Keywords
Wheals · Angioedema · Prevalence · Patient-reported outcomes · Treatment

Abstract
This update on chronic urticaria (CU) focuses on the prevalence and pathogenesis of chronic spontaneous urticaria (CSU), the expanding spectrum of patient-reported outcome measures (PROMs) for assessing CU disease activity, impact, and control, as well as future treatment options for CU. This update is needed, as several recently reported findings have led to significant advances in these areas. Some of these key discoveries were first presented at past meetings of the Collegium Internationale Allergologicum (CIA). New evidence shows that the prevalence of CSU is geographically heterogeneous, high in all age groups, and increasing. Several recent reports have helped to better characterize two endotypes of CSU: type I autoimmune (or autoallergic) CSU, driven by IgE to autoallergens, and type IIb autoim-
The Prevalence of Chronic Urticaria Is High in all Age Groups, Increasing, and Geographically Heterogeneous

A recently published systematic review [1] with meta-analyses on the prevalence of chronic urticaria (CU) revealed three major insights: (1) CU is just as common in children as it is in adults; (2) the prevalence of CU is increasing; (3) there are substantial differences in the prevalence of CU across geographical regions.

Based on the limited published data available, the overall point prevalence of CU across all age groups is estimated at 0.7% [2, 3]. This confirms that CU is a common disease. Interestingly, new data also show that the prevalence of CU in children is as high as or higher than in adults, estimated on average at 1% [1]. In three studies that included both children and adults, the prevalence did not differ significantly between both age groups [4–6]. In a more recent study, the prevalence in children in Europe was 1.1% [7]. In a study from Korea, the prevalence in children was even higher [8]. The point prevalence of CU in women is higher than in men (1.3 vs. 0.8%). Looking at sex differences in children, a subgroup analysis yielded a point prevalence of 1.0% for girls and 1.1% for boys.

When all available studies that assessed point prevalence at different time points in the same region were compared, they all showed increasing point prevalence over time [3]. This was especially so in the studies from Asia (Taiwan and Korea) [5, 9]. Geographical regions with a high point prevalence were Latin America and Asia with estimates of 1.5 and 1.4%, respectively [1]. In contrast, North America showed by far the lowest point prevalence. The reasons for this are currently unclear. Global studies are needed.

Additional unmet needs in our understanding of the prevalence of CU and its increase include the frequencies of chronic inducible urticarias (CIndUs) as well as the reasons for the differences in prevalence seen in women versus men, but not girls versus boys, and those of patients from different parts of the world. Future epidemiological studies should also clarify the rate of CU patients with wheals, angioedema, and both in children and adults as well as the duration of the different subforms of CU. As of now, virtually all studies on the duration of CU have assessed this in patients who still had the disease rather than in patients who had undergone spontaneous remission.

Type I and Type IIb Autoimmunity: Emerging Endotypes of Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CU), the most common form of CU, presents with transient wheals (hives), angioedema, or both, without any definite triggers and reoccurrence of signs and symptoms for > 6 weeks. CU is a mast cell (MC)-driven disease. The degranulation of skin MCs is held to be the initial event in the development of skin changes, such as sensory nerve stimulation, vasodilation and extravasation, as well as the recruitment of basophils, eosinophils, and T cells, which collectively lead to whealing, itch, and angioedema. Over the past year, two groups of MC-degranulating signals have been identified and characterized: IgE autoantibodies to autoallergens and autoantibodies that target activating MC receptors (Fig. 1). These two types of autoimmune hypersensitivity, i.e., type I autoimmunity (also called autoallergy) and type IIb autoimmunity, have been postulated to be the relevant cause in most patients with CU [10].

In type I autoimmune CU, autoantigens crosslink IgE autoantibodies on MCs and basophils to cause the release of vasoactive mediators (Fig. 1). A role of type I autoimmunity in urticaria was postulated as early as 20 years ago, following the demonstration of IgE autoantibodies...
against the thyroid microsomal antigen in the serum of a CSU patient [11]. Since then, many studies have further characterized the prevalence and pathogenic relevance of type I autoimmunity in CSU [12]: Thyroperoxidase (TPO) has been demonstrated to be a common and relevant autoallergen in CSU. In one study, more than half of the 478 analyzed CSU patients were found to have elevated levels of IgE autoantibodies against TPO (IgE-anti-TPO). In Xolair in Chronic Urticaria Induced by serum IgE Targeting Endoallergens, the first multicentric randomized controlled CSU trial with the therapeutic anti-IgE omalizumab, patients with IgE-anti-TPO showed a rate of complete response (i.e., no more wheals) of 70%, higher than that of any subsequent trial in which patients were not required to have IgE-anti-TPO. Basophils loaded with the IgE of CSU patients before exposure to TPO ex vivo show activation and mediator release [13, 14]. Recently, Sánchez et al. [13] reported that 6 and 9 of 50 CSU patients showed a positive response to skin prick testing and intradermal injection of TPO, respectively. Also, whealing in response to TPO skin prick testing was adaptively transferred from CSU patients to healthy subjects [13].

CSU patients also have IgE autoantibodies directed to a large assortment of autoantigens beyond TPO, of which many are expressed in the skin. These include thyroglobulin, tissue factor, and IL-24 [15, 16]. In one study, IgE-anti-IL-24 was recognized by the IgE of 70% of CSU patients. Similar to TPO, exposure of basophils loaded with the IgE of CSU patients to subsequent incubation with IL-24 leads to the degranulation of MCs [16]. The IgE-anti-IL-24 levels of patients with CSU correlate with their disease activity and are reduced by autologous serum therapy in patients who respond to this treatment [17]. CSU patients were also found to have elevated levels of IgE autoantibodies against DNA, but not of IgG against DNA, and in some patients, incubation of their basophils with DNA resulted in degranulation and mediator release [18].

Furthermore, it has been shown in some but not all studies that IgE autoantibodies are responsible for the increased total IgE levels in CSU patients. In the studies demonstrating increased IgE autoantibodies in CSU patients, most of the IgE was found to be directed against autoantibodies in contrast to individuals who did not have CSU.

A type IIb hypersensitivity mechanism in which autoantibodies, usually IgG or IgM, bind to antigen on a target cell (Fig. 1) was first described in CSU in 1988 [19], demonstrating IgG autoantibodies against IgE. Two years later, Grattan et al. [20] confirmed the presence of these autoantibodies in CSU patients with a positive reaction in the autologous serum skin test (ASST), i.e., a wheal and flare response to intradermal injection of their own serum. Another 2 years later, IgG autoantibodies to FcεRI, the high-affinity receptor for IgE on MCs and basophils, were described in CSU patients [21]. Very recently, CSU patients were found to also have IgM and IgA autoantibodies to FcεRI [22]. More CSU patients had IgM autoantibodies to FcεRI (60%) than IgG against FcεRI (24%), and elevated levels of IgM against FcεRI, but not of IgG against FcεRI, were linked to low blood basophil and eosinophil counts, markers of high CSU disease activity [22]. The concept that type IIb autoimmune mechanisms can drive CSU is further supported by the results of basophil tests. The serum of a subpopulation of CSU patients activates heterologous basophils, and this basophil-activating serum activity is linked to the presence of autoantibodies against FcεRI and positive ASST responses [23, 24].

Several independent, albeit indirect, lines of evidence suggest that type I autoimmune and type IIb autoimmune CSU patients differ in their disease features, laboratory markers, and response to treatment (Table 1). Based on the comparison of CSU patients who do or do not express
markers of type IIb autoimmunity (autoantibodies, basophil tests, and/or ASST), type IIb autoimmune CSU patients have been suggested to have higher disease activity and longer disease duration as well as higher rates of comorbid autoimmunity. Basopenia and eosinopenia may also be more common in these patients.

In the recent PURIST study, the first to characterize CSU patients who are positive for all three defining markers of type IIb autoimmune CSU, i.e., IgG-anti-FcεRI/IgE-positive, basophil test-positive, and ASST-positive, 8% of 184 patients were triple-positive, i.e., had bona fide type IIb CSU [25]. These patients showed higher IgG-anti-TPO levels and higher rates of elevated IgG-anti-TPO as well as lower IgE levels and higher rates of low IgE as compared to triple-negative patients. In fact, the IgG-anti-TPO/IgE ratio was found to be the best predictor of type IIb autoimmune CSU. Other markers that have been suggested to be different in type IIb versus type I CSU patients include C-reactive protein and antinuclear antibodies (Table 1).

The efficacy of anti-IgE treatment with omalizumab or ligelizumab supports both type I and type IIb autoimmune pathomechanisms in CSU. Omalizumab reduces the levels of IgE, the driver of type I autoimmune CSU, and of its high-affinity receptor FcεRI, the target of type IIb autoantibodies. More importantly, type I and type IIb autoimmune CSU patients treated with anti-IgE differ in their rates of response and in their speed of onset of improvement [26–30]. Most CSU patients treated with omalizumab become symptom-free within the first month of their first injection. This is in line with type I autoimmunity, where anti-IgE rapidly binds free IgE, including IgE against autoantigens, and IgE/anti-IgE complexes bind autoallergens, thereby reducing MC degranu-

### Table 1. Features of type I and type IIb autoimmune CSU

| Features                                      | Type I versus type IIb autoimmunity |
|-----------------------------------------------|-------------------------------------|
| **Autoantibodies**                            | auto-IgE (e.g., against TPO, TG, TF, IL-24, dsDNA) in type I [12, 13, 15, 111], auto-IgG (against IgE, FcεRI) in type IIb [112–114] |
| **Diagnosis**                                 | total auto-IgE and specific IgE to autoallergens¹ in type I [115], triple positivity: BHRA/BAT+ASST+WB/ELISA+ in type IIb [24, 25] |
| **Disease activity/severity**                 | tends to be higher in type IIb [12, 14, 25, 111]² |
| **Disease duration**                          | tends to be longer in type IIb as shown in some [116, 117] but not all [25] studies |
| **Rates of concomitant autoimmune diseases**  | tend to be higher in type IIb [25, 118–121] |
| **Rates of concomitant allergic diseases**    | might be higher in type I [119] |
| **Total IgE levels**                          | low in type IIb and normal or high in type I [14, 25] |
| **Basopenia rates**                           | might be higher in type IIb [24, 111]² |
| **Eosinopenia rates**                         | tend to be higher in type IIb [122] |
| **C-reactive protein levels**                 | may be higher in type IIb [25, 123] |
| **ANA positivity rates**                     | may be higher in type IIb [124] |
| **Responder rates to sgAHs**                  | may be lower in type IIb [122–125] |
| **Responder rates to omalizumab**             | high in type I [28] and low in type IIb [62, 122, 126] |
| **Speed of response to omalizumab**           | slow in type IIb [127] |
| **Immunosuppressive therapy**                | can be effective in type IIb [128–134]³ |

TPO, thyroperoxidase; TG, thyroglobulin; TF, tissue factor; IL, interleukin; dsDNA, double-stranded DNA; BHRA, basophil histamine release assay; BAT, basophil activation test; ASST, autologous serum skin test; WB, Western blot; ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein; ANA, antinuclear antibodies; sgAHs, second-generation antihistamines. ¹ Measured by ELISA or radioimmunoassay. ² In one study, IgE-anti-IL-24 levels showed a correlation with disease activity and a negative correlation with blood basophil counts. ³ Cyclosporine, plasmapheresis, rituximab, intravenous immunoglobulins, methotrexate, mycophenolate mofetil. Most studies are case reports.
lation. Some CSU patients take months to respond to omalizumab, and this is in line with type IIb autoimmunity, where the reduction of free IgE results in the slow loss of membrane-bound FcεRI from skin MCs, the target of type IIb-driving autoantibodies.

Future studies need to characterize in detail the role and relevance of type I and type IIb autoimmunity in CSU. Standardized and validated diagnostic tests for IgE autoantibodies to autoallergens and for relevant MC-activating autoantibodies need to be developed to better define these CSU endotypes and their differences. A clearer picture of the prevalence, mechanisms, and clinical profiles of type I and type IIb autoimmune CSU will help to develop targeted therapies and facilitate optimal treatment of both subpopulations of CSU patients.

Recent reports [31–35] suggest that additional endotypes of CSU may exist, with evidence pointing to a role of factors of the coagulation pathway, ligands of the MAS-related G protein-coupled receptor X2 (MRGPRX2), basophils, alarmins, and other signals in the pathogenesis of CSU. More research is needed to clarify whether mechanisms of skin MC degranulation other than type I and type IIb autoimmune activation support the existence of distinct and separate endotypes.

### Use of Patient-Reported Outcome Measures Improves the Management of CU

**Why We Should Measure Disease Activity, Impact, and Control in Patients with CU**

Patient-reported outcome measures (PROMs) are essential for optimizing the management of CU [36, 37]. They are also of key importance for assessing treatment effects in clinical trials. Over the past years, disease-specific PROMs have been developed for CU (Table 2). They are widely used in clinical practice and trials, and they assess disease activity, impact, or control. Why is it impor-

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**Table 2. PROMs in CSU and areas of use**

|                          | UAS | CU-Q2oL | UCT | AAS | AE-QoL | AECT |
|--------------------------|-----|---------|-----|-----|--------|------|
| Applicable in patients with: |     |         |     |     |        |      |
| Wheals and no angioedema | +   | +       | +   | –   | –      | –    |
| Wheals and angioedema    | +   | +       | +   | +   | +      | +    |
| No wheals and angioedema | –   | –       | +   | +   | +      | +    |
| Number of items          | 2   | 23      | 4   | 5   | 17     | 4    |
| Retrospective assessment (recall period) | – | + | + | – | – | – |
| 2 weeks                  |     | 4 weeks |     | +   | 4 weeks | + |
| 4 weeks                  |     | 4 weeks |     | +   | 4 weeks | +    |
| 3 months                 |     | 4 weeks |     | +   | 4 weeks | +    |
| Prospective assessment (frequency) | + | – | + | – | – | – |
| 1× or 2×/day             |     | –       | +   | –   | –      | –    |
| 1×/day                   |     | 1×/day  |     | +   | –      | –    |
| MCID                     |    | 11      | 3–15 | 8  | 6     | not yet established |
| Cost-free for:           |     |         |     |     |        |      |
| Patient management       | +   | +       | +   | +   | +      | +    |
| Academic research        | +   | +       | +   | +   | +      | +    |
| Industry studies         | +   | –       | –   | –   | –      | –    |
| Language/country versions available | + | Italian, German, Greek, Hebrew, Korean, Persian, Polish, Portuguese, Spanish, Thai, Turkish | >20 language versions available | >70 language versions available | >25 language versions available | German, American English |
|                         |     |         |     |     |        |      |

AAS, Angioedema Activity Score; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; CU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; MCID, minimal clinically important difference; PROMs, patient-reported outcome measures; UAS, Urticaria Activity Score; UCT, Urticaria Control Test. 1 The UAS is available in several languages. The original source is the EAACI/GA²LEN/EDF/WAO urticaria guideline. Due to its easy structure, the UAS is usually translated but not formally linguistically validated. 2 For more details with regard to available language versions of the AAS, AE-QoL, UCT, and AECT go to www.moxie-gmbh.de. Additional language/country versions may be or are in preparation; for more information, please contact Moxie at info@moxie-gmbh.de. 3 The MCID of the CU-Q2oL has been assessed in two independent studies performed in different patient collectives in Europe and Asia. While one study found an MCID of 3 points [46], the MCID identified in the other study was higher with 15 points [134].
What Tools Should Be Used to Assess Patients with CSU for Disease Activity, Impact, and Control?

Patients with CSU present with wheals, angioedema, or both, which is important in the correct selection of the PROMs to use. In patients with wheals (with or without angioedema), the Urticaria Activity Score (UAS) [42–45], the Chronic Urticaria Quality of Life Questionnaire (CU-QoL) [46–49], and the Urticaria Control Test (UCT) [50–54] are the PROMs of choice to measure disease activity, impact, and control, respectively. In patients with predominant angioedema (with or without wheals), the Angioedema Quality of Life Questionnaire (AE-QoL) [57–59], and the Angioedema Control Test (AECT) [59] should be used (Table 2).

The UAS7 records, over 7 consecutive days, the daily number of wheals and the intensity of itch. It is the guideline-recommended gold standard for measuring disease activity in CSU patients with wheals [60, 61] (Table 2). The two available versions of the UAS7 differ slightly in that they require either a twice-daily or once-daily documentation and in their categories for daily numbers of wheals. Both versions yield comparable results [43, 44]. The once-daily UAS is preferred for routine clinical use: Patients only need to document their wheals and itch once every day, it has been thoroughly validated [60], its minimal clinically important difference (MCID) of 11 points is well characterized [42], and it has been used in numerous randomized controlled trials and real-life studies [17, 62–64]. The UAS7 has several limitations. It has not been validated in children, although a modified version has been reported [65]. It is not suitable for assessing disease activity in patients with CIndU. The documentation of itch and its intensity may reflect non-CSU-related itch. It does not entail angioedema, a common and important clinical manifestation of CSU. The prospective character of the UAS7 makes an ad hoc evaluation impossible, as the results are only available at the next appointment after its administration.

CSU patients experience markedly impaired QoL. General QoL questionnaires and QoL instruments developed for patients with dermatological diseases such as the Dermatology Life Quality Index, the Children’s Dermatology Life Quality Index, the Dermatology Quality of Life Scales, and the Dermatology-Specific Quality of Life instrument have been used in CSU [66, 67]. While these tools are well suited to compare QoL impairment in patients with CSU with that in patients with other diseases, they do not provide information on CSU-specific aspects of QoL impairment nor on its changes over time, e.g., in response to treatment [68]. The CU-QoL was developed to assess the QoL impairment specific to CSU [47, 68] (Table 2). It is the guideline-recommended QoL tool for CSU [61] and available in many languages [48, 49, 69–72]. The CU-QoL shows good sensitivity to change, and its MCID has been found to be 3–15 (3 and 15 in independent studies and patient collectives from Europe and Asia). It has been used in many clinical studies, including pharmacological randomized controlled trials [28, 73, 74]. The CU-QoL also has limitations. Most importantly, it was not specifically designed to assess the QoL impairment due to angioedema, which occurs in many patients and can impact on their disease-specific QoL, and therefore it is not useful in patients with CSU predominantly affected by angioedema. Also, there is no version for the use in children, and it is not suitable for CIndU.

Disease control is a major treatment aim in CSU, and the UCT was specifically developed and validated to measure this in all forms of CU, including CIndU. The UCT is a 4-question retrospective PROM with a minimum value of 0 points (no control) and a maximum value of 16 points (complete control). A score of ≤11 points indicates poorly-controlled urticaria, whereas a score of ≥12 points indicates well-controlled disease. The UCT strongly correlates with the UAS [54, 75], has high levels of validity and reliability, and accurately identifies patients with insufficiently controlled disease. Its MCID is 3 points [52, 53]. No version for children is available as of yet.

The AAS is the tool of choice for the assessment of disease activity in patients with CSU who present with recurrent angioedema without wheals and in patients where
angioedema is a predominant factor. Like the UAS, the AAS is a prospective, diary-type tool. Patients document every day for 4 weeks (AAS28) whether angioedema occurred during the last 24 h, in which case five additional questions on severity and impact are answered [56]. The AAS shows high levels of validity and test-retest reliability and is sensitive to changes of angioedema activity over time, with an MCID of 8 points for the 7-day AAS (AAS7). The AAS has also been used in recent randomized controlled trials [74, 76].

The AE-QoL is the first symptom-specific PROM to assess angioedema-specific QoL impairment in patients with CSU [58]. It consists of 17 questions with 5 answer options each scored from 0 to 4 points, which are summed up to a total score but fall in four different domain scores ("functioning," "fatigue/mood," "fears/shame," "food"), which are each displayed on a 0–100 scale The AE-QoL demonstrates high sensitivity to change, and its MCID is 6 points [59]. The AE-QoL is available in many different languages and has been used in randomized controlled clinical trials [74, 76]. Again, no version for children is available yet.

The AECT is a novel tool that quantifies disease control in CSU patients with angioedema as well as in patients with other forms of recurrent angioedema [77, 78]. The AECT is a retrospective PROM. Two versions exist, one with a 4-week recall period and one with a 3-month recall period. The AECT consists, like the UCT, of only four questions. It is easy to administer, easy to complete, and easy to score.

**What Tools Should Be Used to Assess Disease Activity and Control in Patients with CIndU?**

Disease activity in CIndU is assessed by testing patients for their trigger thresholds. Patients with low disease activity have high trigger thresholds and vice versa. In cold urticaria for example, patients with high disease activity can be made to develop wheals by exposure to warmer temperatures (e.g., 20°C) than those required to produce wheals in patients with low disease activity (e.g., 8 °C). Protocols and test devices are available for threshold testing in cold urticaria, symptomatic dermographism, cholinergic urticaria, pressure urticaria, and solar urticaria [79]. Cold urticaria patients for example are assessed for their individual critical temperature thresholds, i.e., the warmest temperature that is cold enough to produce a wheal, with the help of the Temptest [80]. Trigger threshold measurements for determining disease activity in patients with CIndU can be complemented by the use of CIndU-specific disease activity scores, such as the Cholinergic Urticaria Activity Score [81], that should be validated. Disease activity scores for CIndUs take into account the actual daily exposure of patients to relevant triggers. CIndU-specific QoL questionnaires are available for some CIndUs, for example the Cholinergic Urticaria Quality of Life Questionnaire for cholinergic urticaria [82], but not all. Disease control in patients with CIndU is measured with the UCT.

**PROMs in CU: Unmet Needs and Questions to Be Addressed**

As of now, none of the urticaria-specific PROMs developed are available for use in children. The UAS7, CQoL, and UCT as well as the AAS, AE-QoL, and AECT should be validated in adolescents, and corresponding tools for younger children must be developed. The same holds for the PROMs that were recently developed for CIndUs. Many PROMs, but also CIndU trigger threshold tests, have not yet been investigated for their MCIDs, which is needed for their optimal use in clinical trials and routine specialist practice. The global dissemination of available PROMs needs to be increased. Cross-cultural adaptations, translations, and the validation of PROMs are needed for international studies and for comparing patients from different regions of the world. For this, appropriate procedures must be followed to ensure that questionnaires are adapted to local conditions and that equivalent versions are produced.

**Emerging MC-Targeted Treatment Options for CU**

MCs are the critical effector cells in urticaria; therefore, targeting MC activity is a promising treatment approach [83]. Here, the guideline recommends as third- and fourth-line treatments omalizumab and cyclosporine for CU. Omalizumab inhibits MC activation via the IgE receptor and cyclosporine interferes with MC signal transduction and activation. The next generation of MC-targeted treatments for CU fall into three groups: (1) compounds that inhibit the effects of signals that drive MC activation and numbers, (2) compounds that inhibit intracellular pathways of MC activation and degranulation, and (3) compounds that silence MCs by binding to inhibitory receptors (Fig. 2).

**Drugs Inhibiting the Effects of Signals That Drive MC Activation and Numbers**

Activation of skin MCs via FceRI has been shown to drive the development of the signs and symptoms of CSU,
and treatment with omalizumab, an anti-IgE antibody, is effective in CSU [84–91]. Omalizumab has been shown to dissociate pre-bound IgE from MCs and basophils, resulting in a decrease in degranulation [92]. Ligelizumab is another humanized monoclonal anti-IgE antibody with a 50-fold higher affinity to IgE than omalizumab. It was recently tested in a phase II multicenter randomized controlled trial against placebo and omalizumab. In this trial, ligelizumab demonstrated superiority to both placebo and omalizumab and was characterized by a rapid onset of action and dose-dependent efficacy [63]. Interestingly, ligelizumab also showed a longer time to relapse after the last injection, i.e., 10 versus 4 weeks with omalizumab. Phase III studies are ongoing in adults and adolescents with CSU. This clinical efficacy of ligelizumab may involve effects of this molecule on IgE production by B cells [93].

The alarmins and innate type 2 immunity-inducing cytokines IL-33, IL-25, and thymic stromal lymphopoietin all have effects on MCs and have been implicated in the pathogenesis of CSU [34, 94]. For example, the wheals of CSU patients show markedly more cells that express IL-33, IL-25, and thymic stromal lymphopoietin as compared to their nonlesional skin and the skin of control subjects [34]. Therefore, IL-33, IL-25, and thymic stromal lymphopoietin should be explored as targets of novel treatment strategies for CSU.

Skin MCs express Kit, the receptor for stem cell factor, which is the major driver of MC differentiation, activation, migration, proliferation, and survival [95]. MC numbers are increased in the skin of CSU patients, which may be due to the effects of stem cell factor, which is also a potent activator of MCs [96, 97]. Reducing the number of MCs may help patients with CSU. Neutralization of stem cell factor with anti-stem cell factor may reduce MC numbers and inhibit MC activation.

MCs express receptors for the Th2 cytokines IL-4 and IL-5. Both cytokines have been shown to promote MC survival and to prime them for their FcεRI-mediated production and secretion of proinflammatory cytokines [98, 99]. IL-4 levels are elevated in the serum of patients with CSU, and IL-4-expressing cells are increased in the skin of CSU patients [100, 101]. Recently dupilumab, which inhibits IL-4 and IL-13 effects through blockade of their shared IL-4α receptor subunit, was shown to benefit patients with refractory CSU unresponsive to omalizumab [102]. The effects of dupilumab in CU are currently being assessed in two phase II randomized clinical trials, one in CSU and one in cholinergic urticaria.

IL-5, in addition to its effects on MCs, may contribute to the pathogenesis of CSU by recruiting eosinophils and basophils to lesional skin sites, where they are often found in high numbers. Benralizumab, an anti-IL-5 receptor antibody, as well as the anti-IL-5 antibodies mepolizumab and reslizumab have been successfully used to treat patients with CSU and ChIndU [103, 104]. Benralizumab and mepolizumab are currently in CSU trials.

Several additional receptors, such as the complement C5a receptor (C5aR, CD88) and MRGPRX2, are expressed by MCs and have been proposed to be the targets of signals that drive the development of the signs and symptoms of CU. C5aR is expressed by skin MCs, but not lung or other MCs, and the degranulation of MCs via the MC-activating autoantibodies of type IIb autoimmune CSU patients is, at least in part, mediated by activation of C5aR [105, 106]. MRGPRX2, like C5aR, is preferentially expressed by skin MCs, where its expression is upregulated in patients with severe CSU [32]. Substance P, major basic protein, and eosinophil peroxidase induce histamine release from human skin MCs through activation of MRGPRX2 independent of the NK1 receptor [32]. Furthermore, the levels of substance P, a neuropeptide and agonist of both MRGPRX2 and the NK1 receptor, are in-

Fig. 2. MC-targeted treatments for CU under development. Examples of activating (upper half) or inhibiting (lower half) receptors and signaling molecules (within the cell) that are currently under development for the treatment of CU. Btk, Bruton’s tyrosine kinase; CU, chronic urticaria; MC, mast cell; Syk, spleen tyrosine kinase.
Increased in the serum of CSU patients and correlate with disease activity [107, 108]. Thus, targeting MRGPRX2 and/or its agonists (e.g., substance P) is a promising mechanism for decreasing MC activation in patients with CSU.

**Drugs That Inhibit Intracellular Pathways of MC Activation and Degranulation**

Bruton’s tyrosine kinase and spleen tyrosine kinase are key players in the transduction of signals downstream of the high-affinity IgE receptor FcεRI. Inhibitors of Bruton’s tyrosine kinase or spleen tyrosine kinase inhibit the degranulation of human MCs [109, 110]. Treatment with a Bruton’s tyrosine kinase inhibitor inhibits IgE- and MC-mediated responses in mice and humans [110]. Two Bruton’s tyrosine kinase inhibitors, Fenebrutinib and Remibrutinib, are currently under development for the oral treatment of patients with CSU, and the spleen tyrosine kinase inhibitor GSK2646264 is in clinical trials for cold urticaria and CSU.

**Drugs That Silence MCs by Binding to Inhibitory Receptors**

The vast majority of receptors expressed by MCs are activating receptors, i.e., their engagement by ligands results in degranulation, migration, differentiation, or proliferation. A small set of MC receptors are inhibitory receptors that, upon engagement by ligands, silence MCs and inhibit their activation including degranulation. Siglec-8 and CD200Ra are two of these inhibitory MC receptors, and antibodies targeting them are currently under development for CU. For example antolimab, a monoclonal antibody that targets Siglec-8, was shown to inhibit MC activation and to deplete eosinophils. Antolimab was tested in a phase IIa, open-label pilot study in patients with omalizumab-naïve and omalizumab-refractory CSU as well as patients with symptomatic dermatographism or cholinergic urticaria. The engagement of CD200Ra by agonist antibodies also inhibits MC activation and degranulation [111]. The CD200Ra-targeted antibody LY3454738 is currently under development for CSU.

**Summary, Conclusion, and Outlook**

CU is a heterogeneous, persistent, severely debilitating and often poorly controlled disease. Recent findings suggest that the prevalence of CU and its subforms may be more heterogeneous than previously thought and in need of further studies, across all age groups. Despite many important recent insights on the pathogenesis of CU, the endotypes and pathomechanisms of CSU are still insufficiently characterized and the causes of CIndU remain unknown. Autoallergy and type Ib autoimmunity appear to be distinct endotypes of CSU, but better tests are needed to identify patients with one or the other or neither. This is needed to optimize the treatment of patient subgroups with the drugs available today and to develop treatments that can prevent all of the subforms of CU, alter their course, and cure patients. Antihistamines and omalizumab are the only currently licensed treatments, and additional and better treatments for CU are needed, especially for CIndU. The development of novel treatments for CIndUs and CSU also needs instruments that allow to assess their efficacy. Significant progress has been made with this over the past years, but more efforts are needed to extend the existing tools to children, to develop and validate tools for all forms of CU, and to make urticaria and angioedema PROMs available and their use routine practice on a global scale. The future of urticaria drug development has never been more promising, with several strategies being pursued.

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