Review article

Novel biologics for treatment of chronic spontaneous urticaria

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Chronic idiopathic/spontaneous urticaria (CIU/CSU) causes significant impairments in quality of life and is often unresponsive to antihistamines. Although the anti-IgE mAb omalizumab has been an important addition to the therapeutic armamentarium for the management of patients with CSU, there are still a significant percentage of patients who do not respond to the combination of antihistamines and omalizumab. As a result, additional treatments are needed. With the expanding knowledge of the pathogenesis of CSU and the role of mast cells, novel therapeutic agents targeting unique pathways important in CSU are in development. This review focuses on the rationale behind, and results of, novel therapies trialed in CSU. (J Allergy Clin Immunol 2022;150:1256-9.)

Key words: *Urticaria, biologics, mast cells*

Abbreviations used
BTK: Bruton's tyrosine kinase
CIU/CSU: Chronic idiopathic/spontaneous urticaria
CIndU: Chronic inducible urticaria
UAS: Urticaria activity score

Chronic idiopathic/spontaneous urticaria (CIU/CSU) leads to symptoms that can significantly affect patient's quality of life and lead to both work and school impairment. Current guidelines indicate that second-generation antihistamines at up to 4-fold licensed doses should be used as first-line therapy.[1] However, many patients do not respond or do not achieve an acceptable level of control of symptoms despite high-dose antihistamines. In addition, patients with CSU are often not treated in accordance with guidelines and in some cases receive treatments that are deleterious including first-generation antihistamines and prolonged oral corticosteroids.[2-4] Thus, there is a need to not only follow clinical guidelines for the management of CSU but also to develop newer therapies that can effectively treat patients unresponsive or poorly responsive to high-dose second-generation antihistamines. Biologic therapies provide a therapeutic option that directly affects some of the key pathogenic mechanisms involved in CSU. This review will briefly outline the effects of biologics and other novel therapies for the treatment of CSU (Fig 1). The information for this review was based on a search of clinicaltrials.gov, pubmed.gov, and press releases from the companies sponsoring the research.

ANTI-IgE mAbs

Omalizumab

The anti-IgE mAb omalizumab has been approved by the United States Food and Drug Administration for the treatment of CSU in patients 12 years and older since 2014. Clinical guidelines recommend omalizumab as the next-step treatment for patients refractory to antihistamines.[1] Pivotal studies of patients with CSU on concomitant antihistamines showed that at 24 weeks, more than 50% exhibited complete resolution of their hives and improvement in quality-of-life scores.[6-8] Omalizumab has also been shown to improve coexisting angioedema. Some positive predictors of clinical response to omalizumab include higher baseline levels of serum IgE and basophil FcεRI expression, older age, shorter disease duration, concomitant chronic inducible urticaria (CIndU), negative histamine release test result, and lack of concomitant angioedema.[9,10] In patients with autoantibodies, the clinical response to omalizumab can be delayed.[9] Omalizumab has also demonstrated efficacy in various forms of CIndU.[11] Omalizumab has not been demonstrated to induce long-term disease remission nor is it effective in all patients. Thus, there is a significant unmet need for safe and more effective treatments that can lead to cure or long-term remission.

In addition to omalizumab, there are omalizumab biosimilars in development. CT-P39 is in phase 3 trial for CSU (NCT04426890).

Ligelizumab

Ligelizumab is a second-generation anti-IgE mAb that has an approximately 40-fold higher affinity for IgE and a slower offloading time. Ligelizumab led to better responses than placebo and omalizumab in a phase 2 CSU trial.[12] Recently completed phase 3 trials in CSU showed that ligelizumab was superior to placebo, but not omalizumab.[13] As a result, further development of

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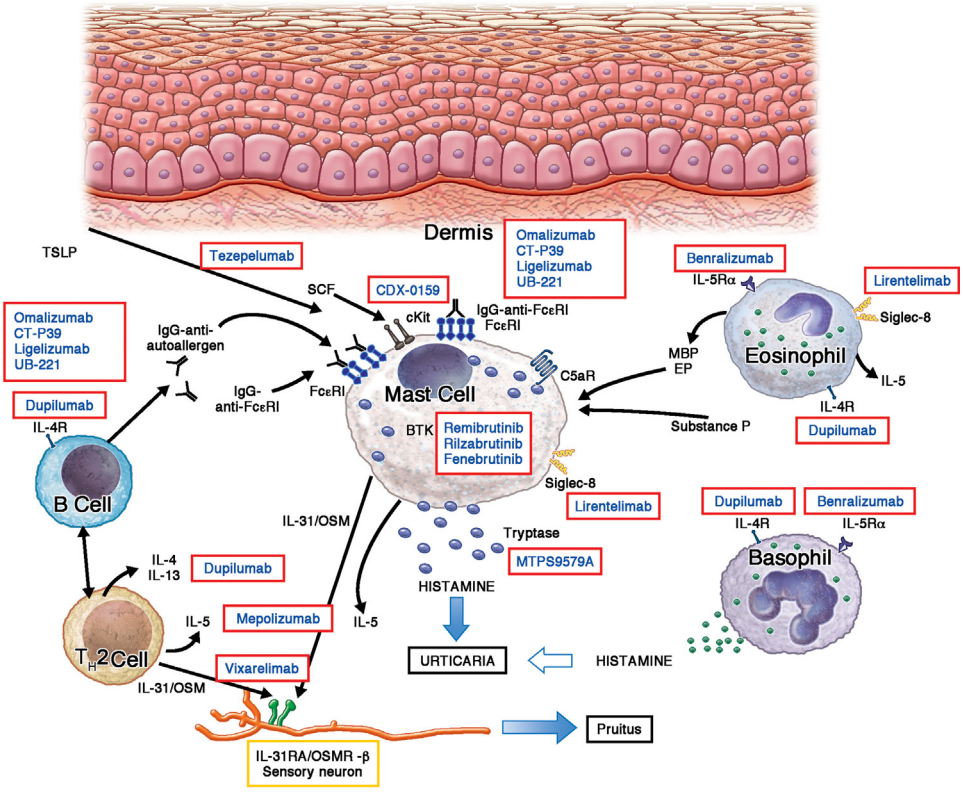

FIG 1. Biologics and sites of action for CSU. The figure depicts biologics under investigation for CSU and their putative sites of action. *OSM,* Oncostatin M; *SCF,* stem cell factor; *Siglec-8,* sialic acid–binding immunoglobulin-like lectin 8; *TSLP,* thymic stromal lymphopoietin. Adapted from Kolkhir et al.[5]

ligelizumab for CSU has been halted. Ligelizumab is being evaluated as a monotherapy for food allergy (NCT04984876).

UB-221

UB-221 is a humanized IgG1 mAb that targets IgE. It has a binding affinity 8-fold higher than that of omalizumab. In addition to lowering IgE levels and FcεRI expression, UB-221 downregulates IgE synthesis by stabilization of membrane-bound CD23 on B lymphocytes.[14] United BioPharma, the manufacturer of UB-221, has completed one study (NCT03632291) and is planning several others to determine the safety, pharmacokinetics, and pharmacodynamics of this anti-IgE mAb administered intravenously to patients with CSU. No results have been published to date.

ANTI–IL-4α mAb

Dupilumab

The importance of T_H2-hi inflammation and IL-4 and IL-13 in CSU has been demonstrated in a number of studies. Dupilumab blocks the IL-4α receptor, resulting in the inhibition of both IL-4 and IL-13 signaling, providing a clear rationale for its potential use to treat CSU.[15]

A case series described 6 patients with a history of CSU with comorbid atopic dermatitis who failed on omalizumab and were subsequently treated with dupilumab.[15,16] The authors reported improvement in urticaria in all 6 patients. In 5 of 6 patients, there was either complete resolution of urticaria (Urticaria Activity Score [UAS] = 0) or UAS less than 3 was achieved at 3 months on dupilumab. Dupilumab phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group studies (NCT04180488) for the treatment of moderate to severe CSU in patients who remain symptomatic despite the use of antihistamines who are naive to omalizumab (CUPID Study A) or who are omalizumab-intolerant or incomplete responders to omalizumab (CUPID Study B) have been completed. Preliminary results from CUPID Study A showed that dupilumab demonstrated clinically and statistically significant efficacy at week 24, compared with standard-of-care antihistamines alone.[17] The results of CUPID Study B have not been published, but a recent press release indicated that the dupilumab study in patients with CSU, who were refractory to omalizumab, will stop because of futility based on a prespecified interim analysis. Although positive numerical trends in reducing itch and hives were observed, the results from the interim analysis did not demonstrate statistical significance for the primary end points.[18]

BRUTON'S TYROSINE KINASE INHIBITORS

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and is expressed in cells of the adaptive and innate immune systems including B cells, macrophages, mast cells/basophils, and platelets. BTK is essential for signaling through FcεR1. Inhibition of BTK leads to inhibition of mast cell and basophil activation/degranulation and allergen-induced airway responses.[19,20] Therefore, BTK inhibition is a potential therapeutic option for mast cell–dependent diseases, including CSU.

The BTK inhibitor remibrutinib was recently evaluated in a multicenter, randomized, double-blind, placebo-controlled phase 2b dose-finding study with 311 patients with CSU who were inadequately controlled by antihistamines (NCT03926611). Preliminary results from this trial showed that remibrutinib treatment led to significant improvements in UAS7 compared with placebo at weeks 4 and 12 and had a favorable safety profile across all tested doses.[21] Three phase 3 trials of remibrutinib for the treatment of patients with CSU who are inadequately controlled by antihistamines are currently recruiting (NCT05048342, NCT05032157, and NCT05030311).

A phase 2 trial with another BTK inhibitor, rilzabrutinib, is currently enrolling (NCT05107115).

Finally, fenebrutinib resulted in dose-dependent improvements in UAS7 at week 8 occurring at 200 mg twice daily and 150 mg daily, but not at 50 mg daily versus placebo. However, asymptomatic, reversible grade 2 and 3 liver transaminase elevations occurred in the fenebrutinib 150-mg daily and 200-mg twice-daily groups.[22]

c-KIT INHIBITOR

CDX-0159 is a humanized IgG1 kappa mAb that specifically binds the extracellular dimerization domain of c-KIT (CD117) and inhibits activation by its ligand, stem cell factor.[23] Because mast cells are key effector cells in urticaria and require the activation of the KIT receptor and its ligand stem cell factor for differentiation, maturation, and survival, targeting mast cells with the anti–c-KIT antibody CDX-0159 could provide a novel therapeutic option for patients with CSU and CIndU. A single dose of CDX-0159 (3 mg/kg) resulted in a rapid and complete response in 95% of patients with CIndU refractory to antihistamines including in patients who had received omalizumab previously and was sustained for a median duration of approximately 2 months. This clinical benefit was accompanied by a rapid and durable depletion of skin mast cells and serum tryptase. Hair color changes (greying) and taste disorders consistent with inhibiting KIT signaling in other cell types were reported.[24] There are several phase 2 studies beginning with CDX-0159 for both CSU and CIndU.

ANTITRYPTASE mAb

MTPS9579A is a full-length humanized IgG4 antibody that binds with high affinity to tryptase, thereby inhibiting tryptase activity by irreversibly dissociating the active tetramer into inactive monomers. Inhibiting tryptase with MTPS9579A is anticipated to block skin inflammation and pruritus secondary to mast cell degranulation. Tryptase-induced pruritus is proteinase-activated receptor-2–dependent.[25] A phase 2, multicenter, randomized, double-blind, placebo-controlled pilot and dose-ranging study of MTPS9579A in participants with refractory CSU (NCT05129423) has recently been initiated in the United States.

ANTI–ONCOSTATIN M Rβ mAb

Vixarelimab

Vixarelimab, KPL-716, simultaneously inhibits 2 cytokines IL-31 and oncostatin M, by targeting their common receptor subunit, oncostatin M Rβ. This fully human mAb is being trialed in pruritic diseases including CSU. A recently completed study (NCT03858634) assigned participants to active treatment or placebo in 5 individual disease-specific cohorts: CIU (n = 4), chronic idiopathic pruritus (n = 14), lichen planus (n = 3), lichen simplex chronicus (n = 4), and plaque psoriasis (n = 14). There were trends for improvement, but the numbers for CIU were too small to draw definitive conclusions.

TABLE I. Novel biologics for the treatment of CSU

Anti-IgE mAbs
Omalizumab
CT-P39
Ligelizumab
UB-221
Anti–IL-4α mAb
Dupilumab
BTK inhibitors
Remibrutinib
Rilzabrutinib
Fenebrutinib
C-kit inhibitor
CDX-0159
Antitryptase mAb
MTPS9579A
Anti-OSMRβ mAb
Vixarelimab (KPL-716)
Anti–Siglec-8 mAb
Lirentelimab (AK002)
Anti–IL-5 mAb
Mepolizumab
Anti–IL-5Rα mAb
Benralizumab
Anti–IL-1β mAb
Canakinumab
Anti-TSLP mAb
Tezepelumab

OSM, Oncostatin M; *Siglec-8*, sialic acid–binding immunoglobulin-like lectin 8.

ANTI–SIALIC ACID–BINDING IMMUNOGLOBULIN-LIKE LECTIN 8 mAb

Lirentelimab

Lirentelimab (AK002) is a humanized non-fucosylated IgG1 mAb directed against sialic acid–binding immunoglobulin-like lectin 8, a member of the CD33-related family of sialic acid–binding immunoglobulin-like lectins. Siglec 8 is an inhibitory receptor that is primarily expressed on mature eosinophils and mast cells, with low expression on basophils. Engagement by lirentelimab can simultaneously inhibit mast cell activation and trigger apoptosis of eosinophils. In phase II trials, lirentelimab improved response in both omalizumab-naive patients and omalizumab-resistant patients. It has demonstrated efficacy in symptomatic dermatographism and cholinergic urticaria as well.[26] Lirentelimab is also being studied for eosinophilic gastrointestinal disorders and atopic dermatitis.

OTHER AGENTS CURRENTLY IN DEVELOPMENT

Other mAbs on the horizon for CSU include anti–IL-5 and anti–IL-5R agents such as mepolizumab and benralizumab, respectively, canakinumab (anti–IL-1β), and the thymic stromal

lymphopoietin inhibitor tezepelumab.[27] The IL-5 blockers have shown promising early results,[28,29] but canakinumab failed to show efficacy in a small proof-of-concept trial.[30]

CONCLUSIONS

Because omalizumab is the only Food and Drug Administration–approved option to treat CSU, it is currently the preferred choice. Patients who fail omalizumab may benefit from other agents with different mechanisms of action. However, this remains to be proven because omalizumab failures treated with dupilumab, for example, did not improve. Moreover, other anti-IgE mAbs, such as ligelizumab, have not proven to be more effective than omalizumab. Thus, although there are many biologics in clinical development for the treatment of CSU and CIndU (Table I), it remains to be determined whether these options will prove more effective than omalizumab and/or capable of relieving symptoms in omalizumab therapeutic failures while having a safety profile at least as good as omalizumab. The challenge will be to define specific phenotypes and corresponding endotypes with point-of-care biomarkers, which can lead to more targeted therapies.

REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA^{2}LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDV, SIAAIC, SIDeMaST, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
2. Costa C, Rosmaninho I, Guilherme A, Ferreira J, Antunes J, Pina A, et al. Chronic urticaria in the real-life clinical practice setting in Portugal: baseline results from the non-interventional multicentre AWARE study. Acta Med Port 2019;32:133-40.
3. Maurer M, Weller K, Bindslev-Jensen C, Giménez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. Allergy 2011;66:317-30.
4. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. Allergy 2017;72:2005-16.
5. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. Ann Allergy Asthma Immunol 2020;124:2-12.
6. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368:924-35.
7. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101-9.
8. Kaplan A, Ferrer M, Bernstein JA, Antonova E, Trzaskoma B, Raimundo K, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J Allergy Clin Immunol 2016;137:474-81.
9. Gimenéz-Arnau AM, Santiago AV, Tomás JB, Presa IJ, Horrillo ML, Miquel FM, et al. Therapeutic strategy according to differences in response to omalizumab in patients with chronic spontaneous urticaria. J Investig Allergol Clin Immunol 2019;29:338-48.
10. Deza G, Ricketti PA, Giménez-Arnau AM, Casale TB. Emerging biomarkers and therapeutic pipelines for chronic spontaneous urticaria. J Allergy Clin Immunol Pract 2018;6:1108-17.
11. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, et al. Omalizumab treatment in patients with chronic inducible urticaria: a systematic review of published evidence. J Allergy Clin Immunol 2018;141:638-49.
12. Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for chronic spontaneous urticaria. N Engl J Med 2019;381:1321-32.
13. Novartis provides an update on phase III ligelizumab [press release]. globenewswire.com; 2021.
14. Kuo BS, Li CH, Chen JB, Shiung YY, Chu CY, Lee CH, et al. IgE-neutralizing UB-221 mAb, distinct from omalizumab and ligelizumab, exhibits CD23-mediated IgE downregulation and relieves urticaria symptoms. J Clin Invest 2022;132:e157765.
15. Maloney NJ, Tegtmeyer K, Zhao J, Worswick S. Dupilumab in dermatology: potential for uses beyond atopic dermatitis. J Drugs Dermatol 2019;18:S1545961619P1053X.
16. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. J Allergy Clin Immunol Pract 2019;7:1659-16561.e1.
17. Maurer M, Casale T, Saini S, Ben-Shoshan M, Amin N, Radin A, et al. Dupilumab significantly reduces itch and hives in patients with chronic spontaneous urticaria: results from a phase 3 trial (LIBERTY-CSU CUPID Study A). J Allergy Clin Immunol 2022;149:AB312.
18. Update on ongoing Dupixent® (dupilumab) chronic spontaneous urticaria phase 3 program [press release]. Sanofi; February 18, 2022.
19. Smiljkovic D, Blatt K, Stefanzl G, Dorofeeva Y, Skrabs C, Focke-Tejkl M, et al. BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. Allergy 2017;72:1666-76.
20. Dispenza MC, Krier-Burris RA, Chhiba KD, Undem BJ, Robida PA, Bochner BS. Bruton's tyrosine kinase inhibition effectively protects against human IgE-mediated anaphylaxis. J Clin Invest 2020;130:4759-70.
21. Maurer M, Berger W, Giménez-Arnau A, Hayama K, Jain V, Reich A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. J Allergy Clin Immunol [E-pub ahead of print September 9, 2022.] https://doi.org/10.1016/j.jaci.2022.08.027.
22. Metz M, Sussman G, Gagnon R, Staubach P, Tanus T, Yang WH, et al. Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Nat Med 2021;27:1961-9.
23. London CA, Gardner HL, Rippy S, Post G, La Perle K, Crew L, et al. KTN0158, a humanized anti-KIT monoclonal antibody, demonstrates biologic activity against both normal and malignant canine mast cells. Clin Cancer Res 2017;23:2565-74.
24. Terhorst-Molawi D, Hawro T, Grekowitz E, Alvarado D, Crowley E, Heath-Chiozzi M, et al. The anti-kit antibody, CDX-0159, reduces disease activity and tryptase levels in patients with chronic inducible urticaria. Allergy 2021;76.
25. Ui H, Andoh T, Lee JB, Nojima H, Kuraishi Y. Potent pruritogenic action of tryptase mediated by PAR-2 receptor and its involvement in anti-pruritic effect of nafamostat mesilate in mice. Eur J Pharmacol 2006;530:172-8.
26. Altrichter S, Staubach P, Pasha M, Singh B, Chang AT, Bernstein JA, et al. An open-label, proof-of-concept study of lirentelimab for antihistamine-resistant chronic spontaneous and inducible urticaria. J Allergy Clin Immunol 2022;149:1683-90, e7.
27. Maurer M, Khan DA, Komi DEA, Kaplan AP. Biologics for the use in chronic spontaneous urticaria: when and which. J Allergy Clin Immunol Pract 2021;9:1067-78.
28. Bernstein JA, Singh U, Rao MB, Berendts K, Zhang X, Mutasim D. Benralizumab for chronic spontaneous urticaria. N Engl J Med 2020;383:1389-91.
29. Bernstein JA, Singh U, Rao MB, Berendts K, Zhang X, Mutasim D. Treatment of chronic spontaneous urticaria with benralizumab: report of primary endpoint per-protocol analysis and exploratory endpoints. Allergy 2021;76:1277-80.
30. Maul JT, Distler M, Kolios A, Maul LV, Guillet C, Graf N, et al. Canakinumab lacks efficacy in treating adult patients with moderate to severe chronic spontaneous urticaria in a phase II randomized double-blind placebo-controlled single-center study. J Allergy Clin Immunol Pract 2021;9:463-8.