

The Expanding Field of Biologics in the Management of Chronic Urticaria



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Learning objectives:

1. To identify the opportunities and limitations for biologics in the management of refractory chronic urticaria.
2. To learn the adverse effects when clinically using these therapies.
3. To understand the mechanisms involved with biologic therapies in altering the pathophysiology of chronic urticaria.

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Chronic urticaria (CU) is the occurrence of urticaria with or without angioedema for at least 6 weeks. Management has traditionally involved antihistamines as first-line therapy with various alternative therapies for refractory cases. Largely based on the success of biologics for various diseases, this class of drugs has come to the forefront of medical research. The first and only Food and Drug Administration–approved biologic for the management of CU is omalizumab (humanized anti-IgE mAb). In the past decade, a substantial amount of research has been centered on the mechanism of action, efficacy, dosing, and safety of omalizumab. This review will focus on the data surrounding the management of CU with omalizumab, off-label use of other biologics for CU, and biologics currently under investigation for

use in CU. We will also discuss management considerations and areas of interest for future research. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:1489-99)

Key words: Chronic urticaria; Biologics; Omalizumab; Monoclonal antibody; Mechanism; Safety

Chronic urticaria (CU) is the occurrence of continuous or intermittent urticarial lesions with or without angioedema for at least 6 weeks.¹ This encompassing term includes chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria, as well as physical (inducible) urticarias. Patients with CU are known to have a significantly lower quality of life and often have systemic symptoms including joint pain, headaches, fatigue, flushing, and gastrointestinal complaints.² As a result, CU may result in a significant burden on society due to the cost of management, missed workdays, and psychosocial factors.³⁻⁵

The standard of care for decades has revolved around the use of antihistamines for symptomatic management. Unfortunately, 40% to 55% of patients are refractory to recommended doses of antihistamines.^{6,7} If not well controlled on antihistamines and a leukotriene antagonist, the 2014 practice parameters on urticaria recommend the use of alternative therapies. These include omalizumab, cyclosporine, dapsone, sulfasalazine, hydroxychloroquine, and colchicine.¹

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Abbreviations used

AE- adverse event
 CU- chronic urticaria
 CIU- chronic idiopathic urticaria
 CRT_{H2}- chemoattractant receptor homologous molecule expressed on T_{H2} cells
 FDA- Food and Drug Administration
 FcεRI- high-affinity receptor for Fc region of IgE
 IVIG- intravenous immunoglobulin
 ISS- itch severity score
 Syk- Spleen tyrosine kinase
 UAS7- weekly urticaria activity score

Omalizumab is the only biologic that is currently Food and Drug Administration (FDA) approved for the management of CIU. As biologics have come to the forefront of medical therapy over the past decade, they will likely continue to play a vital role in the management of CU (Figure 1). This review will focus on the only FDA-approved biologic for CIU, omalizumab, as well as the available data on the use of other biologics that are currently being used for refractory cases of CU (Table 1). We will also discuss biologics currently under investigation as potential agents for CU therapy. Throughout this review, the terms CU, CIU (aka chronic spontaneous urticaria), and physical urticaria (aka inducible urticaria) have been used specifically to distinguish studies evaluating only 1 subtype from those studies including all types of CU.

OMALIZUMAB

The first FDA-approved biologic for the management of CIU is the recombinant humanized IgG₁ monoclonal anti-IgE antibody omalizumab. Omalizumab was first introduced in 2003 for the treatment of patients with poorly controlled moderate to severe allergic asthma. It binds to free IgE at the Fc region, preventing interaction with high-affinity receptor for Fc region of IgE (FcεRI) on effector cells.²⁸

Currently, the pathophysiology of CIU is not well understood. Several theories related to mast cell activation, basophil dysfunction, and autoimmunity have been proposed, but to date a clear mechanism to explain the immunopathogenesis of CIU remains unknown.²⁹⁻³¹

One proposed mechanism of omalizumab in CIU involves the presence of IgG autoantibodies against IgE and/or the α subunit of FcεRI in up to 30% to 50% of patients with CIU.^{32,33} These antibodies may be involved in complement activation, which can lead to skin mast cell degranulation through their complement receptors.^{34,35} Omalizumab has been shown in multiple independent studies to decrease serum-free IgE levels as well as downregulate FcεRI expression on both mast cells and basophils.^{8-11,36} This not only decreases the sensitivity of these cells to antigen activation, but mast cell survival is at least partially dependent on IgE cross-linking of adjacent FcεRI on the cell surface, which prevents apoptosis.^{37,38} Downregulation of FcεRI on dendritic cells also has been shown with omalizumab.³⁹ This may lead to decreased antigen presentation and mediator release. However, the presence of autoantibodies has not been associated with an improved response. A recent retrospective study suggested that the lack of autoantibodies (as measured by upregulation of basophil CD203c) was actually more predictive of a response to omalizumab in CIU.⁴⁰ Another retrospective study

suggested that patients with either enhanced basophil activation or positive autologous serum skin test results were slower to respond to omalizumab.⁴¹

Other mechanisms that have been proposed with the use of omalizumab include a reduction in IgE autoantibodies that target autoallergens such as thyroperoxidase and double-stranded DNA,⁴²⁻⁴⁴ mast cell and basophil reduction in releasability, and a return to normal basophil function and location.⁴⁵ Finally, a recent study by Eggel et al⁴⁶ showed that to a small degree, high concentrations of omalizumab may disrupt precomplexed IgE with FcεRI on the cell surface. At this time, the mechanism or mechanisms responsible for the beneficial effect of omalizumab in CIU remain unclear. Further investigation is needed in this area to better define this mechanism, to help predict response in a given patient, and to help determine other potential therapeutic targets.

Phase III trials

The first successful use of omalizumab for CU (a child with cold urticaria) was reported by Boyce in 2006.⁴⁷ Spector and Tan⁴⁸ reported a case series of 3 patients with refractory CU who were successfully treated with omalizumab soon after. Numerous other small case reports and case series have subsequently been reported along with the first controlled trial by Kaplan et al⁴⁹ in 2008. The 3 central phase III multicenter, randomized, double-blinded studies that led to the FDA indication for CIU were the ASTERIA I,¹² ASTERIA II,¹³ and GLACIAL trials.¹⁴ In total, these trials included 733 patients on omalizumab 75, 150, or 300 mg at 4-week intervals and 242 patients in the placebo control groups.

ASTERIA II included patients receiving either omalizumab 75 mg, omalizumab 150 mg, omalizumab 300 mg, or placebo for a 12-week treatment period with 16 weeks of follow-up. The patients included had already failed treatment with approved doses of H1 antihistamines. Only the omalizumab 150 mg and omalizumab 300 mg groups reached significance for their primary end point of a mean change from baseline in weekly itch severity score (ISS) at 12 weeks (−8.1 with omalizumab 150 mg and −9.8 with omalizumab 300 mg), as compared with placebo. The proportion of patients who had complete resolution of hives and itching was 16%, 22%, 44%, and 5% for omalizumab 75 mg, omalizumab 150 mg, omalizumab 300 mg, and placebo groups, respectively. During the 16-week follow-up period, the ISS for all omalizumab doses increased to levels similar to those of the placebo group.¹³

ASTERIA I was similar to ASTERIA II but with a longer treatment duration. This was a 40-week trial that included 24 weeks of therapy with either omalizumab 75 mg, omalizumab 150 mg, or omalizumab 300 mg given in 4-week intervals with a 16-week follow-up period. The patients who were included had failed H1 antihistamine therapy at licensed doses. All 3 doses of omalizumab met their primary efficacy end point of a reduction in weekly ISS compared with baseline at 12 weeks (−6.46 with omalizumab 75 mg, −6.66 with omalizumab 150 mg, and −9.40 with omalizumab 300 mg). The omalizumab 300 mg group met all secondary end points and reached the minimally important difference response (≥5-point decrease)⁵⁰ in weekly ISS at a significantly shorter duration compared with the other omalizumab doses. Similar to ASTERIA I, weekly ISS returned to placebo levels after omalizumab was discontinued in all treatment groups during follow-up.¹²

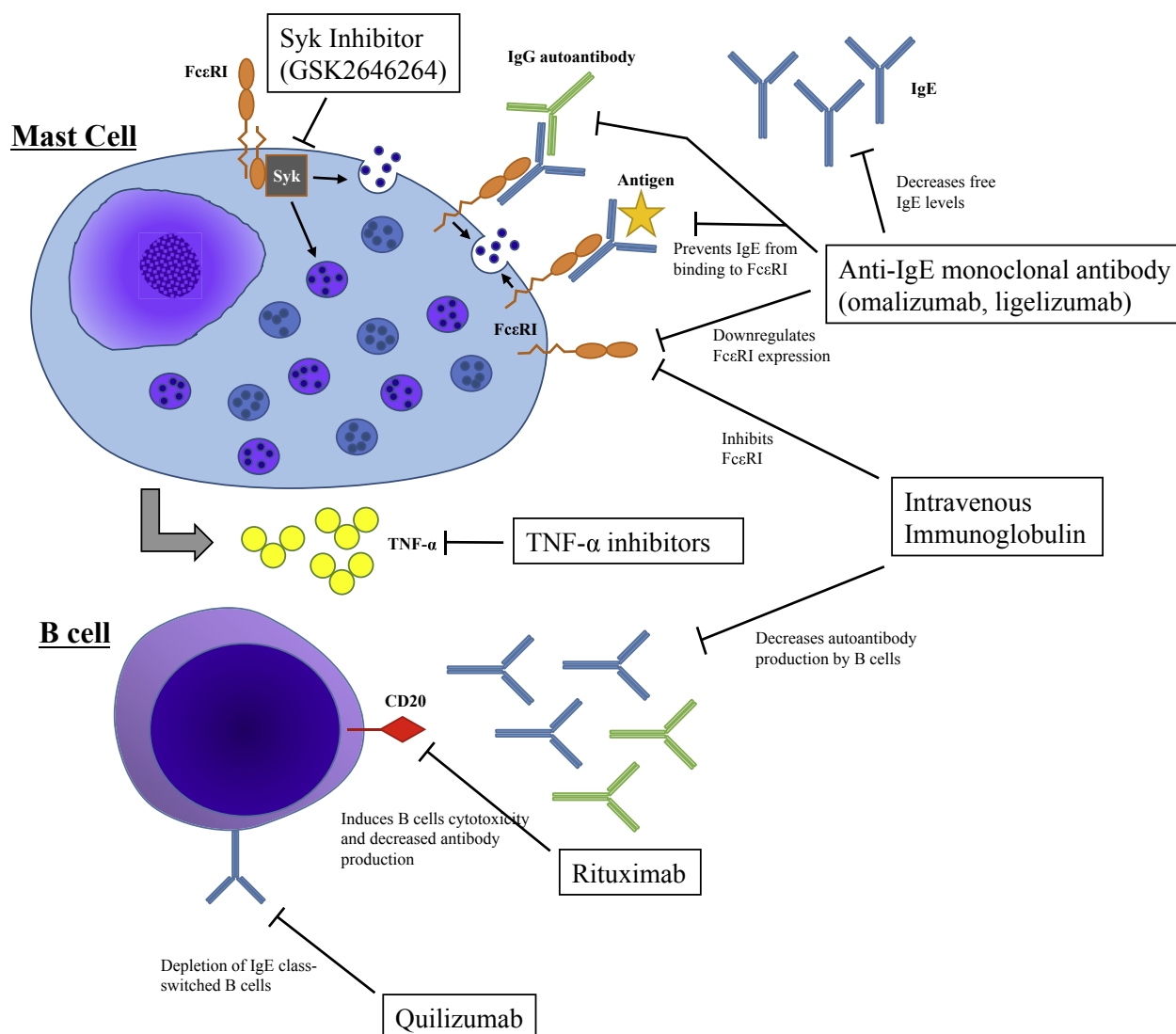


FIGURE 1. Mechanisms of action for biotherapeutics currently being used and under investigation for CU.

The GLACIAL study evaluated patients who had failed H1 antihistamines at up to 4 times the approved doses in addition to approved doses of leukotriene receptor antagonists and/or H2 antihistamines. These patients were given either omalizumab 300 mg or placebo every 4 weeks for 24 weeks followed by a 16-week observation period. The weekly ISS at week 12 compared with baseline was significantly improved in the omalizumab group compared with placebo (−8.6 with omalizumab 300 mg), which is shown in Figure 2. All other secondary efficacy end points also met significance for the omalizumab group including change in weekly urticaria activity score (UAS7), Dermatology Life Quality Index, and proportion of patients who were itch and hive free. As with both ASTERIA trials, the effects of omalizumab appeared to be transient, and weekly ISS increased to placebo levels after treatment with omalizumab was completed.¹⁴

Dosing and frequency

Unlike for allergic asthma, the FDA approved omalizumab for the management of CIU at doses independent of serum IgE or

body weight. Based on the 3 trials discussed earlier, the approved doses are omalizumab 150 mg or 300 mg every 4 weeks. Doses lower than this did not consistently show a significant improvement in efficacy compared with placebo,¹³ and the higher dose of 300 mg dependably showed faster and more robust efficacy.^{12,14,50} Interestingly, higher doses of omalizumab at 600 mg were explored in the dose-ranging single omalizumab dose phase II MYSTIQUE trial.¹⁵ Although no significant difference was noted in the outcome of these patients compared with the omalizumab 300 mg group, there was also no increase in adverse events (AEs). Cases of patients requiring higher than approved doses, up to 600 mg, to reach complete remission have been reported.⁵²

Special populations

Although ASTERIA II and GLACIAL did include patients 12 years and older, none of these larger trials addressed the use of omalizumab in the pediatric population below this age. Although significantly less common in the pediatric population, CU affects 0.1% to 0.3% of children with a similar morbidity profile as the

TABLE I. Overview of biotherapeutics currently being used for management of CU

Biologic	Dosing for CU	Proposed mechanism of action in CU	Supporting data	Adverse reactions
Omalizumab	FDA approved: 150 or 300 mg every 4 wk Off-label: doses up to 600 mg every 4 wk or 300 mg every 2 wk have been used successfully in refractory cases	Binding of IgE at the Fc region reduces free IgE levels. ⁸ This leads to downregulation of FcεRI expression on mast cells, basophils, and dendritic cells, resulting in decreased mediator release ⁸⁻¹¹	Several independent, large, multicenter, randomized, double-blinded studies (ASTERIA I, ¹² ASTERIA II, ¹³ GLACIAL, ¹⁴ MYSTIQUE ¹⁵) with response rates of 75%-86% with 300 mg every 4 wk for 24 wk of therapy. Symptoms recurred after discontinuation	Black box warning for anaphylaxis (lower risk in management of CU compared with asthma); injection- site reaction, headache, nausea, upper respiratory tract infection, cough, arthralgias, fatigue, dizziness, dermatitis, and nasopharyngitis
IVIG	Off-label: 0.15 g/kg/d every 4 wk for 6-51 mo or 2 g/kg over 2 d every 4-6 wk for 3-11 cycles	Blocks FcεRI activity on mast cells, which prevents IgE binding and degranulation. Also, can decrease B-cell production of autoantibodies ¹⁶	5 open-label studies and case series have been reported with mixed efficacy. ¹⁷⁻²¹ The largest study by Pereira et al ¹⁷ showed 26 of 29 patients with refractory urticaria having some improvement and 19 with complete remission. Symptoms relapsed after discontinuation of therapy	Black box warning for thrombosis, renal dysfunction, and acute renal failure; headache, fever, chills, flushing, abdominal pain, nausea, infusion-site reaction, arthralgia, hypotension or hypertension, nasal congestion, and aseptic meningitis
Rituximab	Off-label: 375 mg/m ² weekly injections for 4 wk	Binding to B cells leads to complement-dependent and antibody-dependent cytotoxicity. ²² B-cell depletion results in decreased circulating autoantibody levels ²³	3 case reports with 2 showing complete and prolonged remission, and 1 with no benefit ²³⁻²⁵	Black box warning for severe infusion reactions, mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy; fatigue, rash, chills, neuropathy, headache, tumor lysis syndrome, hypertension, angioedema, and cytopenias
TNF-α inhibitors (etanercept, infliximab, adalimumab)	Off-label: Etanercept 50 mg weekly Infliximab 5 mg/kg every 6 wk Adalimumab 40 mg every 2 wk	TNF-α has been shown to be upregulated in patients with CU, but its specific role in the pathophysiology of CU is not well understood. ^{26,27} Inhibiting TNF-α may lead to disease modification through an unknown mechanism	Several case reports and case series, with the largest by Sand and Thomsen ²⁷ reporting 25 patients receiving a TNF-α inhibitor; 15 of these patients (60%) had complete or almost complete response with sustained remission	Black box warning for malignancies and serious infections including tuberculosis, invasive fungal infections, and opportunistic infections; headache, infection, injection- site reaction, rash, abdominal pain, and diarrhea

adult population.^{53,54} Netchiporouk et al⁵⁵ reported a case series of the use of omalizumab for CU in the pediatric population that included 4 patients ranging in age from 4 to 16 years. The younger patients at ages 4 and 5 years received doses of 150 mg monthly, whereas the older patients at 10 and 16 years of age received 300 mg monthly. All 4 patients obtained complete response without any reported AEs. Although only limited data are available for this population, omalizumab may be a potential therapeutic option for children with CU. Omalizumab has already been approved for children aged 6 to 11 years for asthma on the basis of favorable safety profiles from randomized, placebo-controlled studies.⁵⁶⁻⁵⁸

The EXPECT study evaluated the use of omalizumab during pregnancy.⁵⁹ One hundred ninety-one (191) pregnant women

were included who had moderate to severe asthma and received at least 1 dose of omalizumab 8 weeks before conception or at any time during pregnancy. Based on the known outcomes of 169 pregnancies, there was no significant difference in spontaneous abortions, major congenital anomalies, prematurity, or low birth weight compared with a similar asthma population reported in previous studies.^{60,61} Because of the small number of patients in the study, it is difficult to draw any conclusions of safety on the use of omalizumab during pregnancy for CU. Further studies are needed with larger sample sizes.

Safety

Safety was closely evaluated in all the randomized phase III trials. ASTERIA II reported more headaches in the omalizumab

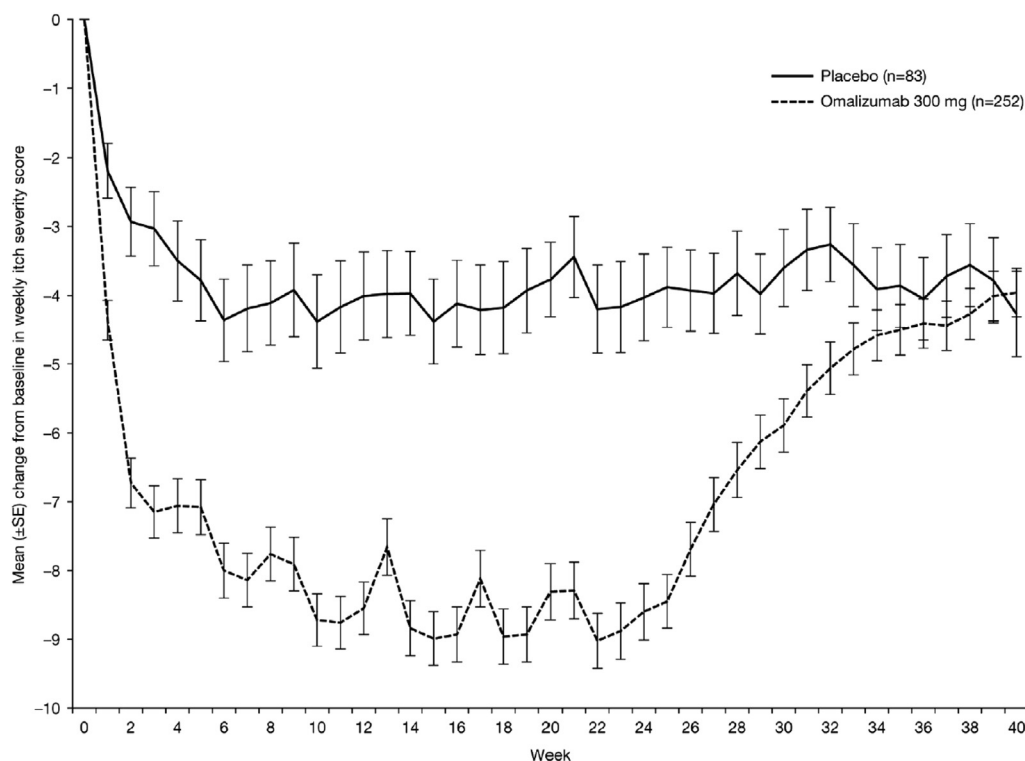


FIGURE 2. Weekly ISS in the GLACIAL trial with placebo versus omalizumab 300 mg.¹⁴ Treatment occurred every 4 weeks for 24 weeks with a 16-week follow-up period.

150 mg group compared with placebo but otherwise had no significant differences in AEs. The GLACIAL study showed no significant difference in AEs between the omalizumab group and placebo but did have some system-specific differences. In ASTERIA I, headaches, arthralgias, and injection-site reactions were more common in the omalizumab groups but there was no significant difference in serious AEs. No deaths, malignancies, or anaphylactic episodes were reported in these trials due to omalizumab.¹²⁻¹⁴

Overall, omalizumab is very well tolerated and adverse reactions have not occurred more frequently in patients on omalizumab compared with those on placebo in prospective, randomized trials for CU. The risk of anaphylaxis in patients with CU appears to be less than in those treated for asthma (Allen Kaplan, written communication, March 2017). In addition, there does not seem to be a dose-related effect on AEs.^{15,43}

Duration of therapy

As shown consistently in all phase III trials, cessation of omalizumab resulted in an increase in weekly symptoms and returning to placebo levels within 16 weeks.¹²⁻¹⁴ There did not appear to be a difference in the time frame of this rise in symptoms based on the duration of therapy with omalizumab. Thus, these controlled trials indicate that omalizumab is effective in controlling symptoms, but they do not provide evidence that omalizumab induces remission of CIU. Therefore, longer durations of therapy may be required for certain patients. The use of omalizumab appears to be safe and efficacious at therapeutic durations of more than 1 year.^{62,63}

Periodic efforts should be attempted at weaning or stopping therapy to evaluate for spontaneous remission because restarting

omalizumab has been shown to be effective.⁶³ Several strategies have been proposed for weaning including reducing monthly doses or lengthening the time between doses.^{64,65} Tontini et al⁶⁶ proposed a patient-tailored tapering protocol to customize weaning regimens on the basis of a patient's UAS7 scores while on omalizumab. Of the 8 patients included in their case series, 1 was able to completely stop omalizumab, 3 were able to lengthen the interval between doses to a maximum of 84 days, and 4 remained on the monthly schedule. At the present time, no uniform approach has been agreed upon for weaning omalizumab therapy. The authors of this review typically treat responders for approximately 6 months at monthly intervals and if no to minimal urticaria activity is present, increase the injection interval by 1-week intervals (ie, every 5 weeks then 6 weeks etc). If a patient can tolerate every 8-week injections over a 4-month period without increased activity, these patients can often have omalizumab discontinued.

Omalizumab nonresponders

Despite the overwhelming data supporting the use of omalizumab in CU, there have been large numbers of nonresponders as well. Omalizumab 300 mg has consistently produced the highest response rate; however, in the ASTERIA II, ASTERIA I, and GLACIAL studies, 48%, 34%, and 48% of patients, respectively, receiving 300 mg doses did not achieve a UAS7 of 6 or less by 12 weeks.⁵¹ Interestingly, of those patients who did not respond at 12 weeks, 58% and 48% did respond with a UAS7 of 6 or less by 24 weeks in the ASTERIA I and GLACIAL trials, respectively. Kaplan et al⁵¹ postulated that there are 2 distinct subgroups of responders, early and late responders. Their data suggest that a trial of 16

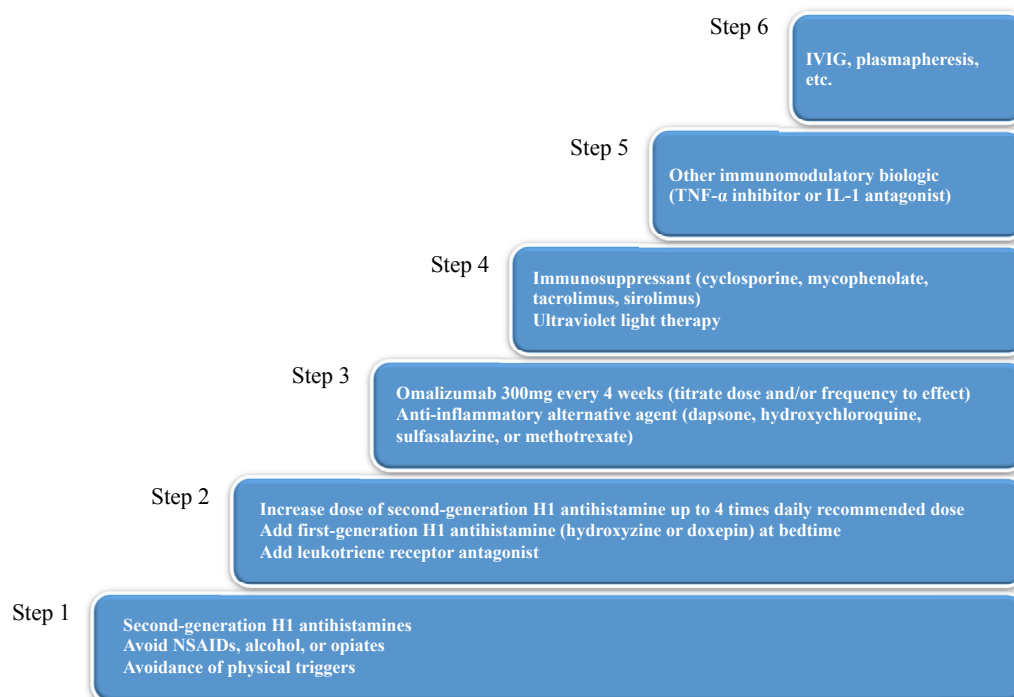


FIGURE 3. Stepwise treatment diagram for CU. *NSAIDs*, Nonsteroidal anti-inflammatory drugs.

weeks would be adequate to determine whether a patient will respond to omalizumab 300 mg every 4 weeks because the response rate after this time period is similar to that of placebo.⁵¹

In patients with partial response, there are anecdotal reports of improved symptom control with more frequent dosing of omalizumab 300 mg every 2 to 3 weeks.⁶² The mechanisms responsible for the variations in response to omalizumab remain elusive and further studies are needed to better characterize these populations.

Physical urticaria and idiopathic angioedema

Although compiled only as case reports or case series, omalizumab has also been shown to be effective in physical urticaria including solar urticaria, symptomatic dermatographism, cholinergic urticaria, cold urticaria, delayed pressure urticaria, and localized heat urticaria.^{47,67-71} Larger, blinded, randomized studies are needed because several omalizumab-resistant cases have also been reported.⁷²⁻⁷⁴

The X-ACT (Xolair Effects on Angioedema in Chronic Spontaneous Urticaria Treatment) study was a randomized controlled trial of 91 patients with CU and angioedema and demonstrated reduction in angioedema-burdened days, size of involved areas, and a prolonged time to recurrence of angioedema with omalizumab.⁷⁵

Angioedema without urticaria has also been evaluated as a potential target for omalizumab.⁷⁶⁻⁷⁸ The largest series of patients published to date is by Azofra et al⁷⁹ that treated 8 patients with angioedema who failed high-dose antihistamines.⁷⁹ All 8 patients had complete resolution of their symptoms within 14 days of initiation of omalizumab, with doses varying from 75 mg to 300 mg.

Summary of omalizumab therapy for CU

Omalizumab is a safe, efficacious, and cost-effective strategy in the management of CU.^{80,81} The most recent US practice parameters for the diagnosis and management of CU have omalizumab as a fourth-line agent¹ while the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization has recommended its use as third-line treatment.⁸² Other approaches have been proposed including using omalizumab as a second-line agent after antihistamines.⁸³ A dose of 300 mg every 4 weeks has been shown to be the most effective and safe dose regardless of background therapy (Figure 3).⁸⁴

OTHER BIOLOGICS FOR CU

Currently, a number of other biologics are being used off-label for the management of CU that is refractory to antihistamine therapy (Table I). The literature of these interventions is mainly based on clinical experience with limited controlled data on efficacy.

Intravenous immunoglobulin

Effectiveness for both low-dose and high-dose intravenous immunoglobulin (IVIG) regimens with refractory CU has been reported since the 1990s. Several open-label studies have been conducted with the largest conducted by Pereira et al,¹⁷ which enrolled 29 patients with autoimmune CU. Subjects were given low-dose IVIG (0.15 g/kg/d every 4 weeks) for a range of 6 to 51 months, and 26 had improvement in urticaria or angioedema while 19 had complete remission of symptoms. Unfortunately, not all patients with CU have been shown to respond to IVIG. A total of 5 open-label studies and case series have been published

TABLE II. Summary of biotherapeutics under investigation for the management of CU

Drug under investigation	Category of drug	Proposed mechanism of action in CU	Clinicaltrials.gov Identifier
Ligelizumab	Anti-IgE	Binding to the Ce3 domain of IgE and preventing interaction with the FcεRI on the surface of mast cells and basophils. This would lead to lower free IgE levels and downregulation of FcεRI similar to omalizumab but with much higher potency ⁹⁰	NCT02477332 NCT02649218
Quilizumab	Anti-IgE	Targets the M1-prime segment of membrane-expressed IgE, leading to depletion of IgE-switched class B cells through antibody-dependent cell-mediated cytotoxicity. This results in a sustained decrease in free IgE levels ⁹¹	NCT01987947
Canakinumab	Anti-IL-1β	Urticarial conditions including CAPS and SchS often present with urticaria and have been shown to have an upregulation of IL-1β. Although the contribution of IL-1β in CU is unclear, inhibition may modify the clinical course ⁹²⁻⁹⁷	NCT01635127
AZD1981	PGD ₂ receptor antagonist	CRT _{H2} , a receptor for PGD ₂ , has been shown to be overexpressed on eosinophils in patients with CU and other allergic diseases. ⁹⁸ Inhibition of CRT _{H2} may lead to anti-inflammatory effects that decrease the frequency and severity of urticarial lesions	NCT02031679
GSK2646264	Syk inhibitor	Syk has been shown to play an important role in mast cell and basophil dysregulation in patients with CU. ⁹⁹ By inhibiting Syk, proinflammatory mediators will be downregulated and may prevent degranulation ^{100,101}	NCT02424799

CAPS, Cryopyrin-associated periodic syndromes; CRT_{H2}, chemoattractant receptor homologous molecule expressed on T_{H2} cells; PGD₂, prostaglandin D₂; SchS, Schnitzler syndrome.

to date, which have all used unique protocols for dose, frequency, and duration of therapy. Efficacy has varied significantly, and frequently, recurrence of symptoms occurs soon after discontinuation of therapy.¹⁷⁻²¹

Despite a relatively good and predictable safety profile, the clinical use of IVIG is limited in the treatment of CU due to its high cost, need for prolonged infusions, and limited data on efficacy. It may be considered if the patient has another indication for the use of IVIG; otherwise, different alternative agents should be used before consideration of IVIG (Figure 3).

Rituximab

Rituximab is a chimeric murine/human anti-CD20 mAb that is FDA approved for the treatment of several hematologic and autoimmune diseases. Rituximab targets the CD20 antigen on the surface of B-lymphocytes, which leads to B-cell depletion.²² Although the role of B cells in CU is not well understood, it is believed that it may inhibit the production of autoantibodies.²³ Only 3 case reports have been published, with 2 showing prolonged or complete remission after 4 infusions of rituximab 375 mg/m² and 1 subject having no benefit.²³⁻²⁵ Because of the limited data available, potential for serious adverse effects, and lack of any randomized studies, there is not sufficient evidence to support the use of rituximab for CU, and it should only be considered in severely refractory patients who have failed multiple other alternative agents for CU.

TNF-α inhibitors

Several TNF-α inhibitors including etanercept, infliximab, adalimumab, and certolizumab are FDA approved for various autoimmune diseases. Despite slightly different mechanisms of action for the drugs, the end result is the inhibition of TNF-α, which has been shown to be upregulated in patients with CU in both lesional and nonlesional skin.^{26,27,80} The first reported efficacious use of etanercept for delayed pressure urticaria was in

2007 by Magerl et al.⁸⁵ Since then, multiple case reports and case series have emerged with similar results for cold-induced urticaria, refractory CIU, and urticarial vasculitis.^{86,87}

Sand and Thomsen^{88,89} have reported the use of monotherapy with either etanercept or adalimumab in 25 patients with refractory CU who had previously failed therapy with antihistamines, oral steroids, cyclosporine A, and/or omalizumab. Sixty percent of these subjects had complete or almost complete resolution of their symptoms while on treatment for 3 to 35 months with a mean duration of 13 months.^{88,89} Although lacking placebo-controlled, randomized studies, TNF-α inhibitors may be a therapeutic option to those who have failed other alternative agents including omalizumab, although further studies are needed to determine which subset of patients would benefit the most (Figure 3).

BIOTHERAPEUTICS UNDER INVESTIGATION FOR THE MANAGEMENT OF CU

Anti-IgE mAbs

There are several novel biologics that are currently being investigated as therapeutic options for CIU (Table II). Ligelizumab is a humanized IgG₁ mAb that acts similarly to omalizumab by binding to the Ce3 domain of IgE, preventing interaction with the FcεRI on the surface of mast cells and basophils. However, pharmacologic studies have shown a 50-fold increase in affinity *in vitro* and 6-fold to 9-fold increase in potency *in vivo* for ligelizumab compared with omalizumab with a similar safety profile.⁹⁰ Currently, a multicenter, randomized, double-blinded phase 2b dose-finding study is underway in regard to its efficacy and safety as add-on therapy for patients with CIU compared with placebo and omalizumab (NCT02477332). In addition, a safety extension study is recruiting subjects for the use of ligelizumab for CIU over a 1-year period (NCT02649218).

TABLE III. Knowledge gaps in the use of biotherapeutics for CU and need for future research

Biologic	Need for future research
Omalizumab	Mechanism of action of omalizumab in CU Safety and efficacy of higher doses or increased frequency in refractory patients or partial responders Safety and efficacy in children younger than 12 y and in pregnant patients Risk of anaphylaxis compared with those using omalizumab for an asthma indication Predicting which subset of patients with CU will respond to therapy Length of trial before determining whether patient is a nonresponder When and how to wean therapy Larger studies to evaluate the efficacy in physical urticarias and idiopathic angioedema without hives
IVIG	Randomized, double-blinded, placebo-controlled studies to evaluate efficacy
Rituximab	Randomized, double-blinded, placebo-controlled studies to evaluate efficacy
TNF- α inhibitors	Randomized, double-blinded, placebo-controlled studies to evaluate efficacy Evaluation of effectiveness between the drugs within this class

Another mAb that is being studied is quilizumab, a humanized IgG₁ that targets the M1-prime segment of membrane-expressed IgE. This has been shown in animal models to deplete IgE-switched B cells and plasmablasts through antibody-dependent cell-mediated cytotoxicity and apoptosis.¹⁰² In comparison to omalizumab, quilizumab has been shown to not only reduce IgE levels in human subjects but have sustained effects 6 months after completion of therapy. Recently, Harris et al⁹¹ published the QUAIL study, which was a randomized, double-blinded, placebo-controlled study evaluating 32 patients with refractory CIU in Canada and Germany.⁹¹ The patients were assigned to either receive quilizumab or placebo for a 20-week period. Although a 30% decrease in serum IgE was found in the quilizumab group as well as a trend in improved urticaria activity score and itch severity score, no statistical difference was observed. The authors believed that the study may not have been powered to detect a significant difference, the time interval of the study may have been too short, and that long-lived IgE plasma cells may play a more prominent role in the pathogenicity of CIU compared with ongoing IgE class switching, which would limit the efficacy of quilizumab based on its mechanism of action.

IL-1 antagonist (canakinumab)

IL-1 was first discovered in the 1970s by Gery et al¹⁰³ as an important proinflammatory cytokine that is vital in the innate immune system.¹⁰⁴ Out of the IL-1 cytokine family, IL-1 β has been the most studied and linked to autoinflammatory and allergic disorders. Cryopyrin-associated periodic syndromes and Schnitzler syndrome are autoinflammatory conditions that often present with urticaria-like lesions. Interestingly, both are

associated with an upregulation in IL-1 β and have had remarkable improvement in symptoms with IL-1 blockade.⁹²⁻⁹⁷

Lenormand and Lipsker¹⁰⁵ reported the use of IL-1 antagonist, anakinra, on 2 patients with refractory delayed pressure urticaria in 2012. Both had previously been treated unsuccessfully with antihistamines, oral corticosteroids, and IVIG before using anakinra 100 mg/d subcutaneously. Symptoms quickly resolved after initiation and had sustained benefits.¹⁰⁵ Similar benefits have also been shown in cold-induced urticaria.¹⁰⁶

At this time, several clinical trials are underway to evaluate the use of IL-1 β antagonists in specific subsets of urticarial conditions including urticarial vasculitis, physical urticaria, cryopyrin-associated periodic syndromes, Schnitzler syndrome, and chronic idiopathic urticaria. A phase II randomized, double-blind, placebo-controlled single-center study is in the recruitment phase to evaluate the use of canakinumab (human anti-IL-1 β mAb) versus placebo in chronic idiopathic urticaria (NCT01635127). IL-1–neutralizing antibodies appear to be a potentially promising therapy but further investigation is needed on its efficacy in CU.

Other biologics under investigation for CU

Pettipher et al¹⁰⁷ have described over a series of publications the relationship between prostaglandin D₂ in the cyclooxygenase pathway with allergic disease including asthma and rhinitis.¹⁰⁷⁻¹⁰⁹

One of prostaglandin D₂'s known receptors, chemoattractant receptor homologous molecule expressed on T_H2 cells, is expressed on basophils, eosinophils, and CD8+ T cells. It has been implicated as a major component of proinflammatory activity in allergic disease, and it has been shown to be overexpressed on eosinophils in patients with CU.⁹⁸ AZD1981, a selective chemoattractant receptor homologous molecule expressed on T_H2 cells receptor antagonist, is being investigated as a potential therapy for CIU in a phase IIa, randomized, placebo-controlled, double-blind study (NCT02031679).

Spleen tyrosine kinase (Syk) has been proposed as an important mechanism in the pathogenicity of CU. The Syk pathway in mast cells and basophils plays an important role in the regulation of transcription factors that are responsible for the synthesis and degranulation of proinflammatory mediators.⁹⁹ Several *in vitro* studies have shown an upregulation of Syk expression in patients with a certain subset of CU.^{100,101} GSK2646264, a topical Syk inhibitor, is currently under investigation in a randomized, double-blind, single and repeat ascending dose study to evaluate for safety, tolerability, and pharmacodynamics in patients with cold urticaria and CIU (NCT02424799).

SUMMARY

Biotherapeutics have revolutionized medical treatment over the past decade. Omalizumab is the first biologic that has been approved by the FDA for the treatment of CIU and several others have shown efficacy in limited case reports. There are still a number of unanswered questions and knowledge gaps that require further investigation (Table III). Additional randomized prospective studies are needed to further evaluate the efficacy of these drugs in CU. Currently, 4 biologics are being evaluated in early clinical trials for use in CU including ligelizumab, quilizumab, canakinumab, and AZD1981. As new therapeutic targets are discovered with a growing understanding of the pathogenesis of CU, biologics will play an even more important role in the management of CU.

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