chosen. 2) <i>Positive reaction</i> : urticarial lesions develop inside the contact area (NICU) or exceed the contact area with or without onset of systemic symptoms (ICU)	N/A	

ICU immunologic contact urticaria, NICU non-immunologic contact urticaria, DPU delayed pressure urticaria, N/A not applicable. TempTest® tools: a Peltier element-based temperature exposure device that can produce a successive temperature gradient from 4 to 44 °C, which are applied to the skin to help with diagnosis of cold urticaria and heat urticaria. FricTest® dermatographometer: a dermatographic tester in the shape of a plastic comb with 4 tips (which are 3.0, 3.5, 4.0, and 4.5 mm in length, respectively). HTZ dermatographometer: a calibrated dermatographometer device shaped like a pen, with a spring-loaded smooth steel tip of 2.3 mm in diameter, whose scale settings from 0 to 15 are equivalent to a range of tip pressures from approximately 20 to 160 g/mm² (196–1569 kPa)

of treatment algorithm recommended by the guidelines and compare the treatment responses between CIndU and CSU has revealed that patients with CIndU were more likely to fail the standard-dose treatment of sgAHs than patients with CSU (40.3% vs 31.8%), and that higher doses of sgAHs were effective for controlling symptoms in these patients with CIndU [178]. Though recommended as the first- and second-line therapy for CIndU, it is suggested that patients with CIndU can take sgAHs in an on-demand way other than a routinely consecutive administration [2].

The off-label use of omalizumab has been recommended for sgAHs-resistant CIndU patients. Recently, systemic reviews have summarized the off-label use of omalizumab in sgAHs-resistant CIndU patients, and come to a conclusion that there was a strong evidence for its therapeutic efficacy in symptomatic dermatographism, cold urticaria, and solar urticaria [168]. As for symptomatic dermatographism, an RCT including 55 patients demonstrated that three monthly subcutaneous injections of omalizumab with either 150 or 300 mg led to a pronounced, clinically meaningful reduction in disease activity (44% and 53%, respectively) and an improvement in QoL (72% and 58%, respectively) [166]. Besides, in contrast to CSU, there is no statistically significant difference between the efficiency of these two dosages. The application of omalizumab in cold urticaria was studied by Metz et al. [160] in a multicenter RCT. In this clinical trial, patients with cold urticaria refractory to antihistamines received 150 and 300 mg of omalizumab, respectively, every 4 weeks for 3 consecutive months, and achieved a complete response rate of 40% and 44%, respectively, compared with 0% in the placebo group. A phase II trial was designed to study the therapeutic effect of omalizumab, 300 mg monthly for three consecutive months, in solar urticaria in 10 patients. The outcomes at week 12 showed a moderate response, with 30% of patients having a complete clinical response (UAS7=0) [179]. In addition, patients with various kinds of CIndU refractory to antihistamine have also been described in case reports or other types of studies as responsive to omalizumab at a dose of 150–300 mg.

Incremental doses of omalizumab have been confirmed beneficial for non- or poor-responders. A retrospective study including 16 patients with cholinergic urticaria found that 67.7% (4/6) of patients who had shown no response or poor response to standard dose of omalizumab achieved major or complete response by increasing the dose to 450 mg every 4 weeks or 2 weeks, indicating a potential benefit of omalizumab-updosing for treatment-resistant cholinergic urticaria [180]. Similar results were reported in a case series including 5 patients with solar urticaria, in which a monthly dose increment of omalizumab to 450–600 mg resulted in better clinical improvements in 2 patients [181]. An observational retrospective multicenter study enrolling 80 patients with CIndU further supported the efficacy of

up dosing for nonresponders. It is reported that 50% (7/14) of nonresponders achieved complete or satisfactory disease control of CIndU when the dose was adjusted to 450 mg monthly, and 1 out of 4 remaining nonresponders achieved satisfactory or complete disease control when the dose was further increased to 600 mg per 4 weeks. Furthermore, it is indicated that the best response to omalizumab (63% complete response) was achieved in patients with solar urticaria, and the poorest response (22.7% complete response) in patients with symptomatic dermatographism. Meanwhile, a slow response to omalizumab was observed in patients with cholinergic urticaria [182].

There are several other therapeutic agents, supported by evidence derived from different types of studies, that could be taken into account in treatment for some types of CIndU. The results of 4 RCTs showed that adding an H2-antihistamine might augment the efficacy of H1-antihistamine in symptomatic dermatographism [177]. Two RCTs conducted by Nettis et al. [176] successively drew a conclusion that the combination of antihistamine and montelukast tended to achieve a better efficacy in delayed pressure urticaria. The application of dapsone as well as sulfasalazine in delayed pressure urticaria has been studied in retrospective studies or case series, and both drugs were suggested as beneficial in the treatment of this subtype of urticaria and thus could be considered in recalcitrant cases [176]. For cases with cold urticaria refractory to the aforementioned treatments, therapy with doxycycline at a dose of 200 mg/day was demonstrated as a potentially beneficial therapy by a retrospective study, which enrolled 26 patients with cold urticaria [183].

Conclusion and Future Perspectives

Chronic urticaria is an important dermatological disorder that impairs patients' quality of life dramatically and has high incidence rate in population [4]. Over the past few years, great advances have been made in the understanding of the underlying pathogenesis of CU which subsequently promotes the advancement of therapeutic strategies. With the application of normalized therapies with antihistamines and omalizumab, control of symptoms can be achieved in a large proportion of patients. Nonetheless, individualized stepwise approaches with a goal of minimizing side effects and economic costs while maintaining a complete symptom control of CSU are still needed, and well-designed clinical trials providing high-quality evidence of treatment options for different types of CIndU are warranted. The development of new therapies, especially for patients recalcitrant to standard treatment, counts on the further advances in identification of key target molecules and processes in the pathogenesis, which may be quite distinct between CSU and different types of CIndU. Taken together, both types of CU deserve

further in-depth exploration in their pathogenesis and management optimization, and biologics and small molecule compounds are definitely the next frontier for the treatment.

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Declarations

Ethics Approval and Informed Consent Not applicable.

Research Involving Human Participants and/or Animals Not applicable.

Conflict of Interest The authors declare no competing interests.

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