Clinical Commentary Review

Biologics for the Use in Chronic Spontaneous Urticaria: When and Which

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Learning objectives:

1. To understand the current knowledge of the pathogenesis of chronic spontaneous urticaria (CSU) and its autoimmune endotypes.

2. To understand the mechanisms of action of omalizumab and its efficacy and use in routine clinical practice.

3. To identify the biologics that are currently used off-label for the treatment of patients with CSU.

4. To understand which novel biologics are being developed and what they target.

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Guidelines for the treatment of chronic spontaneous urticaria (CSU) recommend the use of the IgE-targeted biologic omalizumab in patients with antihistamine-refractory disease. The rationale for this is supported by the key role of IgE and its high-affinity receptor, FcεRI, in the degranulation of skin mast cells that drives the development of the signs and symptoms of CSU, itchy wheals, and angioedema. Here, we review the current understanding of the pathogenesis of CSU and its autoimmune endotypes. We describe the mechanisms of action of omalizumab, the only biologic currently approved for CSU, its efficacy and ways to improve it, biomarkers for treatment response, and strategies for its discontinuation. We provide information on the effects of the off-label use, in CSU, of biologics licensed for the treatment of other diseases, including

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Abbreviations used
CIndU- Chronic inducible urticaria
CSU- Chronic spontaneous urticaria
FDA- Food and Drug Administration
mAb- Monoclonal antibody
MC- Mast cell
NK- Natural killer
RCT- Randomized controlled trial
SCF- Stem cell factor
Siglec-8- Sialic acid—binding immunoglobulin-like lectin-8
TSLP- Thymic stromal lymphopoietin

dupilumab, benralizumab, mepolizumab, reslizumab, and secukinumab. Finally, we discuss targets for novel biologics and where we stand with their clinical development. These include IgE/ligelizumab, IgE/GI-310, thymic stromal lymphopoietin/tezepelumab, C5a receptor/avdoralimab, sialic acid—binding Ig-like lectin 8/lirentelimab, CD200R/LY3454738, and KIT/CDX-0159. Our aim is to provide updated information and guidance on the use of biologics in the treatment of patients with CSU, now and in the near future. **© 2020 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2021;9:1067-78)**

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The therapy of diseases of the immune system, particularly those with immune-mediated inflammation, has evolved rapidly during the past decade. Many of these advances are the result of successful employment of biologic agents, particularly monoclonal antibodies (mAbs), directed to key constituents of the inflammatory response, the result of which is improved control of disease manifestations. In some instances, this can be quite dramatic. Disruption of TNF-α-dependent pathways has revolutionized our approach to the treatment of rheumatoid arthritis (including mavrilimumab and molimumab[1]) and Crohn's disease (such as adalimumab[2]), inhibition of IL-17 (using bimekizumab[3]) and its receptor (including AMG 827 and brodalumab[4,5]) treats psoriasis, combined inhibition of IL-4 and IL-13 has markedly improved the ability to contain severe atopic dermatitis[6] (and is effective for allergic asthma as well[7]), inhibition of IL-1 is the key to control of numerous autoinflammatory diseases,[8,9] and mAbs to IL-5[10] and its receptor[11] are being increasingly used to treat asthma, chronic sinusitis with eosinophilic polyposis,[12] Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis),[13] and subtypes of hypereosinophilic syndromes.[14] These are but a few of the uses of mAbs, and one should note that "biologics" can include replacement therapy such as administration of the C1 inhibitor for hereditary angioedema, or antihemophilic globulin for factor VIII deficiency, or α1-antitrypsin for familial emphysema. In this review, we focus on the current and future use of biologic therapy (mainly mAbs) for the treatment of chronic spontaneous urticaria (CSU). We have one available at present, namely, omalizumab (anti-IgE), which has revolutionized the approach to CSU, yet many new, potentially effective targets have been identified, and we anticipate the testing and hopefully approval of a host of new therapeutic agents, which will be the focus of this review.

CHRONIC SPONTANEOUS URTICARIA (CSU): A RATIONALE FOR THERAPY BASED ON PATHOGENIC CONSIDERATIONS

We know that CSU is an "internal" skin disorder that is not due to any exogenous agent.[15,16] Although the cause is still being debated, all the evidence points to an autoimmune etiology because of its association with other autoimmune disorders (Hashimoto's thyroiditis, vitiligo, type I diabetes), an increased incidence of autoantibody production (positive speckled-pattern antinuclear antibodies, 30%; IgG antithyroid antigens, 25%; and IgE anti-thyroperoxidase, 70%) as well as autoantibodies presumed to be pathogenic, although absolute proof is lacking. These include IgG anti—high-affinity IgE receptor (IgG anti-FcεRI) (30%-45%),[17,18] anti-IgE (5%-10%),[19] and IgE anti-IL-24 (70%-80%).[20] CSU in patients with IgE autoantibodies can be subclassified as autoallergy.[21] The initial proposal of omalizumab as a therapeutic agent for CSU[22] was based on its binding IgE and downregulation of IgE receptors,[23] hence, decreasing the antigen density to which IgG anti-FcεRI is directed. Cross-linking of receptors, a requirement for cell activation,[22,24] is diminished, as is complement activation, thereby eliminating the augmentation of secretion contributed by C5a interaction with the C5a receptor.[25] The identification of IgE anti-IL-24 was based on microarray analyses of serum reactivity to more than 9000 human proteins seeking ligands for IgE associated with CSU based on prior observation of elevated levels of IgE anti-thyroperoxidase.[26]

CSU is characterized by cutaneous mast cell (MC) activation, the release of histamine, leukotrienes, platelet-activating factor (vasoactive factors, the most important of which is histamine), and numerous MC-derived cytokines and chemokines (Figure 1). The latter proteins cause endothelial cell activation, and chemokines cause blood cell migration to the skin in a perivascular distribution around small cutaneous venules. The infiltrate includes T lymphocytes (the most abundant cell type with predominance of the Th2 subtype and a smaller number of Th1 cells), eosinophils, monocytes, and basophils[27,28] and an increased number of MCs.[27,29] Although these are well characterized, the contribution, if any, of Th17 cells, natural killer (NK cells), NK T cells, or T reg cells has not been reported. There are no B lymphocytes. The skin infiltrating cells are presumably activated and secretory, the best evidence being for T lymphocytes (local cytokine production), eosinophils (eosinophil major basic protein in the interstitium is abundant),[30] and basophils. Basopenia and eosinopenia may reflect migration into the skin,[31,32] with activation by anti-FcεRI IgG or by chemokines such as monocyte chemoattractant protein 1 and 3 (histamine-releasing factors) within the skin.[33]

The rationale for the development of new agents to be tested for putative efficacy in CSU is dependent on assumptions about which of the aforementioned contributions to hive formation can be inhibited to significantly suppress symptoms. The approaches being considered at present will require double-blind, placebo-controlled studies in large numbers of patients, and perhaps, head-to-head comparative studies with omalizumab. The most general sites that can be targeted involve the activation, function, and recruitment of cutaneous MCs, inhibition of critical

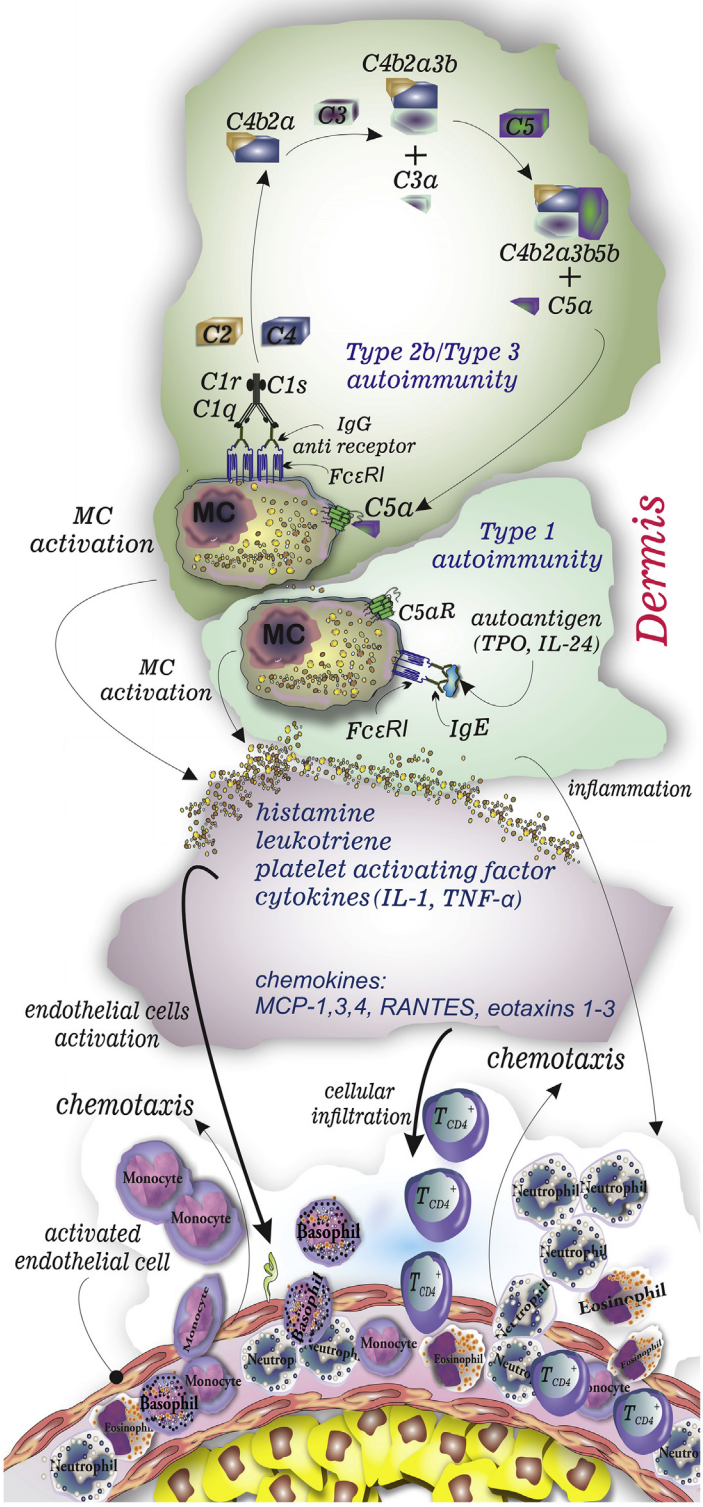

FIGURE 1. Autoimmune mechanisms operative in CSU. In type 1 autoimmune CSU, IgE autoantibodies to autoantigens (such as throperoxidase [TPO] and IL-24) activate mast cells (MCs) to secrete vasoactive mediators, cytokines, and chemokines. These, in turn, activate endothelial cells, increase vascular permeability, and promote the migration of blood cells to the dermis. In type 2b/3 autoimmune CSU, IgG autoantibodies to the IgE receptor or IgE itself activate MCs with the same consequences as described above. Two IgG molecules in proximity activate complement (type 3) to liberate C5a, which augments MC secretion and is a separate chemotactic factor for granulocytes and monocytes. We can antagonize mediators (with antihistamines for example), downregulate MCs and basophils (omalizumab), impair cellular recruitment into the dermis (eg, corticosteroid), or block secretion of MCs, basophils, and CD4+ lymphocytes (cyclosporine).

vasoactive substances, and inhibition of the perivascular cellular infiltrate and/or critical constituents of that infiltrate. Thus far we have only 4 drugs in which there is a general agreement of efficacy, antihistamines, omalizumab, cyclosporine, and glucocorticoids, but only the 3 former ones are recommended[34]: (1) antihistamines target the H1 receptor to block major effects of histamine; (2) omalizumab targets IgE, downregulates IgE receptors, and may also dissociate bound IgE from the receptor[35] to suppress MC (and basophil) responsiveness; (3) cyclosporine inhibits T-cell function globally and inhibits histamine release from basophils and MCs[36]; and (4) glucocorticosteroids, although not affecting MC function, inhibit eosinophil recruitment from the bone marrow and block the egress of all blood cells into the interstitium so that the perivascular infiltrate is targeted at many levels. Although not recommended for long-term therapy because of prohibitive side effects, their efficacy speaks to the long-neglected contribution of the cellular infiltrate beyond consideration of MC activation and function.

With this in mind, we can envision new approaches to treat CSU. The cellular infiltrate is predominantly Th2,[37] which is dependent on thymic stromal lymphopoietin (TSLP), IL-33, IL-4, IL-13, and the prostaglandin D2 receptor CRTH2. An approach employing mAbs to any of these is certainly reasonable and many are already developed and ready for testing. Eosinophils are closely associated with the Th2 response, and the role of eosinophils in CSU is not yet entirely clear. However, their selective inhibition in terms of numbers and function would give an answer. Thus, mAbs to IL-5 and the IL-5 receptor can be tried as is being done for asthma.[38] The interaction of very late antigen-4 on eosinophils and basophils with vascular cell adhesion molecule-1 on endothelial cells is needed for their egress into the skin and these could be targeted. Sialic acid—binding immunoglobulin-like lectin-8 (Siglec-8) is present on both MCs and eosinophils; thus a target such as anti-Siglec 8 could simultaneously inhibit the function of both cell types. Other inhibitory ligands on MCs are also being considered, and depletion of MCs may be possible because maturation and recruitment are dependent on c-kit (CD117) and its ligand, stem cell factor (SCF).

OMALIZUMAB, THE ONLY LICENSED BIOLOGIC FOR THE USE IN CSU

Omalizumab is the first Food and Drug Administration (FDA)-approved biologic for the treatment of CSU. A recombinant humanized IgG1 anti-IgE mAb has been used widely since its approval in 2014 for the management of patients with CSU refractory to antihistamines. The most recent international guidelines on chronic urticaria including CSU recommend its use in the third step of therapy, in patients who have failed standard or high-dose (up to 4 times) second-generation antihistamine, the recommended first- and second-line treatment, respectively.[39]

The mechanisms of action of omalizumab in CSU

The precise mechanism(s) for the efficacy of omalizumab in CSU remains unclear (Figure 2). Omalizumab was initially developed as an antibody with high affinity for free IgE to prevent allergen-specific IgE to attach to FcεRI. The reduction in free IgE levels results in the reduction in the number of FcεRI receptors, which may occur as early as 3 days in basophils after a

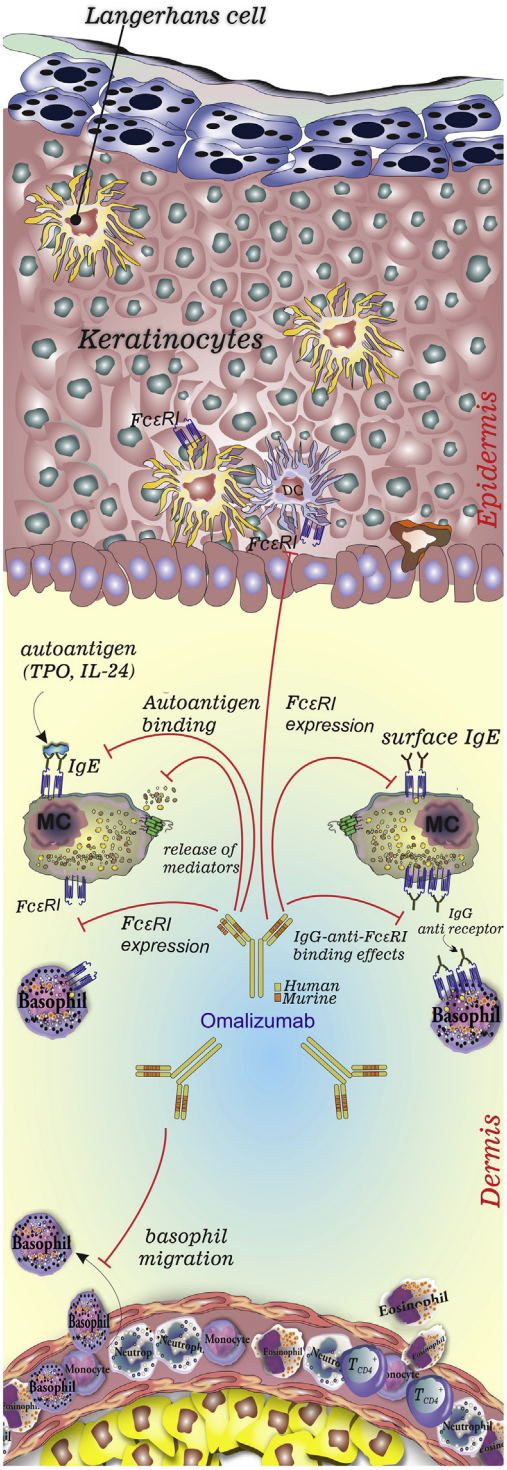

FIGURE 2. Omalizumab mechanisms of action. Omalizumab has multiple potential mechanisms of action in chronic urticaria. Its effects on mast cells (MCs) and basophils include reversing basopenia and eosinopenia, reducing the release of mediators, decreasing FcεRI expression and surface bound IgE, thereby reducing effects of IgG-anti-FcεRI, IgG-anti-IgE, autoantigen binding, and IgE-autoantibodies (including IgE-anti-TPO and IgE-anti-IL-24). Omalizumab also decreases the expression of FcεRI on epidermal dendritic cells and Langerhans cells. *TPO*, Throperoxidase.

single dose of omalizumab.[40] Studies of FcεRI basophil expression have shown that patients with multiple types of chronic urticaria have increased expression compared with healthy controls and that omalizumab can reduce FcεRI within 4 weeks.[41] Omalizumab also results in the reduction of MC FcεRI expression, but this takes longer than in basophils. Mean levels of FcεRI-positive skin cells in patients with CSU treated with omalizumab 300 mg were decreased at week 12 but not week 4.[29] Many patients with CSU respond to omalizumab within days, whereas some take weeks or months of therapy to see a response. There are several potential mechanisms that may explain this varied timing of response. In those patients with CSU driven by an autoallergy (eg, those with IgE anti-IL-24 autoantibodies), the rapid reduction of free IgE by omalizumab would result in rapid depletion of IgE autoantibodies. The majority of patients who respond in 4 to 16 weeks can be explained by receptor downregulation, but that process is continuous, that is, not all-or-nothing.

Omalizumab has multiple other effects that may have relevance to its mechanism in CSU including reducing MC releasibility, reversing basopenia and improving basophil function, and reducing plasma IgE autoantibodies.[42] Besides, omalizumab has effects on gene expression in the skin. A recent double-blind, placebo-controlled study of 30 patients with CSU randomized 20 patients to omalizumab and 10 to placebo and performed lesional and nonlesional skin biopsies and performed microarray analyses to evaluate changes in gene transcripts.[43] Among omalizumab-treated patients, 79% had signature genes that changed toward that of healthy controls compared with 54% of controls. Importantly, only omalizumab responders had normalization of their lesional skin "signature" gene expression.

Efficacy of omalizumab in subtypes of chronic urticaria

The efficacy of omalizumab has been well established in randomized controlled trials (RCTs) of CSU including the 3 pivotal trials that led to its FDA approval involving 733 patients treated with various doses of omalizumab.[44-46] Subsequently, several systematic reviews and meta-analyses have shown the quality of evidence for the safety and efficacy of omalizumab in both controlled trials[47,48] and real-world applications.[49] In addition to CSU, omalizumab has also been used in patients with chronic inducible urticaria (CIndU). A systematic review from 2018 found the strongest evidence for effectiveness of omalizumab in symptomatic dermographism, cold urticaria, and solar urticaria.[50] Subsequently, a randomized mixed double-blind and open-label placebo-controlled study of omalizumab in cholinergic urticaria evaluated its efficacy in regard to an exercise challenge test.[51] Although no difference was seen during the first 4 months of the blinded study, improved outcomes were noted compared with baseline during the 8-month open-label portion, suggesting that longer treatments may be required for cholinergic urticaria. A recent open-label study of 23 patients with normocomplementemic urticarial vasculitis found 4 and 13 patients who had complete and partial responses, respectively, to omalizumab.[52] Whether this was an effect on concomitant spontaneous urticaria or the actual vasculitis is less clear. In addition to improving pruritus and wheals of CSU, omalizumab has also been shown to be effective in reducing concomitant angioedema.[53,54] Case reports involving 28 patients also suggest effectiveness of omalizumab in the treatment of isolated angioedema in the absence of wheals.[55]

Changing dosing and frequency in poor responders

Omalizumab is approved for CSU at doses of 150 or 300 mg every 4 weeks; however, international guidelines recommend starting at 300 mg. Analyses of the pivotal studies demonstrated that the 300 mg dose produced the highest response rates, faster response, a higher likelihood of complete response, and more patients had sustained responses than other doses.[56] However, even at the 300 mg dosage, approximately 30% of patients treated for 6 months may not achieve adequate control. Although not approved by the FDA, several studies have found that a higher proportion of patients with CSU can be effectively treated with doses of omalizumab higher than 300 mg.[57] Although no RCTs have evaluated the efficacy of higher dosing, many of these retrospective studies used protocols to updose omalizumab in a stepwise fashion based on control of the disease, often with standardized instruments such as the Urticaria Control Test[58,59] or Urticaria Activity Score.[60,61] Many studies increased omalizumab to a maximum of 450 mg every 4 weeks[62-64]; however, a few studies increased to 600 mg every 4 weeks[65,66] and 1 study increased to 600 mg every 2 weeks.[67] This latter study from the Netherlands used a protocol of 300 mg every 4 weeks, and after 5 doses, if the response was insufficient, updosing was offered at either 450 or 600 mg every 4 weeks. If the response was still insufficient after 3 higher doses of 600 mg, the dose was given every 2 weeks for 2 consecutive doses. A total of 122 patients were treated with 300 mg, 11 with 450 mg, and 33 with 600 mg. Updosing resulted in improvement in 61% of patients (n = 27) who failed conventional doses, with 14 having a complete response and 13 a partial response. In the 9 patients updosed to 600 mg every 2 weeks, none responded. One study from Spain analyzed differences in 187 patients receiving standard doses versus 79 requiring updosing.[66] Predictors of a response to updosing included obesity, age >57 years, and prior treatment with cyclosporine. Unlike asthma where dosing of omalizumab is based on weight and doses of 375 mg every 2 weeks are approved, such dose adjustments have not been considered in CSU. Other strategies to control patients failing omalizumab 300 mg every 4 weeks have been to shorten the dosing interval to every 2 to 3 weeks.[68-70] Changing from 300 mg every 4 weeks to 150 mg every 2 weeks is a practical option that does not require approval for "off-label" dosing and was demonstrated effective in a small case series.[70]

Biomarkers of response

Multiple studies have evaluated various biomarkers to predict omalizumab responders in CSU. One of the most commonly cited biomarkers is total IgE, with many studies showing that a low baseline total IgE is associated with a poor response phenotype.[71-75] One prospective study found that measuring the ratio of IgE at week 4 of treatment to baseline total IgE was a better predictor of nonresponder phenotype than total IgE alone.[72] This "2 × 4 rule" demonstrated that if the baseline total IgE does not double after 4 weeks of omalizumab, the response is only 32% (Table I). Lower reductions in FcεRI on basophils have also been shown in partial/nonresponders at 3 months compared with baseline.[76] Patient serum responses (*in vitro* and *in vivo*) have also been evaluated as biomarkers. One study showed that omalizumab responders had serum that was less

TABLE I. Examples of the "2 × 4" rule as a biomarker for response to omalizumab

Example	Total IgE baseline (IU/mL)	Total IgE at week 4 of omalizumab (IU/mL)	Ratio of week 4 IgE:baseline IgE	Predictive ratio	Expected response to omalizumab (%)
1	100	300	3	≥2	99
2	20	30	1.5	<2	32

Examples are based on the study by Ertas et al.[72]

likely to induce expression of basophil CD203c, an activation marker of basophils.[77] A positive basophil activation test or autologous serum skin test has been suggested to be associated with a slower response phenotype to omalizumab.[74,78] Eosinopenia (<50 cells/μL) and basopenia (<10 cells/μL) have been associated with poor response to omalizumab.[32] High-sensitivity C-reactive protein >3 mg/mL has been reported to be associated with omalizumab resistance.[79] In contrast, baseline d-dimer has not been found to predict omalizumab responsiveness.[80] Clinical factors that have been linked to poor response to omalizumab include obesity, worsening of CSU after initiation of omalizumab, and prior use of immunosuppressants.[81,82]

Duration and weaning

CSU is generally a self-limited disease though in many patients it may persist for many years. Omalizumab has not been shown to be disease-modifying or curative and thus is used to control symptoms as long as CSU remains active. Relapse of symptoms occurs in almost half of patients when treated for either 24 or 48 weeks with omalizumab.[83] A small study of 19 patients with well-controlled CSU on omalizumab treated for at least 6 months had the interval of therapy extended by 1 week for each treatment. If they remained well controlled after 8 to 9 weeks, omalizumab was stopped.[84] Nine patients (42%) were able to discontinue omalizumab in this fashion, whereas those who failed typically had relapses at the 5- to 6-week interval of dosing. The authors of this study suggested that a minimum of 8 weeks between doses should be used to determine readiness to discontinue omalizumab, and we agree with this approach. The optimal duration of omalizumab before considering tapering is unknown, but factors associated with the longer duration of CSU such as higher disease severity at onset, concomitant CIndU, angioedema, and older age of onset should be considered.[55]

Special populations

Omalizumab is approved for treatment of CSU down to the age of 12 years. Although data are limited, there is a growing experience with the use of omalizumab in children and adolescents with CSU.[85,86] A systematic review of children <12 years old treated with omalizumab identified 14 patients with a median age of 9.5 years (range, 2-11 years) treated for CSU, solar, or cold urticaria with most responding and no adverse effects reported.[87] Thus, although controlled studies are lacking, omalizumab appears to be safe and effective in children with CSU. Data on the use of omalizumab in pregnant or breast-feeding patients with CSU are extremely limited.[55] However, data from the EXPECT study of 230 pregnant women treated with omalizumab for asthma found no increased risk for congenital anomalies or fetal deaths/stillbirths with omalizumab exposure.[88]

Adjunctive therapy in nonresponders

Many alternative therapies have been used in patients failing omalizumab. A recent study evaluated 21 patients who had failed both omalizumab 300 mg/month and cyclosporine 3 mg/kg/day for 4 months each and were then treated with both drugs together.[89] Sixteen patients (76%) responded to the combination of omalizumab and cyclosporine with a time to response of combined therapy ranging from 1 to 4 months.

Adverse effects

Omalizumab is generally well tolerated in patients with CSU with similar rates of adverse effects in patients treated with omalizumab and placebo.[47] Several cases of transient hair loss,[90,91] including alopecia areata,[92] have been reported in patients with CSU treated with omalizumab, but not with asthma. A single case of methemoglobinemia was reported in a patient with CSU in association with omalizumab.[93]

THE OFF-LABEL USE, IN CHRONIC URTICARIA, OF BIOLOGICS LICENSED FOR THE TREATMENT OF DISEASES OTHER THAN CSU

The off-label use of available biologics in chronic urticaria includes the treatment of patients with dupilumab, benralizumab, mepolizumab, reslizumab, secukinumab, and omalizumab (for CIndU) (Figure 3, Table II).

Dupilumab

CSU exhibits features of Th2-driven disease, with elevated IgE levels and a high rate of sensitizations to autoallergens in many patients. The Th2 cytokines IL-4 and IL-13 promote isotype class switching to IgE and act on MCs, eosinophils, and basophils, all of which are involved in the pathogenesis of CSU. IL-4 levels have been reported to be elevated in the serum of patients with CSU, and IL-4-expressing cells are increased in the skin of patients with CSU.[28,110] Dupilumab (Sanofi/Regeneron), a fully human mAb directed against the IL-4 receptor alpha subunit, inhibits IL-4 and IL-13 receptor binding. Dupilumab has shown efficacy in multiple diseases with underlying type 2 inflammation and is held to be a promising novel treatment option for chronic urticaria. Dupilumab has been reported to reduce IgE levels in patients with atopic dermatitis, asthma, and other diseases. In preclinical studies, dupilumab blocked several functions of MCs, the key drivers of the pathogenesis of CSU. Recently, a case study reported the benefit of dupilumab treatment in 6 patients with CSU who had failed to respond to omalizumab.[94] Two ongoing phase II investigator-initiated multicenter RCTs, 1 in CSU and 1 in cholinergic urticaria, aim to characterize the effects of dupilumab in chronic urticaria.

Benralizumab, mepolizumab, and reslizumab

IL-5 may contribute to the pathogenesis of CSU by direct effects on skin MCs and by promoting the recruitment of eosinophils and basophils to skin sites of wheal development. Eosinophils and basophils are elevated in the lesional skin of patients with CSU, where they bidirectionally interact with

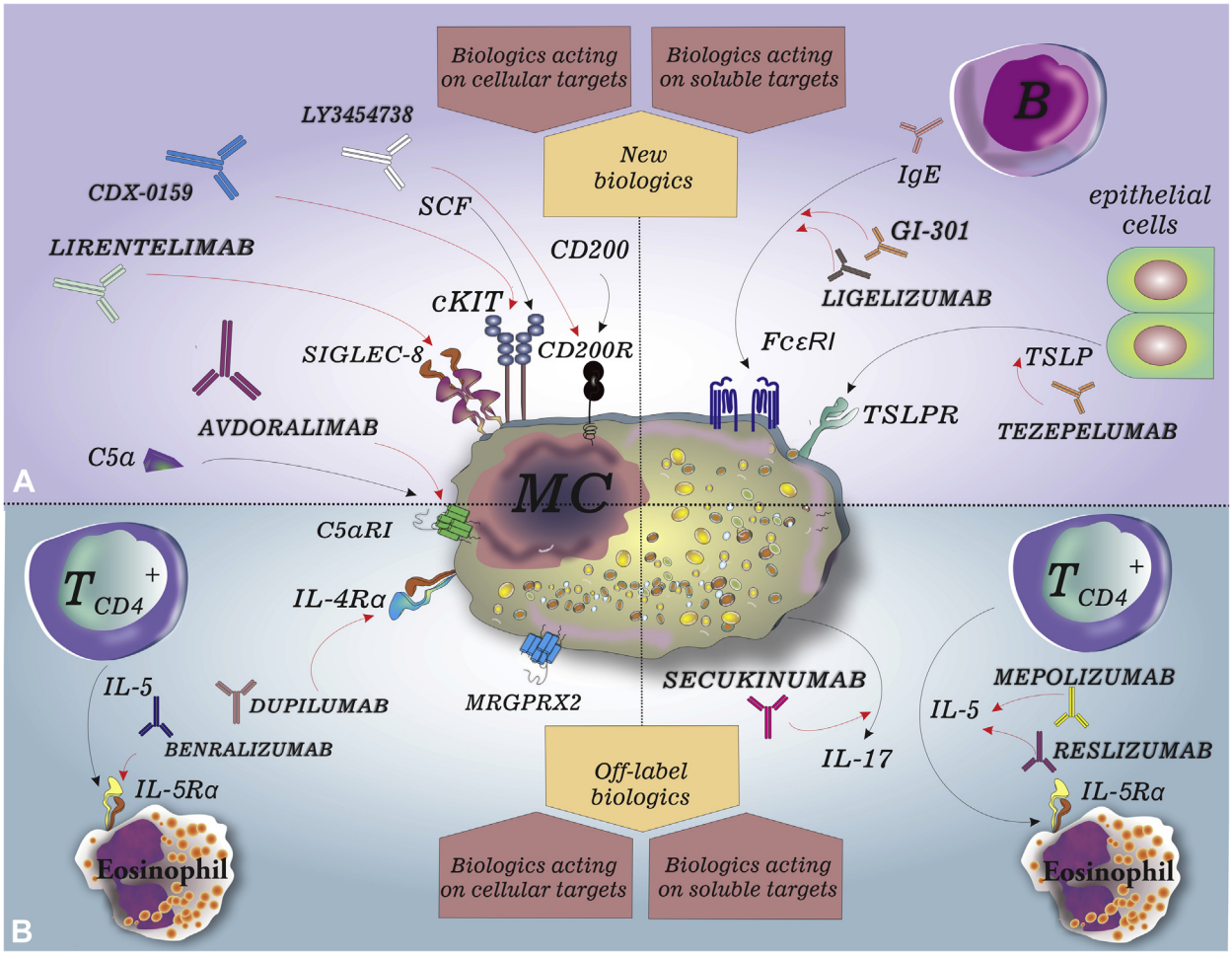

FIGURE 3. Classification of biologics for the use in chronic spontaneous urticaria. **A,** New biologics: these include biologics that act on cellular targets (LY3454733 triggers CD200R and AK-002 targets SIGLEC-8, both are inhibitory receptors; CDX-0159 binds to KIT and suppresses SCF effects; avdoralimab acts on C5aRI and suppresses the binding of C5a) and biologics that act on soluble targets (ligelizumab and GI-301 bind IgE and decrease IgE:FcεRI binding; tezepelumab binds to thymic stromal lymphopoietin [TSLP] released mainly by epithelial cells). **B,** Off-label biologics: these also include biologics that act on cellular targets (dupilumab acts on IL-4Rα, and benralizumab binds to IL-5Rα) and biologics that target soluble mediators (mepolizumab and reslizumab both bind to IL-5, and secukinumab targets IL-17). *MC*, Mast cell; *SCF*, stem cell factor.

MCs.[111] Furthermore, high disease activity, in CSU, is linked to eosinopenia and basopenia.[32] Benralizumab (AstraZeneca), an anti-IL-5 receptor antibody, and the anti-IL-5 antibodies mepolizumab (GSK) and reslizumab (Teva) are licensed and used for the treatment of patients with asthma. All have been successfully used to treat patients with CSU, CindU, or both.[95-97] Benralizumab and mepolizumab are currently being assessed in CSU trials.

Secukinumab

IL-17 is associated with many autoimmune disorders, and blood levels of IL-17 in patients with CSU have recently been reported to be elevated and linked to high disease activity.[42] Moreover, the expression of IL-17 was found to be upregulated in the skin of patients with CSU. In a recent study, the anti-IL-17 mAb secukinumab (Novartis) markedly reduced disease activity in patients with CSU who were refractory to other treatments including omalizumab and cyclosporine.[98]

Omalizumab for CIndU

A growing number of studies including RCTs indicate that omalizumab has substantial benefits in the off-label treatment of patients with CIndUs. The evidence, currently, is strongest for symptomatic dermographism, cold urticaria, and solar urticaria.[50,51,112-116]

NOVEL BIOLOGICS UNDER DEVELOPMENT FOR CHRONIC URTICARIA

New biologics that are currently under development for the treatment of patients with chronic urticaria aim to reduce MC activation, by blocking activating pathways or engaging inhibitory receptors, or MC numbers (Figure 3, Table II). Ligelizumab and GI-301 are novel anti-IgE biologics, avdoralimab and tezepelumab inhibit the effects of C5a and TSLP, respectively, AK002 and the anti-CD200R mAb LY3454738 trigger

TABLE II. Approved, off-label, and novel biologics for chronic urticaria

Biologic	Cellular/pathway target of treatment	Approval status	Trial status	Ref.
Omalizumab (Novartis/ Genentech)	Reduction of free IgE	Approved for CSU since 2014	–	Kaplan et al,[22] Kikuchi and Kaplan,[24] MacGlashan et al,[40] Deza et al[41]
	Reduction of FcεRI expression on MCs			
Off-label biologics under development for chronic urticaria				
Dupilumab (Sanofi/ Regeneron)	Targets IL-4Rα, inhibiting IL-4 and IL-13	Approved, but not for CSU	Phase III	Lee and Simpson[94]
	Reduces IgE levels in atopic individuals			
Benralizumab (Astra-Zeneca)	Targets IL-5R	Approved, but not for CSU	POC completed	Bergmann et al,[95] Magerl et al,[96] Maurer et al[97]
Secukinumab (Novartis)	Binds to Interleukin-17	Approved, but not for CSU	POC completed	Sabag et al[98]
Novel biologics under development for chronic urticarial				
Ligelizumab (Novartis)	Reduction of free IgE	Not approved	Phase III	Gasser et al,[99] Maurer et al[100]
GI-301 (GI Innovation)	Reduction of free IgE	Not approved	Phase I	Lee et al[101]
Tezepelumab (Amgen/Astra-Zeneca)	Binds TSLP	Not approved	Phase I	Corren et al[102]
Avdoralimab (Innate Pharma)	Targets C5aR1	Not approved	Phase II	Carvelli et al[103]
Lirentelimab (Allakos)	Binds to Siglec-8, an inhibitory receptor	Not approved	Phase II	Youngblood et a,[104] Leonardi,[105] Maurer,[106] Siebenhaar et al[107]
	Silences mast cells, depletes eosinophils			
LY345473 (Lilly)	Binds to CD200R, an inhibitory receptor	Not approved	Phase II	Potter et al[108]
CDX-0159 (Celldex)	Binds to Kit, depletes mast cells	Not approved	Phase II	Maurer[109]

CSU, Chronic spontaneous urticaria; *MC*, mast cell; *POC*, proof of concept study; *Siglec-8*, Sialic acid–binding immunoglobulin-like lectin-8; *TSLP*, thymic stromal lymphopoietin.

inhibitory receptors, and the anti-KIT mAb CDX-0159 aims to reduce MC numbers.

Ligelizumab

Ligelizumab (Novartis), like omalizumab, is a humanized IgG mAb that binds IgE. It is similar to omalizumab in that its binding to specific epitopes in the Cε3 region of IgE blocks the interaction of IgE with its receptors, FcεRI and FcεRII, and that it does not mediate IgE receptor cross-linking, that is, is non-activating. Ligelizumab is different from omalizumab in its binding epitope of IgE, its higher affinity for IgE and lower off rate, its strong suppression of skin prick test responses to allergens, and in that it does not dissociate prebound IgE from MCs and basophils.[99] Ligelizumab, in a recent phase II RCT, demonstrated superior efficacy compared with placebo and omalizumab, with a rapid onset of effects, a dose-dependent benefit, and longer time to relapse after treatment discontinuation.[100] Phase III studies are ongoing in adults and adolescents with CSU.

GI-310

GI-301 (GI Innovation), a novel long-acting IgE Trap-Fc fusion protein, binds circulating IgE, like omalizumab and ligelizumab. GI-301 exhibits higher and more durable binding to IgE than omalizumab and inhibits IgE-driven human MC degranulation more potently.[101] Unlike omalizumab, GI-301 does not bind to FcγR, and therefore, comes with a reduced risk of inducing hypersensitivity reactions.[117] GI-301 is under development for the treatment of CSU.

Tezepelumab

The alarmin and innate type 2 immunity-inducing cytokine TSLP is an epithelial cell–derived cytokine that is produced in response to proinflammatory stimuli and drives inflammatory responses, primarily through its activity on dendritic cells, MCs, and type 2 innate lymphoid cells.[118] MCs express TSLP receptors, and TSLP induces MC development and prevents apoptosis in skin MCs.[119] TSLP is markedly upregulated in the wheals of patients with CSU.[37] Tezepelumab (Amgen) is an

anti-TSLP human mAb that prevents TSLP/TSLP receptor interaction. Tezepelumab is efficacious in the treatment of patients with asthma[102] and was also demonstrated to bring on substantial and persistent decreases in blood eosinophil counts as well as progressive reduction in total serum IgE levels. Tezepelumab is being developed for the treatment of CSU.

Avdoralimab

The C5a receptor (C5aR) is expressed by human skin MCs, but not lung or other MCs, and its engagement by C5a results in their activation and degranulation.[120] The effects of MC-activating autoantibodies of patients with type IIb autoimmune CSU are, at least in part, mediated by the activation of C5aR.[25,121] The activation of human MCs by these autoantibodies is augmented by complement, and C5a is the complement agonist that is responsible for this.[121] Subsequent work on basophils that used an antibody directed to the C5a receptor showed inhibition of the release of histamine induced by C5a or by the sera of patients with CSU.[25] Recent work has demonstrated that polymorphisms in C5AR1 are associated with CSU susceptibility and the efficacy of antihistamine treatment in patients with CSU.[122] In a comprehensive analysis of potential biomarkers of CSU, C5a was found not to be elevated in the blood of patients, suggesting that the activation of complement and the effects of C5a on MCs are limited to the skin.[123] Avdoralimab (Innate Pharma) is a fully human therapeutic mAb that specifically binds and blocks C5aR1. In mouse models of acute lung injury, avdoralimab was found to block the strong influx of proinflammatory cells to the lungs and the associated lung damage. Avdoralimab is currently evaluated for the treatment of severe pneumonia induced by COVID-19[103] and is also assessed for its effects in CSU and bullous pemphigoid in multicenter investigator-initiated RCTs. Avdoralimab is currently under development for the treatment of COVID-19 and assessed for its effects in CSU in multicenter investigator-initiated RCTs.

Lirentelimab

Most MC receptors are activating receptors, that is, their ligand engagement induces MC degranulation, migration, differentiation, or proliferation. MCs also express inhibitory receptors, which silence MCs and inhibit their degranulation when engaged by ligands. Siglec-8 is one of these inhibitory MC receptors,[124] and mAbs that engage this receptor have been shown to inhibit MC degranulation and cytokine production.[64] Lirentelimab, a humanized IgG1 anti-Siglec-8 mAb, inhibits MC activation and depletes eosinophils.[104] Lirentelimab has shown activity in several disease settings and was found to reduce disease activity in patients with CSU, including omalizumab-refractory CSU, as well as in patients with symptomatic dermographism or cholinergic urticaria in a phase IIa, open-label proof-of-concept study.[105-107]

LY3454738

CD200R is an inhibitory receptor expressed on MCs and basophils, and engagement of CD200R by agonist antibodies inhibits MC activation and subsequent degranulation as well as cytokine production and release.[125-127] LY3454738 (Lilly) is a humanized mAb that binds to and agonizes CD200R and does not block binding of the endogenous ligand, CD200.[108] LY3454738 is currently under development for the treatment of patients with CSU.

CDX-0159

KIT (CD117), the receptor for SCF, is the major driver of MC differentiation, activation, migration, proliferation, and survival.[128,129] MC numbers are increased in the skin of patients with CSU, which may be due to the effects of SCF, and reducing the number of skin MCs is expected to reduce disease activity in patients with CSU.[130-134] CDX-0159 (Celldex), an mAb that specifically binds the extracellular dimerization domain of Kit, inhibits activation of KIT by SCF. In a recent phase 1 study, CDX-0159 resulted in a dose-proportional, profound, and sustained suppression of plasma tryptase, indicative of systemic MC ablation.[109] CDX-0159 is under development for the treatment of CSU and CIndU.

SUMMARY

CSU is an autoimmune disease with mechanisms for hive formation dependent on IgG and IgE antibodies. Both of these pathways of MC degranulation are addressed by the biologic omalizumab, which removes free IgE, downregulates the surface antigen with which the IgG antibody reacts, and represents our safest and most effective therapeutic agent for CSU to date. New treatment approaches are being sought including agents with more potent interactions with IgE as well as biologics (typically other mAbs) that target IL-4, IL-5, IL-13, and IL-17, MC activating and inhibitory receptors, eosinophil and basophil migration and functions, and MC survival. These biologics are at various stages of development, and their status as therapeutic agents for CSU is reviewed herein.

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