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Pathophysiology, Diagnosis, and Management of Chronic Spontaneous Urticaria: A Literature Review

Benjamin Greiner[1,3] · Savannah Nicks[2] · Michael Adame[1,3] · Jennifer McCracken[1,3]

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Abstract

Chronic spontaneous urticaria (CSU) is characterized by recurring wheals that last 6 weeks or longer without an identifiable cause. The estimated point prevalence of CSU worldwide is 1%. Furthermore, it has a significant impact on quality of life in both adults and pediatric patients and their families. Although it is most often a self-limited disease, some patients have urticaria refractory to first-line treatment: second-generation H1 antihistamines. In these patients, the use of targeted monoclonal antibodies is necessary. While omalizumab is the only Food and Drug Administration-approved monoclonal antibody for CSU, others, including ligelizumab, dupilumab, benralizumab, and several orally administered Bruton's tyrosine kinase inhibitors, are also promising therapeutics for reducing the morbidity of CSU. Novel therapies, among others discussed here, are rapidly being developed with new trials and therapeutics being released nearly monthly. Thus, we performed a scoping literature review of randomized controlled trials studying targeted therapies for CSU. We also discuss the pathophysiology, diagnosis, prognosis, and future research directions in CSU.

Keywords Chronic spontaneous urticaria · Chronic idiopathic urticaria · Management · Targeted therapy · Systematic review

Introduction

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is characterized by urticaria lasting 6 weeks or longer without an identifiable cause [1]. The estimated point prevalence of CSU in children is roughly 1.4% and 0.9% in adults with a higher prevalence in Latin America and Asia compared to Europe and North America [2, 3]. Urticaria may occur anywhere on the body and typically occur most days of the week lasting between 4 and 24 h [4]. Furthermore, nearly 60% of patients with CSU have experienced angioedema which significantly impacts feelings of fear, shame, and mood [1]. In most cases, it is a self-limited disease with most cases resolving within 2–5 years after onset [4]. It has a significant impact on quality of life with 20% of patients missing greater than 1 h of work per week and many experiencing difficulty with sleep as a result of urticaria related pain and pruritus [1].

Although systemic steroids are useful in CSU, the dose and duration of therapy precludes their use aside from extreme and acute situations. First-line medications include second-generation H1 antihistamines which provide relief to roughly 50% of patients with CSU [4] with step-up therapy to 4 times the daily recommended dose [5, 6]. Patients who do not respond to high dose H1 antihistamines should be initiated on omalizumab [7]. In patients refractory to the above regimens, the American Academy of Allergy, Asthma, and Immunology recommends initiating immunosuppressants like cyclosporine [8]. Doxepin, methotrexate, and montelukast are weakly supported by evidence although may be useful as third-line agents in some circumstances [7]. The use of cyclosporine is efficacious as a third-line agent but has greater toxicities than the more widely used omalizumab [9]. Omalizumab is the only biologic currently approved for the treatment of CSU with many clinical trials providing evidence to support its use in reducing the frequency and severity of urticaria [10, 11]. However, nearly 40% of patients

✉ Benjamin Greiner
bhgreine@utmb.edu

1 Department of Internal Medicine, Medical Branch, University of Texas, 301 University Blvd, Galveston, TX, USA

2 Department of Otolaryngology, McLaren Oakland Hospital, Pontiac, MI, USA

3 Division of Allergy & Immunology, University of Texas Medical Branch, Galveston, TX, USA

taking omalizumab for CSU continue to have moderate or poor control of symptoms [12] and 11.8% have no response to the medication [13] which warrants further research into novel CSU therapies.

Several monoclonal antibodies have been proposed and studied in phases 1 and 2 trials for CSU; notably ligelizumab in the Maurer et al. phase 2b trial. Other targeted therapies include benralizumab [14] and remibrutinib, a Bruton tyrosine kinase inhibitor [15]. While some literature reviews have discussed novel medications for CSU [16, 17], new trials have been released since their publications, warranting an updated literature review. Therefore, our objective was to perform a scoping literature review of novel targeted agents for adult and pediatric patients with CSU.

Methods

Search Strategy

A scoping literature review of randomized controlled trials of CSU targeted therapies was conducted using SCOPUS, ClinicalTrials.gov, EMBASE, MEDLINE, and PubMed from database inception through 09/29/2021 using the following search query: *(("chronic idiopathic urticaria" OR "chronic spontaneous urticaria") AND (("management") OR "treatment") OR "drugs"))*.

Inclusion and Exclusion Criteria

Trials were included if they studied CSU treatments using monoclonal antibodies or other targeted therapies. Studies were excluded if the manuscript could not be located in English.

Study Selection

Two reviewers (BG and SN) independently evaluated trial titles and abstracts, followed by full texts, for qualifying criteria. Discrepancies were reviewed and consensus achieved.

Pathophysiology

The exact cause for CSU is still largely unknown and is a topic of debate, although it is considered to be primarily a mast cell driven disorder [18]. To date, multiple potential mechanisms have been proposed. Possible etiologies are primarily inflammatory in nature and include autoimmune conditions, cell surface proteins of the coagulation cascade, and infectious agents [19].

Autoimmunity is the most widely accepted cause for CSU to date [20]. One of the first studies to suggest this theory demonstrated that 7 out of 12 subjects living with CSU had a positive test, i.e., a wheal-and-flare reaction, when injected intradermally with a sample of their own serum. A different study discussed Autologous Serum Skin Testing (ASST) in relation to CSU and its relationship to autoimmunity. This study investigated the activation of mast cells, a key inflammatory mediator, after a sample of each patient's own serum was injected into their skin. From this study, scientists now know that half of patients with CSU will have a positive ASST. A potential mechanism underlying this autoimmunity may be a result of IgG antibodies reactive to the α subunit of the IgE receptor; a theory supported by several studies [21, 22]. Autoimmunity as a cause for CSU is further supported by the increased propensity for autoimmune disease in patients with an established diagnosis of CSU [23]. The most common autoimmune condition seen in patients with CSU is hypothyroidism, seen in nearly 10% of patients.

One potential mechanism that is particularly controversial is one of infectious etiology, *Helicobacter pylori* (*H. pylori*) [24]. *H. pylori*, a gram-negative bacteria, triggers an inflammatory response in the body that is suspected to contribute to the development of several inflammatory conditions, including, but not limited to, gastritis, MALT lymphoma, and peptic ulcer disease [24]. For similar reasons to the aforementioned conditions, it may contribute to the development of CSU. In one study, the majority (56%) of patients diagnosed with CSU had a positive C urea breath test, an exam used to make an initial diagnosis of *H. pylori* [25]. Of the patients that tested positive for *H. pylori* in the same study and were actively suffering from CSU, 44% demonstrated improvement in CSU symptoms after eradication of *H. pylori* [25].

There has also been a suspected connection between CSU and the activation of the coagulation cascade, specifically the extrinsic pathway. A function of eosinophils that has come to light is their role as a reservoir for tissue factor (TF), or factor III of the extrinsic coagulation cascade [26]. The role of factor III in the coagulation cascade is the conversion of fibrinogen to fibrin, forming a blood clot. A study from Cugno et al. investigated TF and its relationship to CSU. This study found evidence of TF in skin samples from patients with confirmed CSU [27]. In the same study, there was no evidence of TF in patients without CSU. The role of eosinophils in CSU has also been acknowledged with histologic evaluations identifying eosinophils in biopsied urticaria lesions [28, 29]. Furthermore, eosinophils are able to interact with mast cells via surface receptors sialic acid-binding immunoglobulin-like lectin 7 and sialic acid-binding immunoglobulin-like lectin 8 (Siglec 7 and Siglec 8) [18]. As a result, activation of eosinophils by IL-5 or other mediators may provoke unregulated mast cell degranulation.

Diagnosis and Clinical Presentation

Chronic urticaria is the presence of urticarial lesions with or without angioedema which persist for more than 6 weeks. CSU is designated for cases in which no underlying cause can be identified. The diagnosis of CSU starts with a thorough history and physical exam. The history should include details regarding onset, frequency, pattern of symptoms, precipitating factors, environmental exposures, associations with angioedema or other systemic symptoms, medications, known allergies, and a family history. The most recent practice parameter update from the Journal of Allergy and Clinical Immunology [8] and a position paper from the European Journal of Allergy and Clinical Immunology [7] suggest starting with a proper history, physical examination, and selective labs as initial workup for chronic urticaria. Both guidelines agree that few tests are needed and other papers have reiterated this point [4, 7, 8, 30]. CSU is primarily a diagnosis of exclusion, and directed lab testing can be performed if clinically indicated. In the JACI Practice Parameter update, a majority of task force members expressed consensus for a CBC with differential, ESR or CRP or both, liver enzymes, and TSH as initial workup of chronic urticaria. Additional evaluation with skin biopsy, physical challenge tests, C3, C4, stool analysis, urinalysis, chest radiography, antinuclear antibody, rheumatoid factor, anti-citrullinated protein, cryoglobulin levels, serologic testing for hypersensitivity, thyroid autoantibodies, and serum protein electrophoresis can be performed based on the patient's circumstances [8]. Testing for infections such as *H. pylori*, hepatitis B, hepatitis C, or underlying malignancy may be warranted if there is clinical suspicion although these tests are not routinely performed. Other investigational labs which may be considered include autologous serum skin tests, antibodies to the IgE receptor or Fc region of IgE, tryptase, and skin biopsy [7, 30]. At this time, there is no correlation between the number of screening labs and detection of underlying diagnosis in patients whose clinical picture is consistent with CSU [8].

Non-targeted Therapy

Management of chronic urticaria should focus on treating the underlying precipitating factor. However, in many instances, such as CSU, it is idiopathic. Current guidelines thus recommend treating symptomatically with the goal of relieving wheals. Monotherapy with standard doses of H1 antihistamines is currently recommended by the EAACI and World Health Organization as first-line therapy [7]. First-generation H1 antihistamines have fallen out of favor and are no longer recommended for use in adult or pediatric patients due to their anticholinergic side effects [31]. Compared to first-generation H1 antihistamines, second-generation medications have far safer safety profiles and are now recommended for first-line treatment. Multiple second-generation H1 antihistamines have been studied in CSU specifically. A meta-analysis of 22 randomized controlled trials found that olopatadine improved total symptom, pruritus, and wheal scores better than fexofenadine, bilastine, rupatadine, and levocetirizine. Nonetheless, this study noted that risk of bias was high in many of the included trials [32]. Large scale, head to head trials are needed to make accurate recommendations for specific second-generation H1 antihistamines.

Updosing antihistamines to fourfold dosage is recommended for patients with continued wheals on standard dose antihistamines [7]. This second-line therapy has been identified to be efficacious using levocetirizine [33], desloratadine [34], and others [35]. Somnolence and headache are the most frequent side effects in patients on updosed antihistamines [6].

The same dosing schedules are recommended for first- and second-line therapy, including updosing (weight and age adjusted), for CSU in pediatric patients [7]. Second-generation H1 antihistamines are not licensed for use in children less than 6 months old in many countries. Cetirizine [36], desloratadine [37], fexofenadine [38], levocetirizine [39], bilastine [40], and loratadine [36] have all been studied and found to be safe in pediatric patients.

Third-line agents include the addition of cyclosporine or omalizumab [7]. H2 antihistamines such as famotidine, LTRAs, and dapsone and other anti-inflammatories were previously recommended in clinical practice guidelines; however, have since fallen out of favor due to lack of strong evidence for their efficacy in CSU. Cyclosporine is frequently avoided due to a poor side effect profile [41] while omalizumab can be cost prohibitive.

Finally, in patients who report a clear increase in urticaria symptoms following ingestion of salicylates, a low salicylate diet may be useful. This intervention may be particularly useful to trial in pregnant patients who wish to pursue non-pharmacologic interventions first [42]. Salicylate is a naturally occurring compound in plants that is common in vegetables, fruit, nuts, spices, alcohol, coffee, and tea.

Targeted Therapy

Omalizumab

Currently, the only approved monoclonal antibody for CSU is omalizumab. It is recommended in persons with continued CSU despite maximal antihistamine therapy. Omalizumab is a recombinant humanized IgG1 monoclonal antibody which targets free IgE and, subsequently, lowers free IgE resulting in downregulation of the FCεRI receptor on basophils and mast cells [43]. It has been studied in multiple phase 3 randomized controlled trials (RCTs) with results

showing significant improvement in weekly itch severity score, dermatology life quality index, and urticaria activity score (UAS-7) [11, 44, 45]. These studies also identified a dose–response relationship with greater improvement in symptoms with the higher 300 mg every 4 weeks dosing. This dosing regimen was further strengthened by a recent meta-analysis of RCTs which showed significant improvement in clinical symptoms with 300 mg every 4 weeks [43]. Omalizumab has also been deemed safe with a meta-analysis of 4 large RCTs showing a relative risk for adverse drug events of 1.37 (95% CI 0.67–2.82), although a small sample size may have impacted the lack of statistical significance [43]. One RCT reported having one episode of anaphylaxis [46]. Notably, although omalizumab is approved for CSU in patients aged 12 and older, the 3 groundbreaking trials — ASTERIA I [44], ASTERIA II [45], and GLACIAL [11] — only assessed 18, 10, and 11 adolescents in this age group, respectively. The largest trial of adolescents aged 12–17 was composed of 29 children and while 26 (89.6%) patients achieved complete response, as determined by the UAS-7 score, and only one patient (3.4%) reported an adverse event (angioedema), the need for larger sample sizes to ensure safety and efficacy in this population is warranted [47].

Ligelizumab

Ligelizumab (QGE031) is a humanized IgG1 monoclonal antibody that binds to IgE with a higher affinity than omalizumab. In two phase 1 RCTs using both intravenous and subcutaneous injections of ligelizumab compared to omalizumab in atopic patients, ligelizumab was noted to be superior in reducing free IgE and basophil surface expression of FCεRI [48]. These findings were then replicated in a phase 2b dose finding RCT by Maurer et al. in patients with CSU [49]. This study of 382 patients found that 44% and 40% of patients receiving 72 mg and 240 mg of ligelizumab, respectively, had complete control of urticaria, as compared to 26% of patients receiving the FDA recommended omalizumab 300 mg every 4 week. Most recently, a phase 2b dose finding RCT in adolescents aged 12–17 years was completed in August 2021 although results have not been published yet (NCT03437278). In this study, adolescents who received ligelizumab 24 mg every 4 weeks had a reduction in mean UAS-7 score (representing improvement in urticaria symptoms) of 20.36 (SD 12.96) and 22.5 (SD 13.5) in the group who received 120 mg. The UAS-7 is scored from 0 to 42 with higher numbers representing worsened symptoms. In the RCT by Maurer et al., 74% of patients receiving 240 mg every 4 weeks had an adverse event with the most common adverse events being upper respiratory tract infections, headaches, and injection site irritation [49]. It was noted that upper respiratory tract infections were noted more frequently in the placebo group than in the treatment arms which suggests this adverse event may not have been related to ligelizumab. A safety extension trial of 226 patients receiving ligelizumab for 12 months was recently published in November 2021 [50]. In this study, 84.1% of patients experienced at least 1 adverse event with the majority being mild. Maurer et al. also found 75.8% of patients had complete responses in urticaria after 12 months of therapy. Similar to omalizumab, the phase 2b RCT in adolescents had a disproportionate race distribution with 77.6% White, 20.4% Asian, and 2% Black (NCT03437278).

Dupilumab

Dupilumab is a humanized IgG4 monoclonal antibody which binds IL-4Rα and, thus, inhibits IL-4R signaling induced by IL-4 and IL-13; both of which are elevated in TH2 cell inflammation seen in allergic disorders [51]. The result of IL-4R inhibition is downregulation of the FCεRI receptor — the high affinity receptor for IgE. Dupilumab has been approved for the use of asthma, chronic rhinosinusitis with nasal polyps, and atopic dermatitis, although has yet to be studied extensively in CSU. One case series of 6 patients who had refractory urticaria after receiving high dose omalizumab had improvement in UAS-7 scores after treatment with dupilumab suggesting there may be benefit in its use for CSU [52]. Another case report showed improvement in adrenergic urticaria after administration of off-label dupilumab [53]. RCTs that are currently underway include a phase 2 clinical trial located in Germany (NCT03749135) in patients with CSU with results expected in the near future and one phase 3 RCT in the USA of 246 patients with results expected in March 2024 (NCT04180488).

Benralizumab

Benralizumab is an IL-5Rα monoclonal antibody and is currently approved for use in severe eosinophilic asthma. A recent phase 4, single blinded RCT published in the *New England Journal of Medicine* studied the use of benralizumab 30 mg every 4 weeks in 12 patients with CSU [14]. Of the 12 patients who started the study, 9 completed the trial with 5 having complete resolution of urticaria symptoms and 2 having partial response to the treatment (determined by the UAS-7 score). One phase 2 RCT (NCT04612725) studying benralizumab in patients with CSU is currently recruiting patients with an estimated study completion date of May 2023; however, no other trial is currently underway.

Mepolizumab

Mepolizumab is a monoclonal antibody which targets IL-5 and, therefore, selectively inhibits the growth, differentiation, recruitment, and activation of eosinophils [54].

As a result, eosinophil driven inflammation and mast cell degranulation is reduced. Mepolizumab is approved for use in severe asthma, chronic rhinosinusitis with nasal polyps, hypereosinophilic syndrome, and granulomatosis with polyangiitis. While it is highly efficacious in improving the above diseases [55–57], it has yet to be studied in CSU. One phase 1, open label trial is currently recruiting patients with CSU and has an estimated study completion date of June 2022 (NCT03494881).

Remibrutinib and Fenebrutinib

Remibrutinib and fenebrutinib are highly selective inhibitors of Bruton's tyrosine kinase (BTK). FCεRI cross-linking activates BTK in both basophils and mast cells and is a key contributor to release of histamine and tryptase and production of leukotrienes, and other inflammatory mediators [58]. Thus, inhibition of BTK has the potential to reduce allergic symptoms such as urticaria. Both medications have recently been studied for the management of CSU. A phase 2b RTC released in December 2021 in patients with CSU showed that remibrutinib was highly effective at improving the UAS-7 score [59]. Similarly, fenebrutinib was studied in a phase 2 RCT published in November 2021 in patients with CSU and found significant improvements in urticaria [60]. Both trials had relatively few serious adverse drug events although non-serious, and reversible transaminitis was noted in the trial with fenebrutinib. Two phase 3 RCTs are currently ongoing for remibrutinib in patients with CSU with both expecting results in March 2024 (NCT05032157 and NCT05030311). No RCTs for fenebrutinib are currently ongoing. One major benefit to these two medications is that they are orally administered.

TNF-α Inhibitors

TNF-α inhibitors, including etanercept, infliximab, and adalimumab, are also possible therapies for CSU. TNF-α is one mediator released from activated mast cells and has been found to be upregulated in patients with chronic urticaria in preclinical studies [61]. This has been further characterized in a small number of patients; one case series of 6 patients identified dramatic improvement in urticaria with TNF-α inhibitors [62]. No clinical trial is currently underway nor were there any observational studies using TNF-α for the treatment of CSU.

Others

In patients with CSU whose autoimmunity is believed to be the cause for urticaria, anti-CD20 therapeutics, such as rituximab, may be beneficial. Mature B cells, which express CD-20, produce IL-4 and IL-10 and can act as antigen presenting cells which ultimately supports the activation and autoreactivity of T cells [63]. Thus, blocking CD-20 has the potential to improve urticaria indirectly through the reduction of autoimmunity. One case report was identified that found a significant improvement in urticaria in a patient who had continued symptoms while on omalizumab [64]. Similar findings were noted in another case report. No clinical trials on rituximab in CSU are currently active. Thymic stromal lymphopoietin (TSLP) is also a notable target and is the basis for tezepelumab, an IgG2 monoclonal antibody that binds TSLP. TSLP is an epithelial cell derived cytokine that upregulates Th2 cells [65]. As expected, TSLP is higher in the airways of patients with asthma [66]. One RCT is currently ongoing for this drug with results expected in March 2023 (NCT04833855). IL-17 is another potential target molecule in patients with CSU. IL-17 was noted to be strongly positive in CD4 + T cells and mast cells identified in urticaria skin biopsies of patients with CSU [67]. Of the 8 patients with elevated IL-17 levels, all had resolution of the urticaria after receiving secukinumab, an IL-17A antibody.

Prognosis

A retrospective analysis of ASTERIA I [44] and ASTERIA II [45] trials using a predictive logistic regression model identified two key associations in patients with CSU who were more likely to experience symptom relapse: higher baseline urticaria activity score over 7 days and late treatment response [68]. Serum markers have also been utilized to identify predictors of response to monoclonal antibodies. Serum baseline IgE, change in IgE after treatment with omalizumab, and autologous serum skin test positivity all predict clinical response as well as relapse times [69, 70]. Likewise, baseline FCεRI expression on basophils predicts clinical response to omalizumab [71]. While the total number of complete responders seems to favor ligelizumab over omalizumab, both are efficacious at improving symptoms. Relapse continues to be an issue. The median time to relapse for ligelizumab treated patients is 38 weeks [50]. An observational study of 42 patients treated with 6 months of omalizumab found that 66% relapsed and required further treatment [72].

Future Research Efforts

Target molecules that are currently being studied in randomized trials are listed in Table 1. Many medications have yet to have been studied in a high quality trial, as discussed above. While many novel biologics are currently being studied, certain areas exist which have yet to be adequately addressed in the current literature. Notably, the racial demographics from the largest trials for omalizumab (ASTERIA I, ASTERIA II, and GLACIAL) largely differed from the US

Table 1 Active trials by CSU pharmaceutical, phase, and number of patients

Cell target	Molecule	Drug	Phase	Number of patients	Trial number
Mast cell	IgE	Omalizumab			Approved
		Ligelizumab	3	1713	NCT04210843
			3	428	NCT05024058
			1	68	NCT04513548
			3	66	NCT03907878
			3	1050	NCT03580369
			3	1079	NCT03580356
		UB-221	1	32	NCT04175704
	IL-4	Dupilumab	2	72	NCT03749135
			3	246	NCT04180488
	Tryptase	MTPS9579A	2	240	NCT05129423
	KIT	CDX-0159	1	40	NCT04538794
Eosinophil	IL-5R	Benralizumab	2	160	NCT04612725
	IL-5	Mepolizumab	1	20	NCT03494881
B cell	BTK	Remibrutinib	3	450	NCT05032157
			3	450	NCT05030311
			3	70	NCT05048342
			2	195	NCT04109313
		Rilzabrutinib	2	152	NCT05107115
T cell	TSLP	Tezepelumab	2	270	NCT04833855
	IL-2	IL-2	2	56	NCT04893980

population. For example, Saini et al. had 79–91% representation of Whites with only 6–13% Blacks between study arms [44] and Maurer et al. had 78–89% Whites between study arms [45]. The GLACIAL trial had 89% Whites and did not report other races or ethnicities [11]. Furthermore, ASTERIA II and GLACIAL utilized racial categories White and Nonwhite or White alone, respectively; neither of which categories are recommended by the American Medical Association [73]. This finding was also noted in the only clinical trial assessing ligelizumab for CSU in which 2% of the study population was Black and < 1% was Native American [49]. The lack of analyses in racial minority populations may impact drug efficacy as races other than White have been identified as risk factors for predicting non-response to biologics in other diseases including psoriasis [74]. Although differences in response to omalizumab in patients with allergic asthma who are Black compared to White have not been identified [75], comparisons among other racial backgrounds and in patients with CSU have yet to be studied.

Conclusions

CSU is a debilitating disorder that affects an estimated 1% of the population. In patients with refractory urticaria after high dose antihistamines, omalizumab is the recommended therapy. However, ligelizumab has shown increased efficacy compared to omalizumab in reducing symptoms suggesting a pivotal change may occur in the near future when treating patients with CSU. Other potential targets are also being studied currently as we discussed in this study. Further research should expand on head to head trials between omalizumab and other biologics, such as the trial conducted by Maurer et al. [49]. Clinical trials are also needed to assess the use of biologics for CSU in adolescents as well as racial minority populations; both weaknesses in current trials.

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Declarations

Conflict of Interest The authors declare no competing interests.

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