



CME Review

New treatments for chronic urticaria



Pavel Kolkhir, PhD^{*,†}; Sabine Altrichter, MD^{*}; Melba Munoz, PhD^{*};
Tomasz Hawro, MD^{*}; Marcus Maurer, MD^{*}

^{*} Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[†] Division of Immune-Mediated Skin Diseases, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

Key Messages

- Omalizumab is currently the mainstay of treatment of antihistamine-resistant chronic spontaneous urticaria.
- The use of omalizumab in chronic inducible urticaria, up-dosing in chronic spontaneous urticaria and treatment of children younger than 12 years, currently off-label, are supported by evidence, and further studies should be performed.
- Ligelizumab and UB-221 are novel anti-IgE monoclonal antibodies with a 40- to 50-fold and 8-fold greater affinity to IgE, respectively, compared with omalizumab and are currently being studied in clinical trials of chronic spontaneous urticaria.
- Other drugs for the treatment of CSU are promising, including interleukin (IL) 5–targeted monoclonal antibodies (mAbs), a chemoattractant receptor–homologous molecule expressed on T_H2 cell antagonist, a mAb to Siglec-8, Bruton tyrosine kinase inhibitors, a spleen tyrosine kinase inhibitor, and dupilumab, an anti-IL-4/13 mAb.
- New pathogenically important targets in chronic spontaneous urticaria include Mas-related G-protein–coupled receptor X2; the histamine₄ receptor; C5a and its receptor; inhibitory mast cell receptors other than Siglec-8; IL-33, IL-25, and thymic stromal lymphopoietin, and stem cell factor.

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ABSTRACT

Objective: Chronic urticaria (CU) is a common, heterogeneous, and debilitating disease. Antihistamines and omalizumab are the mainstay therapies of CU. Additional treatment options are needed. Here, we review the off and beyond label use of licensed drugs, novel treatments that are currently under development, and promising new targets.

Data Sources: MEDLINE was searched for recent reports of the successful use of treatments in CU and promising targets for the development of novel treatment options. We also searched [ClinicalTrials.gov](https://clinicaltrials.gov) for recent and ongoing randomized clinical trials in CU.

Study Selections: Relevant articles were selected and reviewed.

Results: Omalizumab, the treatment of choice in patients with antihistamine-resistant chronic spontaneous urticaria (CSU), should be explored for use in chronic inducible urticaria in children younger than 12 years with CSU and at higher doses. The off-label use of dupilumab, reslizumab, mepolizumab, and benralizumab can be effective in CU. Ligelizumab and UB-221, 2 novel anti-IgE monoclonal antibodies, are in clinical trials for CU. Other promising drugs that are currently under development for CU are a chemoattractant receptor

Reprints: Marcus Maurer, MD, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany; E-mail: marcus.maurer@charite.de.

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—homologous molecule expressed on T_H2 cell antagonist, a monoclonal antibody to Siglec-8 (AK002), Bruton tyrosine kinase inhibitors (fenebrutinib and Lou064), a spleen tyrosine kinase inhibitor, and dupilumab. Promising targets of future therapies include the Mas-related G-protein–coupled receptor X2; the histamine₄ receptor; C5a and its receptor; inhibitory mast cell receptors other than Siglec-8; interleukin 33, interleukin 25, and thymic stromal lymphopoietin, and stem cell factor.

Conclusion: Novel and better treatments for CU are very much needed. Some agents are in clinical trials already (eg, ligelizumab), and additional ones should be developed, making use of the many promising targets recently identified and characterized.

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Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Identify which patients would benefit from omalizumab therapy for chronic urticaria.
- Identify novel therapeutic targets for treatment of chronic urticaria.

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Introduction

Chronic urticaria (CU) is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks.¹ The current international urticaria guideline classifies the disease as chronic spontaneous urticaria (CSU, also called chronic idiopathic urticaria), without a definite eliciting factor involved, or as chronic inducible urticaria (CIndU), where defined and definite eliciting factors reproducibly trigger signs and symptoms and are required for their occurrence.¹ The point prevalence of CU is approximately 0.5% to 1%. CU is unpredictable in its course and duration, and it persists for several years in many patients.²

CU is a disabling condition that leads to substantial deterioration in quality of life, comparable with that experienced by patients with severe ischemic heart disease.³ Furthermore, psychosocial factors, such as anxiety, depression, somatization, interpersonal sensitivity, insomnia, and stressful life events, are present in 46% of patients with CU.⁴ In addition, care of patients with CU is time-consuming and costly.³

No curative treatment exists for CU, and all currently recommended treatment options are intended to control and prevent the symptoms of CU. Second-generation histamine₁ (H₁)-antihistamines are the first-line (standard doses) and second-line (high doses) therapies.¹ A systematic review and meta-analysis reported that only 39% of patients with CSU respond to standard doses of second-generation H₁-antihistamines and 63% of nonresponders improve on up-dosed second-generation H₁-antihistamines.⁵ Although omalizumab, the third-line therapy, remains the mainstay of treatment of second-generation H₁-antihistamine-resistant CU, there are patients who are nonresponders or slow responders or who have drug intolerance. Accordingly, further safe and effective alternative treatment options are needed. In this report, we describe the off-label and beyond-label use of licensed drugs in CU, discuss novel therapies that are currently under development for CU, and review promising new targets of future CU treatments. (Fig. 1)

Data Sources and Study Selection

The PubMed database was searched for recent reports of successful treatments of patients with CU and newly identified or characterized drivers of urticaria pathogenesis and targets for future treatments. The [ClinicalTrials.gov](https://clinicaltrials.gov) database was searched with the keyword *chronic urticaria*. Of 101 identified studies, 33 complete or ongoing studies were included in the review. Studies with unknown recruitment status and studies that were terminated or withdrawn were excluded (n = 68). An additional search with the keywords *cholinergic urticaria* OR *cold urticaria* OR *symptomatic*

dermographism identified 15 studies, and 7 of them were included in the review. In total, 40 studies were included in the review (Table 1).

Licensed Drugs and Their Off-Label and Beyond-Label Use

Omalizumab: A Monoclonal Anti-IgE Antibody

Omalizumab is the only nonantihistamine drug licensed for the treatment of CSU. It is a recombinant, humanized, monoclonal antibody (mAb) against IgE that is approved for the treatment of antihistamine-resistant CSU in patients 12 years or older. The development of omalizumab for the treatment of patients with CSU is based on the fact that IgE and its high-affinity receptor FcεRI are important in urticaria pathogenesis. The presence of IgE against autoantibodies in CSU (eg, IgE antithyroperoxidase, IgE antitissue factor, and IgE anti-interleukin [IL] 24) has been described as type I autoimmune (autoallergic) CSU.^{6,7} In type IIb autoimmune CSU,⁸ patients with CSU have IgG against IgE or FcεRI on mast cells and basophils.⁹

Omalizumab reduces the levels of circulating IgE due to binding to the C3 domain of the IgE heavy chain. This results in a subsequent downregulation of the expression of FcεRI on mast cells and basophils.¹⁰ In contrast to asthma, the use of omalizumab in CSU is not determined based on patients' IgE level or weight. Although recent studies have found that low levels of total IgE can predict nonresponse to the drug in patients with CSU, several questions still have to be addressed.¹¹ For example, why do nonresponders to omalizumab have low levels of IgE? Is it necessary to reduce free IgE to 15 kU/L as in asthma?

Several systematic reviews and meta-analyses summarize the real-world evidence and evidence from randomized clinical trials (RCTs), including 3 pivotal studies, ASTERIA (Aspirin vs Triflusal for Event Reduction in Atherothrombosis Secondary Prevention) I and II and GLACIAL (Clinical Study of Non-inferiority With Participants Diagnosed With Primary Knee OA), of omalizumab treatment in CSU.^{10–14} Taken together, this evidence shows that treatment with omalizumab results in significant improvement in disease activity and quality of life in patients with CSU. Omalizumab has a good safety profile and is approved for self-administration in some countries but not the in the United States.

Interestingly, 70% of patients with CSU who benefit from omalizumab respond within the first week of treatment,¹⁵ and early response is linked to IgE autoantibodies.¹⁶ In contrast, slow response to omalizumab treatment is associated with positive autologous serum skin test, and basophil histamine release assay results, diagnostic tests for type IIb autoimmune CSU.^{15,17} In CSU,

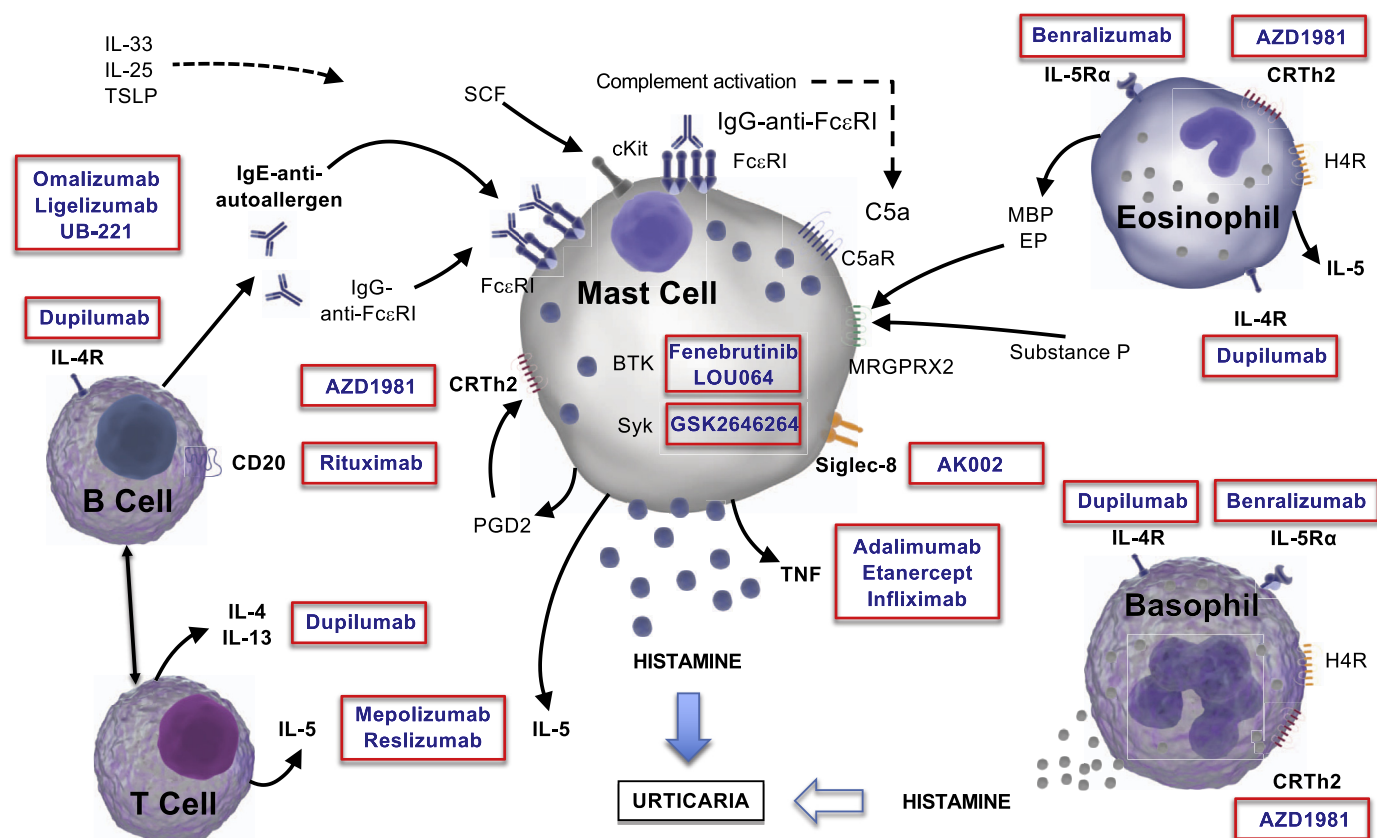


Figure 1. Promising drugs and potential targets in chronic urticaria. BTK: Bruton tyrosine kinase; CRTh2: chemoattractant receptor–homologous molecule expressed on TH2 cells; MRGPRX2: Mas-related G-protein coupled receptor X2; Syk: spleen tyrosine kinase; MBP: major basic protein; EP: eosinophil peroxidase; SCF: stem cell factor; TSLP: thymic stromal lymphopoietin.

nonresponse to omalizumab is predicted by low baseline total IgE levels, unchanged total IgE levels within the 4 weeks after the first injection,¹¹ and low baseline levels of FcεRI on basophils.¹⁸

Patients with CSU with partial or no response to 300 mg of omalizumab can benefit from up-dosing. For example, disease control was achieved in 13 of 18 patients with CSU (77%) and 13 of 22 patients with CSU (59%) with 450 and 600 mg of omalizumab, respectively, who failed to respond after 3 to 6 doses of 300 mg of omalizumab.¹⁹ The use of beyond-label doses of omalizumab (ie, 450 and 600 mg) should be considered because of its efficacy and safety in patients with CSU who do not achieve disease control with 300 mg.

Reportedly, omalizumab is effective and safe in several studies, including patients with CSU younger than 12 years. In a systematic review of these studies, omalizumab induced partial improvement or complete remission in all 13 patients.²⁰ In asthma, omalizumab is licensed for use in children 6 years or older. The beyond-label use of omalizumab in children with antihistamine-resistant CSU who are younger than 12 years should be considered and explored in clinical trials.

A systematic review of 43 studies found omalizumab to be effective in patients with therapy-refractory CINDU, especially in symptomatic dermatographism, cold urticaria, and solar urticaria.²¹ For instance, in patients with symptomatic dermatographism, both 150 and 300 mg of omalizumab resulted in a rapid reduction of disease activity and an increase of trigger thresholds.²² Omalizumab is the recommended treatment in patients with CINDU who do not respond to an antihistamine, but this use is off-label.

Taken together, omalizumab is a valuable treatment for CU beyond its current label (ie, at higher doses than 300 mg in patients with CSU) in children younger than 12 years with CSU and in patients with CINDU.

Mepolizumab, Reslizumab, and Benralizumab: 3 IL-5–Targeted mAbs

Studies suggest that eosinophils contribute to the pathogenesis of CSU. Eosinophils have been detected in the lesional and nonlesional skin of patients with CSU.²³ Mast cells may recruit eosinophils to urticaria lesions by releasing IL-5 and other chemotactic mediators.^{23,24} Patients with CSU and eosinophilic skin infiltrate had high disease activity,²⁵ and blood eosinopenia is linked to high disease activity and poor response to treatment (Kolkhir et al, in press, 2019).

Mepolizumab and reslizumab, unique anti-IL-5 mAbs, as well as benralizumab, an anti-IL-5 receptor mAb, have been successfully used for the treatment of patients with CSU and CINDU.^{8,26,27} The efficacy of benralizumab and mepolizumab is currently under evaluation. In an ongoing study, benralizumab is given once a month for 3 months to patients with H₁-antihistamine refractory CSU (NCT03183024). In another study, patients with CSU are treated with 100-mg subcutaneous injections of mepolizumab at weeks 0, 2, 4, 6, and 8 for a total of 5 doses (a phase 1 study, NCT03494881).

Dupilumab: An Anti-IL-4/13 mAb

IL-4 and IL-13 contribute to T_H2-type immune response through their effects on T-cell differentiation and IgE class switching. Dupilumab is an mAb that inhibits IL-4 and IL-13 signaling through blockade of their shared IL-4α receptor subunit. It has been approved by the US Food and Drug Administration for the treatment of moderate-to-severe atopic dermatitis as well as asthma and chronic rhinosinusitis with nasal polyposis.²⁸

Table 1
Clinical Trials in Chronic Urticaria

Target	Drug	Type of chronic urticaria	Age of patients, y	Antihistamine-resistant or inadequately controlled urticaria	Study description	ClinicalTrials.gov identifier	Location	Recruitment status
IgE	Omalizumab	CSU	18-70	+	RCT	NCT00481676	Germany	Completed
			≥18	+	RCT	NCT01713725	Spain	Completed
			18-70	+	RCT	NCT01803763	Switzerland	Completed
			18-80	+	RCT	NCT00130234	United States	Completed
			18-75	+	Phase 4, single arm, and open-label	NCT02550106	France	Completed
			12-75	+	Phase 3 RCT	NCT01292473	Multicenter worldwide	Completed
			18-75	+	Single center, noncomparative exploratory	NCT02814630	United States	Completed
			12-75	+	Phase 4 RCT	NCT02392624	United States (multicenter)	Completed
			18-75	+	RCT	NCT01723072	Germany (multicenter)	Completed
			12-75	+	Phase 2 RCT	NCT00866788	Multicenter worldwide	Completed
			12-75	+	Phase 3 RCT	NCT01264939	Multicenter worldwide	Completed
			12-75	+	Phase 3 RCT	NCT01287117	Multicenter worldwide	Completed
			≥18	+	Randomized, open label	NCT02161562	Multicenter worldwide	Completed
			12-75	+	Phase 3 RCT	NCT02329223	Japan, Republic of Korea	Completed
			18-75	+	RCT	NCT03328897	China	Recruiting
		Cholinergic urticaria	≥14	+	RCT	NCT02012387	Spain	Completed
		Cold contact urticaria	≥18	+	RCT	NCT01580592	Germany	Completed
		Symptomatic dermographism	≥18	+	RCT	NCT02169115	Germany	Completed
	Ligelizumab (QGE031)	CSU	18-75	+	Phase 2 RCT	NCT02477332	Multicenter worldwide	Completed
			12-18	+	Phase 2b, RCT	NCT03437278	Multicenter worldwide	Recruiting
			18-75	+	Open-label, extension	NCT02649218	Multicenter worldwide	Active, not recruiting
			≥12	+	Phase 3 RCT	NCT03580356	Multicenter worldwide	Recruiting
			≥12	+	Phase 3 RCT	NCT03580369	Multicenter worldwide	Recruiting
Siglec-8	UB-221	CSU	≥18	+	Open-label	NCT03907878	Japan	Recruiting
			20-65	ND	Phase 1, open-label, dose escalation	NCT03632291	Taiwan	Recruiting
			18-85	+	Phase 2a, open-label	NCT03436797	United States, Germany	Active, not recruiting
			18-65	+	Phase 2a RCT	NCT02031679	United States	Completed
			≥18	+	RCT	NCT01960283	France	Completed
			18-70	+	Phase 1/2, open-label	NCT00886795	United States	Completed
			≥18	ND	RCT	NCT03789422	France	Not yet recruiting
			≥18	+	Open-label, single arm, exploratory	NCT03494881	United States	Not yet recruiting
			19-70	+	Nonrandomized, single-blind	NCT03183024	United States	Recruiting
			18-60	+	Randomized, prospective	NCT03250143	India	Completed
CRT _H 2	AZD1981, anti-CRT _H 2	CSU	18-65	+	Phase 2a RCT	NCT02031679	United States	Completed
Dihydrofolate reductase	Methotrexate	CSU	≥18	+	RCT	NCT01960283	France	Completed
T lymphocytes	Abatacept	Chronic urticaria	18-70	+	Phase 1/2, open-label	NCT00886795	United States	Completed
Fibrinolysis	Tranexamic acid, an antifibrinolytic agent	CSU	≥18	ND	RCT	NCT03789422	France	Not yet recruiting
IL-5	Mepolizumab	CSU	≥18	+	Open-label, single arm, exploratory	NCT03494881	United States	Not yet recruiting
IL-5 receptor α	Benralizumab	CSU	19-70	+	Nonrandomized, single-blind	NCT03183024	United States	Recruiting
Purine synthesis, T-cells	Azathioprine vs cyclosporine	CSU	18-60	+	Randomized, prospective	NCT03250143	India	Completed
IL-4/13	Dupilumab	CSU	18-75	+	Phase 2a RCT	NCT03749135	Germany (multicenter)	Recruiting
IL-4/13	Dupilumab	Cholinergic urticaria	18-75	+	Phase 2a RCT	NCT03749148	Germany (multicenter)	Recruiting
Spleen tyrosine kinase	GSK2646264 topical cream	CSU, cold urticaria	18-70	ND	RCT	NCT02424799	Germany, United Kingdom	Completed
Bruton tyrosine kinase	Lou064	CSU	18-99	+	Phase 2a RCT	NCT03926611	ND, multicenter	Not yet recruiting
Bruton tyrosine kinase	Fenebrutinib (GDC-0853)	CSU	18-75	+	Phase 2a RCT	NCT03137069	United States, Canada, Germany	Recruiting
Bruton tyrosine kinase	Fenebrutinib (GDC-0853)	CSU	18-75	+	Phase 2, open-label, extension	NCT03693625	United States, Canada, Germany	Recruiting
IL-1	Rilonacept	Cold contact urticaria	≥18	+	Phase 2 RCT	NCT02171416	Germany	Completed

Abbreviations: CRT_H2, chemoattractant receptor—homologous molecule expressed on T helper type 2; CSU, chronic spontaneous urticaria; IL, interleukin; ND, not defined; RCT, randomized clinical trial.

Table 2

Summary of Relevant Licensed Drugs and Their Off-Label and Beyond-Label Use in the Treatment of Chronic Urticaria

Drug	Drug description	Licensed for CU?	Evidence on efficacy in CU	Dosage and dosing schedule used in CU	Onset of improvement in most patients with CU	Main indication(s)	Possible adverse effects ^a
Omalizumab	An anti-IgE mAb	Yes, CSU only	Many studies, including RCTs (CSU and CIndU) ^{11-13,20}	150-300 mg SC every 4 weeks	1-2 weeks	CSU and asthma	High safety profile, anaphylaxis is rare. In >10%: injection site reactions, viral infections, sinusitis, headache, pharyngitis
Benralizumab	An anti-IL-5 receptor mAb	No	A non randomized, single-blind study ongoing (CSU)	30 mg SC once a month for 3 months	ND	Severe eosinophilic asthma	Headache (8%), pharyngitis (5%), pyrexia (3%), hypersensitivity reactions (3%)
Mepolizumab	An anti-IL-5 mAb	No	A case report, ²⁵ an open-label pilot study ongoing (CSU)	100 mg SC every 4 weeks for 16 weeks or at week 0, 2,4,6, and 8	Within first week after injection	Severe eosinophilic asthma	Headache (19%), injection site reactions (8-15%). Hypersensitivity reactions and infection have been reported
Reslizumab	An anti-IL-5 mAb	No	A case report (CSU an CIndU) ⁷⁰	300 mg/mo IV	Immediately after the first injection	Severe eosinophilic asthma	Treatment-emergent antibody response (5.4%), oropharyngeal pain (2.6%), malignant tumor (0.6%), anaphylaxis (0.3%)
Dupilumab	An anti-IL-4/13 mAb	No	Case series, ³¹ RCTs ongoing (CSU and CIndU)	A 600-mg loading dose followed by 300 mg SC every 2 weeks	Within 3 months	Moderate-to-severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis	Hypersensitivity reactions, eosinophilia and infections have been reported. Injection site reactions and conjunctivitis in 10%
Tranexamic acid	Antifibrinolytic	No	A few studies (CSU and CIndU), ³⁴ RCT ongoing	1.25-4 g/d PO	Within 2 weeks	Menorrhagia	Visual defects, thromboembolism and anaphylaxis have been reported. In >10%: headache, nasal and sinus symptoms, back pain, abdominal pain, musculoskeletal pain
Adalimumab, etanercept, infliximab,	TNF- α inhibitors	No	A few studies (CSU and CIndU) ^{38,39}	Adalimumab: 40 mg SC twice monthly or etanercept 25-50 mg/wk SC or twice a week for 3-35 months or infliximab 5 mg/kg every 6 weeks SC	Within the first month after initiating therapy	Autoimmune diseases	Pyrexia, hepatitis, sarcoidosis, malignancy, demyelinating disorders, Stevens-Johnson syndrome, deep vein thrombosis and other severe adverse effects have been reported
Rituximab	An anti-CD20 antibody	No	A few cases ⁴⁰	2 doses of IV 1000 mg with a 2-week interval or 4 weekly infusions of 375 mg/m ²	Within 1-6 weeks after infusion	Malignant tumor, autoimmune diseases	Severe, including fatal, infusion-related reactions may occur. Increased risk of potentially fatal malignancy, infections, hepatitis B virus reactivation, cardiac adverse reactions and other.
Canakinumab, rilonacept, anakinra	IL-1-targeting biologics	No	Case reports, ^{42,43} RCTs ongoing (CSU and CIndU)	Canakinumab SC 150 mg or rilonacept SC 160-320 mg/wk or anakinra SC 100 mg/d	After 1-2 anakinra injections	Autoinflammatory syndromes	Risk of infections, reactivation of latent hepatitis, lymphoma, vertigo and infections

(continued on next page)

Table 2 (continued)

Drug	Drug description	Licensed for CU?	Evidence on efficacy in CU	Dosage and dosing schedule used in CU	Onset of improvement in most patients with CU	Main indication(s)	Possible adverse effects ^a
Abatacept	A T-cell costimulation modulator	No	An open-label pilot study is ongoing. ⁴⁴	4 doses IV at baseline, 2 weeks, 4 weeks, and 8 weeks	Within 3 months	Autoimmune diseases	Higher risk for serious infections and lymphoma
Intravenous immunoglobulins	Immunomodulator	No	Isolated cases or case series (CSU and CIndU) ⁴⁵	0.2–0.5 mg/kg IV daily for 1–5 days or 2 g/kg IV every 4–6 weeks	In some patients, after the first cycle	Autoimmune and infectious diseases, primary immunodeficiency	Anaphylaxis in patients with IgA deficiency, acute renal failure, thrombosis, severe cutaneous vasculitis, aseptic meningitis and other

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; IL, interleukin; –: not defined or no data; IV, intravenous; mAb, monoclonal antibody; PO, orally (per os); RCT, randomized clinical trial; SC, subcutaneous; TNF- α , tumor necrosis factor α .

^aAccording to data from [medscape.com](https://www.medscape.com).

The inhibition of IL-4 and IL-13 signaling and IgE production can be beneficial for patients with CU. Levels of IL-4 and/or IL-13 are elevated in the serum of patients with CSU.²⁹ Furthermore, skin biopsy specimen of patients with CSU exhibit an increase in the number of cells expressing IL-4 at the mRNA level.³⁰

Lee and Simpson³¹ described 6 patients with refractory CSU who were unresponsive to 300 to 600 mg of omalizumab but responded favorably to dupilumab.³¹ Two ongoing phase 2a RCTs evaluate the efficacy and safety of dupilumab in CU (1 in patients with CSU and 1 in patients with cholinergic urticaria), with a loading dose of 600 mg of dupilumab and further treatment with 300 mg every 2 weeks for a total of 16 weeks.

Tranexamic Acid

A role of the coagulation system in the pathophysiology of CSU has been discussed for years.³² Blood markers of thrombin generation, fibrinolysis, and inflammation (eg, D-dimer) are elevated in patients with CSU and reportedly correlate with disease activity and response to treatment.³³ In clinical practice, the use of anti-coagulants and inhibitors of fibrinolysis, such as tranexamic acid in patients with CSU, yields inconsistent results, which is confirmed by a recently published systematic review of 5 studies in a total of 39 patients.³⁴ In a double-blind study with 17 patients with CSU, no difference was found between placebo and treatment with tranexamic acid.³⁵ In another study, tranexamic acid in combination with nadroparin was effective in 5 of 8 patients with CSU with elevated D-dimer levels.³³ Recently, a multicenter RCT has been launched to evaluate the efficacy and safety of a combination of 10 mg/d of levocetirizine with 2 g/d of tranexamic acid vs 20 mg/d of levocetirizine alone in the treatment of CSU (NCT03789422).

Adalimumab, Etanercept, and Infliximab: TNF- α Inhibitors

Activated mast cells are known to produce several proinflammatory mediators, including tumor necrosis factor α (TNF- α). TNF- α is upregulated in the serum and the skin of patients with CU,^{36,37} and anti-TNF- α therapy can be beneficial in these patients. Sand and Thomsen³⁸ reported complete response after administration of adalimumab and etanercept in 15 of 25 patients with CU (60%), some of them omalizumab refractory. Wilson et al³⁹ treated 6 patients with CU with the TNF- α inhibitors adalimumab, etanercept, or infliximab. All patients had complete remission or partial improvement of CU, in most cases lasting for several years. RCTs are missing and needed.

Rituximab: an anti-CD20 mAb

Rituximab, a chimeric murine/human mAb directed against CD20 on B cells, is used in malignant and autoimmune diseases (eg, rheumatoid arthritis or systemic lupus erythematosus). In CSU, it may inhibit the production of functional IgG autoantibodies against Fc ϵ RI α or IgE via depletion of memory B lymphocytes. Rituximab has been reported to be effective in several cases of autoimmune CSU refractory to antihistamines, omalizumab, and/or immunosuppressive therapy.⁴⁰ According to 1 report, 4 of 5 patients with CSU showed improvement within 1 to 6 weeks after rituximab infusions with improvement duration of more than 8 months. Completed RCTs are missing (1 RCT was stopped because of safety concerns [NCT00216762]), and the potential adverse effects of rituximab limit its use in CSU.

Anakinra, Canakinumab, and Rilonacept: IL-1–targeting biologics

IL-1 is linked to the development of wheals in patients with cryopyrin-associated periodic syndrome, Schnitzler syndrome, and other autoinflammatory diseases that respond to IL-1–targeted

therapies, such as anakinra, canakinumab, and rilonacept. Canakinumab, a long-acting, fully humanized, monoclonal anti-IL-1 β antibody, was also effective in urticarial vasculitis.⁴¹ Anakinra, an IL-1 receptor antagonist, improved refractory delayed-pressure urticaria and idiopathic cold urticaria in individual patients.^{42,43} The results of the 2 RCTs on IL-1–targeted treatment in CU, one on rilonacept, an IL-1 soluble receptor transmembrane protein, in cold urticaria (NCT02171416) and one with canakinumab in CSU (NCT01635127), have not yet been published.

Abatacept: A T-Cell Costimulation Modulator

Abatacept is a soluble fusion protein that links the extracellular domain of human cytotoxic T-lymphocyte–associated antigen 4 to the modified Fc portion of human IgG1. An open-label, single-group study assessed abatacept in antihistamine-resistant CSU with evidence of underlying autoimmunity (NCT00886795). Preliminary results showed that 3 of 4 patients with CSU had complete resolution of their CSU within 3 months of abatacept treatment.⁴⁴

Intravenous Immunoglobulins and Other Treatments

Intravenous immunoglobulins can be effective in the treatment of patients with severe and therapy-resistant CSU, including patients with a positive autologous serum skin test result,⁴⁵ but RCTs are not available and needed. Multiple other licensed treatments may be of benefit for patients with CU, including but not limited to anti-IL-6, anti-IL-17, and anti-IL-23. IL-17, for example, is a signature cytokine of inflammatory/autoimmune diseases. Mast cells and other inflammatory cells that contribute to the pathogenesis of CU produce IL-17.⁴⁶ Blood levels of IL-17 are increased in patients with CSU, and increased levels of IL-17 are linked to disease activity.^{46,47} Patients with CU treated with these drugs for other concomitant diseases should be monitored for effects of these treatments on their CU.

The risk of therapies that have potentially severe adverse events should be taken into account in the context of CU, a nonfatal condition (Table 2). For example, rituximab treatment may result in infections or cancer. These therapies might only be considered in the case of severe autoimmune CU resistant to other therapy or if specific biomarkers are identified, allowing better patient selection rather than omalizumab failure.

Drugs Under Development for the Treatment of Patients With CU

Ligelizumab and UB-221: 2 Novel Anti-IgE mAbs

Ligelizumab (QGE031) is a new promising humanized monoclonal anti-IgE antibody under development for the treatment of patients with CSU. It has a 40-fold to 50-fold greater affinity to IgE compared with omalizumab.⁴⁸ In a phase 2b multicenter RCT, patients with antihistamine-refractory CSU were randomized to 300 mg of omalizumab, placebo, or 24, 72, or 240 mg of ligelizumab administered by subcutaneous injection monthly for 20 weeks (NCT03437278). Ligelizumab demonstrated rapid onset of action, dose-dependent efficacy, and superiority to omalizumab (Maurer et al, unpublished data, 2019). More than 50% of patients taking 240 mg of ligelizumab were complete responders (Urticaria Activity Score summed during 7 days of 0), a response rate twice that seen in the omalizumab group. Furthermore, the mean time to relapse after the last injection was 4 weeks for omalizumab vs 10 weeks for ligelizumab. Placebo, omalizumab, and ligelizumab had similar side effect profiles, although 240 mg of ligelizumab had higher rates of mild injection site reactions (6% vs 2%). Phase 3 studies in adults (PEARL [A Study to Evaluate the Safety and

Effect of the Experimental Drugs ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 in Subjects With Chronic Hepatitis C] 1 and 2) have been initiated, and more than 2000 patients with CSU will be recruited.

Another anti-IgE drug, UB-221, is being evaluated in a phase 1, open-label, dose-escalation study as an add-on therapy in 15 adults with CSU (NCT03632291). Compared with omalizumab, UB-221 has an 8-fold higher binding affinity to free IgE and down-regulates IgE synthesis by binding to IgE on CD23.

AK002: A Humanized Monoclonal Antibody to Siglec-8

Siglec-8 is an inhibitory receptor of the CD33-related family of sialic acid–binding, immunoglobulin-like lectins. Selective expression of Siglec-8 on the surface of mast cells, eosinophils, and basophils supports targeting Siglec-8 in mast cell–associated diseases, including CU and mastocytosis.⁴⁹ AK002, a humanized monoclonal antibody to Siglec-8, inhibits mast cell activity and depletes eosinophils. A phase 2a, open-label pilot study of the safety and efficacy of AK002 is ongoing (NCT03436797). This study includes patients with CSU, omalizumab naïve and omalizumab refractory, as well as patients with cholinergic urticaria and patients with symptomatic dermographism.

AZD1981: a CRTH2 Antagonist

Prostaglandin D₂, a product of activated mast cells, induces the chemotaxis of eosinophils and basophils via its receptor, chemoattractant receptor–homologous molecule expressed on T_H2 cells (CRTH2). Oliver et al⁵⁰ found that CRTH2 expression on basophils and eosinophils in patients with CSU is decreased, possibly because of prostaglandin D₂ effects. Preliminary results of an ongoing phase 2 RCT of AZD1981, an oral CRTH2 antagonist (NCT02031679), show reductions in patient reported itch, reduced prostaglandin D₂–induced eosinophil shape change, and increased blood eosinophils in AZD1981-treated patients with antihistamine-refractory CSU.⁵¹

Fenebrutinib and LOU064: 2 BTK Inhibitors

Bruton tyrosine kinase (BTK) is an enzyme involved in the signal transduction downstream of Fc ϵ RI and the B-cell receptor. BTK is essential for Fc ϵ RI-mediated mast cell activation and the maturation and function of B cells. Treatment with a BTK inhibitor inhibits IgE- and mast cell–mediated responses in mice and humans.⁵²

Fenebrutinib (GDC-0853), a potent, selective, noncovalent BTK inhibitor, is now being tested in an ongoing phase 2a, multicenter RCT in patients with antihistamine-resistant CSU (NCT03137069).⁵³ Fenebrutinib is administered orally twice daily for 56 days. Efficacy and safety of another BTK inhibitor, LOU064, is currently being assessed in a phase 2b, multicenter, dose-finding RCT in adults with antihistamine-resistant CSU (NCT03926611). LOU064 is given orally once or twice daily for 85 days.

GSK2646264: A Syk Inhibitor

Spleen tyrosine kinase (Syk) is a cytoplasmic tyrosine kinase, a signaling molecule in the Fc ϵ RI pathway, and a promoter of mast cell degranulation and histamine release.^{54,55} Syk has been implicated in the pathogenesis of CSU. For example, Saini et al⁵⁶ reported significantly increased Syk levels in cultured mast cells from patients with CSU with a basophil histamine release of greater than 10% compared with mast cells from patients with CSU with a basophil histamine release of less than 10% or of healthy individuals.⁵⁶ GSK2646264, a small-molecule Syk inhibitor, applied via skin microdialysis fibers or topically in a cream, inhibited histamine release by human skin mast cells in situ.⁵⁷ The results of a

RCT on the safety, local tolerability, pharmacokinetics, and pharmacodynamics of GSK2646264 as a 0.5% and 1% topical cream in healthy individuals, patients with cold urticaria, and patients with CSU is expected to be reported soon (NCT02424799).

Interesting Targets for Future CU Therapies

The following peptides, receptors, and surface molecules are examples of promising targets for future CU therapies. Like many other potential targets, they are linked to mast cells, the key effector cells in CU. Given the rapid expansion of our knowledge on the biology of mast cells in recent years, we predict (and hope) that even more targets for better treatments of urticaria and other mast cell–driven diseases will emerge in the near future (Mauer et al, unpublished data, 2019).

The Mas-Related G Protein–Coupled Receptor X2

Mast cells express the Mas-related G protein–coupled receptor X2 (MRGPRX2), and they can be activated via this receptor by several groups of signals, including neuropeptides, drugs, and eosinophil mediators. MRGPRX2 expression on skin mast cells is upregulated in patients with severe CSU.²² Substance P, major basic protein, and eosinophil peroxidase induce histamine release from human skin mast cells through activation of MRGPRX2 independent of the NK1 receptor.²² Furthermore, the levels of substance P, a neuropeptide and agonist of both MRGPRX2 and the NK1 receptor, are increased in the serum of patients with CSU and correlate with disease activity.^{58,59} Thus, targeting MRGPRX2 and/or its agonists (eg, substance P) is a promising mechanism for decreasing mast cell activation in patients with CSU.

The Histamine₄ Receptor

Drugs that engage the H₁ receptor (H₁R) are the first-line treatment of patients with CU, and the histamine₄ receptor (H₄R) is another interesting target for the inhibition of the effects of histamine in CU. The H₄R is expressed by mast cells, eosinophils, and nerves and is involved in histamine-induced inflammation and itch responses.⁶⁰ Recently, the H₄R antagonist JNJ 39758979 was explored for its effects on histamine-induced pruritus in humans (NCT01068223). Treatment with JNJ 39758979, but not placebo, markedly reduced the itch sensation induced by intradermally injected histamine.⁶¹ Another H₄R antagonist, ZPL-3893787, led to improvement of atopic dermatitis in a recently published RCT.⁶² Pharmacologic targeting of H₄R may, therefore, be useful for the treatment of CU.

C5a and Its Receptor CD88

The notion that C5aR and CD88 are involved in the pathogenesis of CSU is supported by C5a, via CD88, serving as a strong mast cell degranulator. CD88 is expressed by skin mast cells but not other mast cells, including lung, uterus, and tonsillar mast cells. The mast cell–activating IgG autoantibodies of patients with CSU induce degranulation of mast cells and basophils that require activation of the complement cascade and C5a production.^{63,64} In vitro, histamine release from basophils stimulated with serum samples from patients with CU was inhibited after blocking of CD88.⁶⁴ Finally, avacopan (CCX168), a C5aR inhibitor, was effective in another autoimmune disease: antineutrophil cytoplasmic antibody–associated vasculitis. Taken together, C5a and its receptor are promising targets for novel treatments of CSU.

Inhibitory Mast Cell Receptors Other Than Siglec-8

Mast cells express multiple inhibitory receptors in addition to Siglec-8, including CD200R1, CD300a, and FcγRIIb.⁶⁵ The engagement of CD200R1 or CD300a by agonist antibodies or ligands

potently inhibits mast cell degranulation and cytokine secretion responses in a dose-dependent manner.⁶⁶ Several studies have found inhibition of IgE-dependent degranulation of mast cells and basophils after coaggregation of FcεRI and FcγRIIb, and fusion proteins that coaggregate FcεRI and FcγRIIb produced promising results in preclinical studies with nonhuman primates.⁶⁷ Clearly, targeting of inhibitory mast cell receptors is a promising strategy for the development of new CU treatments.

Type 2 Immunity-Inducing Cytokines: IL-33, IL-25, and TSLP

IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) are predominantly epithelial cell–derived cytokines that initiate type 2 immunity (ie, they trigger the production of the type 2 cytokines IL-5, IL-9, and IL-13). IL-33, IL-25, and TSLP have effects on mast cells and have been implicated in the pathogenesis of CSU.^{23,47} Serum levels of IL-33, IL-25, and TSLP have been reported to be increased in CSU in some, albeit not all, studies.⁴⁷ Importantly, cells that express IL-33, IL-25, and TSLP are increased in the dermis of lesional skin of patients with CSU compared with nonlesional skin and skin of healthy individuals.²³ Recently, an anti-TSLP mAb, tezepelumab (AMG 157), was reported to be effective in the treatment of atopic dermatitis and asthma. Collectively, IL-33, IL-25, and TSLP are prime candidates to be targeted by novel treatment strategies for CSU.

Stem Cell Factor

Stem cell factor (SCF) is produced by fibroblasts and endothelial cells and is the ligand of the mast cell receptor Kit. SCF is the major driver of mast cell differentiation, activation, migration, proliferation, and survival.⁶⁸ The number of mast cells in the skin of patients with CSU was elevated,⁶⁹ and SCF may be responsible for this. An ongoing project evaluates the expression of SCF in the skin of patients with CSU (NCT03443362). SCF is also an activator of mast cells.⁷⁰ Reducing the number of mast cells may help patients with CSU. Neutralization of SCF with anti-SCF could inhibit mast cell activation.

When Will We Be Able to Cure Chronic Urticaria?

All current treatments of CU as well as the ones that are currently under development are aimed at the control of the disease and the prevention of its signs and symptoms, not its cure. Sustained remission of CU achieved with these treatments is owed to the spontaneous resolution of the disease rather than disease-modifying or curative effects. Recent insights on the etiopathogenesis of CU (ie, on the crucial role of functional IgE autoantibodies against autoantigens and IgG autoantibodies against IgE/FcεRI) offer the possibility of developing novel treatment concepts, including curative approaches. B-cell–targeted and immunosuppressive therapy (eg, rituximab) results in a longstanding remission of severe refractory autoimmune CU in individual patients. However, the experience with other autoimmune diseases (eg, systemic lupus erythematosus) is almost universally treatment without cure. In CSU caused by IgE autoantibodies, specific immunotherapy with relevant autoantigens may be effective and safe and may result in cure. Future studies should explore this potentially curative treatment option. For this, we need to better understand the mechanisms that drive the development of disease-driving autoantibodies in patients with CSU, and we need to characterize the mechanisms involved in its spontaneous resolution. We also need to better define the targets of these autoantibodies and start to develop these antigens for in vivo application for both diagnostic and therapeutic purposes. The cure of CU must remain the long-term goal of the development of novel treatments.

Conclusion

CU is a heterogeneous, persistent, severely debilitating, and often poorly controlled disease. Antihistamines and omalizumab are the only currently licensed treatments, and additional and better treatments are needed. The off-label use of dupilumab, mepolizumab, and benralizumab can be effective in CU, and these drugs are currently in clinical trials for CSU. Novel IgE-targeted antibodies (ie, ligelizumab and UB-221) are also in clinical testing in CSU (ligelizumab in phase 3 trials). Other promising drugs that are currently under development for CU are a CRT_{H2} antagonist, a monoclonal antibody to Siglec-8 (AK002), BTK inhibitors (fenebrutinib and Lou064), and a Syk inhibitor. Additional drugs should be developed, making use of the many promising targets recently identified and characterized, including MRGPRX2; the H₄R; C5a and its receptor; inhibitory mast cell receptors other than Siglec-8, IL-33, IL-25, and TSLP; and SCF. The ultimate goal remains the development of treatments that can prevent CU, alter its course, and cure patients.

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