

R E V I E W

Biologic drugs in chronic spontaneous urticaria

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Abstract. Chronic spontaneous urticaria (CSU) is a condition defined by the presence of recurrent urticaria, angioedema, or both, which persist for more than six weeks in duration and occurs in the absence of an identifiable trigger. Both children and adults can develop CSU, although it is more common in adults and in women than in men, with a peak occurrence in the third to fifth decades of life. It imposes a significant burden on patients, families and healthcare systems. The goal of therapy in patients with CSU is to achieve a level of symptom control and improvement in quality of life that is acceptable to the patient, while minimizing therapy-related side effects. The recent introduction of biologic drugs has changed the management of the disease. This work aims to provide a narrative review of the current state of biological therapy and the promising drugs under development for CSU. (www.actabiomedica.it)

Key words: biologics, children, adult, chronic spontaneous urticarial, clinical trials

Introduction

Chronic spontaneous urticaria (CSU) is a condition defined by the presence of recurrent urticaria, angioedema, or both, which persist for more than six weeks in duration and occurs in the absence of an identifiable trigger (1). Both children and adults can develop CSU, although it is more common in adults and in women than in men, with a peak occurrence in the third to fifth decades of life. The true prevalence and incidence of CSU are not indeed known. It has been estimated that CSU affects from 0.5 to 5% percent of the general population, while the annual incidence is reported around 1.4% (2, 3).

The clinical manifestations of CSU are usually limited to the skin. However, some patients report accompanying systemic symptoms, such as headache, fatigue, pain or swelling of joints, wheezing, flushing, gastrointestinal symptoms, and palpitations (4). This subgroup may have more severe and longer-lasting disease, compared with CSU patients without systemic symptoms (4, 5). Also, CSU is associated with various atopic and autoimmune disorders. Atopic comorbidities, including food allergy, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, and asthma, have been associated with CSU in a large, cross-sectional nationwide population of adolescents (6-8). In adults, an association with autoimmune conditions

was observed: thyroid disorders, celiac disease, Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes mellitus. Antinuclear antibodies were also more prevalent than in the general population (9, 10).

The pathogenesis of CSU is still debated, but it is clear that the activation of mast cells and basophils gives rise to the release of proinflammatory mediators supporting the generation of urticaria (1). In this context, IgE and its high-affinity receptor, FcεRI, play a key role in the degranulation of skin mast cells that drives the development of the signs and symptoms of CSU, itchy wheals, and angioedema (11).

The more commonly accepted theory refers to an autoimmune etiology of CSU, as an increased incidence of autoantibodies (antinuclear antibodies, IgG antithyroid antigens, IgE anti-thyroperoxidase, IgG anti-high-affinity IgE receptors (FcεR1), IgG directed against the Fc region of IgE (anti-IgE) (anti-IgE), and IgE anti-IL-24) has been recognized to be prevalent in a subgroup of patients with CSU (12). The pathogenic activation of mast cells and basophils can occur via these IgG- or IgE- antibodies-mediated pathways.

The second pathogenetic theory generally proposes that patients with CSU present defects of intracellular signaling pathways within mast cells and basophils that lead to dysregulated trafficking, signaling, and/or function of these cells (13).

Other theories hypothesize a role for coagulation factors, in particular tissue factor and thrombin, in the disease pathophysiology. Experimental models demonstrated that eosinophils are a primary cellular source of tissue factor, a protein that promotes activation of the extracellular coagulation cascade and generation of thrombin, which can increase vascular permeability directly acting on endothelial cells and indirectly inducing degranulation of mast cells with histamine release. Also, D-dimer was found to be increased during urticaria exacerbations, so that it has been proposed as a biomarker of severity and resistance to H1-antihistamines in CSU patients (14).

Although mast cells and basophils are the primary effectors of CSU, other cell types including monocytes, eosinophils, and T lymphocytes (more Th2 than Th1) have been observed within the inflammatory infiltrates of patients with CSU (15, 16). Once activated, these

cells may also play a role in the pathogenic degranulation of mast cells.

CSU imposes a significant burden on patients, families and healthcare systems. Results from a recent international observational study showed that almost 50% of patients had moderate-to-severe disease activity as reported by Urticaria Activity Score (UAS) and had significant impairment in their quality of life (QoL), including significant interference with sleep and daily activities (17, 18).

The goal of therapy in patients with CSU is to achieve a level of symptom control and improvement in quality of life that is acceptable to the patient, while minimizing therapy-related side effects. The current therapeutic algorithm for CSU, endorsed by international guidelines, entails treatment escalation of second-generation H1-antihistamines up to 4-fold if symptom control is not adequate. If complete response is not achieved, omalizumab is additionally administered. If there is no therapeutic success after six months of treatment with omalizumab, the guidelines recommend off-label use with cyclosporin A in addition to existing therapy with H1-antihistamines. In case of acute exacerbations, oral corticosteroids (OCS) can be given for a short period (up to a maximum of ten days) to reduce the duration and activity of the disease (1, 19). The recent introduction of omalizumab, the only licensed biologic for refractory CSU, has changed the management of the disease.

This work aims to provide a narrative review of the current state of biological therapy and the promising drugs under development for CSU. To select relevant literature for inclusion in this review, we conducted a literature search using the PubMed database and Clinicaltrials.gov. An electronic search was performed to identify studies, case reports, guidelines, reviews, and clinical trials focused on the new targets for CSU treatment, both approved and under investigation.

Omalizumab

Omalizumab is the first available humanized monoclonal anti-IgE with a pediatric indication (age ≥6 years) It is now recommended as add-on treatment for severe allergic asthma, CSU, and severe chronic rhi-

nosinusitis with nasal polyps (20-22). In CSU, omalizumab was approved in 2014 as an add-on to existing treatment in patients aged 12 years or over who have failed standard or high-dose (up to 4 times) second-generation H1-antihistamines (Table 1) (1, 19).

By binding to free IgE, omalizumab inhibits the interaction between IgE and its high-affinity receptor FcεRI, preventing mast cell and basophil activation and release of mediators, and blocks IgE binding to CD23 on B cells and antigen-presenting cells. Also, it down-regulates FcεRI expression on mast cells and basophils, thereby reducing the effects of IgG-anti-FcεRI, IgG-anti-IgE, autoantigen binding, and IgE-autoantibodies. Moreover, omalizumab exerts other potential therapeutic effects in CSU, such as reducing mast cell releasability, reversing basopenia and improving basophil function, and reducing eosinopenia, typically noted in patients with CSU (23). Besides these multiple effects, omalizumab also exerts an effect on gene expression in the skin of patients with CSU. Metz et al. characterized the gene expression profiles of lesional and nonlesional skin of CSU patients before and after 12 weeks of treatment with omalizumab and skin from healthy controls: among omalizumab-treated responders, a “normalization” of the signature gene transcripts has been observed towards that of healthy controls (24).

Accumulating evidence from randomized clinical trials (RCTs) have confirmed the effectiveness and safety of omalizumab, as it reduces the signs and symptoms and burden of CSU, improves QoL, and decreases the use of reliever medications, both in the pediatric population 12-17 years old and in adults (25-35). The European Academy of Allergy and Clinical Immunology (EAACI) recently conducted a systematic review focused on the efficacy and safety of omalizumab for CSU (36). In this study, evidence from 1620 subjects aged 12 to 75 years old treated with omalizumab for 16

to 40 weeks in ten RCTs was evaluated: an improvement in symptoms score and better efficacy of omalizumab 300 mg over the 150 mg dose were reported, in line with the results of previous systematic reviews on this subject. The highest response rates and faster and more sustained response have been observed at the 300 mg dosage. Both doses were found to increase the drug-related adverse events, while omalizumab 300 mg resulted in a reduction of drug-related serious AEs (RR 0.77; 95%CI 0.20 to 2.91) (36). Thus, international guidelines recommend starting at 300 mg. Omalizumab is generally well-tolerated; it has been used safely in pregnant women and is the treatment of choice for refractory CSU during pregnancy (37). Most commonly reported side effects include injection-site reactions, viral infections, upper respiratory tract infections, sinusitis and headaches. Hypersensitivity reactions to omalizumab including anaphylaxis, urticaria, and injection site reactions have unfrequently been reported. In general, anaphylaxis may occur in approximately 1 to 2 in 1000 patients receiving omalizumab; for CSU, one single study reported a single anaphylactic episode during its open-label phase (33). Subsequent observational/real-life studies and CSU registries reported a similar impact of omalizumab on CSU severity as in RCTs with an acceptable safety profile (38).

Recently, several predictors of response to omalizumab treatment in CSU have been described. They include higher baseline serum IgE levels (39-41), a greater than twofold increase in IgE after four weeks of treatment compared with baseline IgE (40), higher baseline levels of FcεRI on blood basophils, and greater reduction of FcεRI on basophils after four weeks of treatment (42). Recently, eosinophils emerged as novel cellular biomarkers in CSU; in particular, eosinopenia in patients with CSU has been associated with high disease activity and poor response to treatment

Table 1. Recommendations for omalizumab treatment in CSU.

| <i>European Medicine Agency (EMA)</i> | <i>Food and Drug Administration (FDA)</i> |
|---|--|
| Add-on therapy for the treatment of CSU in adults and adolescents (12 years and above, 300 mg s.c. every 4 weeks) with inadequate response to H1- antihistamine treatment | Additional treatment of CIU (150 or 300 mg s.c. every 4 weeks) in adults and adolescents (12 years of age and older) who remain symptomatic despite H1-antihistamine treatment |

CIU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; s.c.: subcutaneous.

(43). Based on available evidence and expert opinions, partial responders or non-responders can benefit from omalizumab up dosing or adding or switching to cyclosporine (44, 45). The optimal duration of therapy has not been determined, and patients may relapse when omalizumab is tapered or discontinued. Also, omalizumab has not been shown to have a long-term disease-modifying effect in CSU.

Although the available data supporting the efficacy and safety in the pediatric population is limited, there is growing evidence of the use of omalizumab in children < 12 years old with CSU (Table 2) (46-49). Although omalizumab appears to be an effective and safe treatment for CSU in the pediatric population, more robust and controlled evidence is still needed in order to formulate strong recommendations for its use.

Ligelizumab

Another anti-IgE monoclonal antibody, ligelizumab, with approximately 50-fold greater affinity for IgE, has been recently evaluated for CSU treatment (50). Ligelizumab has been shown to inhibit allergen-induced skin test responses and reduce IgE levels to a greater degree than omalizumab (50, 51).

A phase 2, dose-finding randomized trial evaluated ligelizumab effects at three different doses (24 mg, 72 mg, and 240 mg) and compared them to omalizumab (300 mg) or placebo in over 338 adults with moderate to severe CSU despite H1 antihistamines

at usual or high doses, in combination with H2 antihistamines and leukotriene antagonists (52). Complete control of hives at week 12 was achieved in 30, 51, and 42 % of the ligelizumab treated subjects, compared with 26 % of those receiving omalizumab and none in the placebo group. Ligelizumab was well tolerated, with mild to moderate injection site reactions being the main treatment-related adverse reaction. Higher doses of ligelizumab had a more prolonged effect after discontinuation with loss of complete response occurring 10.5 weeks after discontinuation of the 240 mg dose (52). The results from phase 3 trials, two of them including more than 1000 patients each, are awaited.

Mepolizumab

Mepolizumab is a humanized monoclonal antibody directed against IL-5 currently approved as an add-on treatment for severe eosinophilic (>150 cells/ μ L) asthma in patients \geq 12 years and a history of exacerbations. In light of the evidence of high eosinophils number in the skin of patients suffering from CSU compared to healthy controls (53), it has recently been postulated the efficacy of mepolizumab in treating CSU (54). Magerl et al. (55) firstly reported a therapeutic response to mepolizumab in a 27-year-old woman affected by severe refractory eosinophilic asthma and CSU. The patient was treated with mepolizumab, 100 mg every four weeks. She experienced

Table 2. Summary of case series reporting omalizumab use for chronic urticaria in children younger than 12 years.

| | Diagnosis | Angioedema | Omalizumab dosage (every 4 weeks) | Response | Duration (months) | Adverse events | Reference |
|---|-----------|---------------|---|--|-------------------|----------------|------------------------------|
| 3 | CIU | Yes, in 2 pts | 150 mg in 2 pts 300 mg in 1 pt | Complete in 2 pts, partial in 1 pt | 6 | None | Netchiporouk et al 2015 (46) |
| 2 | CIU | Yes, in 1 pt | 300 mg | Complete | 4 | None | Al-Shaikhly et al 2019 (47) |
| 6 | CSU | NR | 300 mg | Complete in 2 pts, partial in 3 pts (first course), no response in 1 pt | 6 | None | Passanisi et al 2019 (48) |
| 9 | CSU | NR | 150 mg in 1 pt, 300 mg in 7 pts, 600 mg in 1 pt | Complete in 8 pts, no response in 1 pt | 6-24 | None | Ari et al 2020 (49) |

CIU: chronic inducible urticaria; CSU: chronic spontaneous urticaria; NR: not reported; Pt: patient.

a significant improvement in her urticarial symptoms from the day after treatment initiation (55).

Currently, a phase 1, interventional, single-arm, open-label, enrolling 20 adults older than 18 years is ongoing to evaluate the efficacy of 10 weeks of treatment with mepolizumab in the treatment of CSU (56).

Dupilumab

Dupilumab, a monoclonal antibody targeting the IL-4/IL-13 axis, is indicated as an add-on maintenance treatment for patients older than 12 years with moderate-to-severe eosinophilic asthma or with OCS-dependent asthma regardless of phenotype. In adult patients (age major than 18 years), dupilumab is also indicated as add-on maintenance treatment in inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). Lastly, in November 2020, dupilumab has also been approved by European Commission as the first biologic medicine for children aged 6 to 11 years with moderate-to-severe uncontrolled atopic dermatitis (57).

Recently, Lee et al. reported the first case of a 40-year-old woman with environmental and food allergies, moderate-to-severe AD, autoimmune hypothyroidism, and CSU who remained symptomatic despite 13-months of omalizumab treatment. After 3-months of dupilumab treatment, the patient's CSU duration and severity resolved (58). To date, to the best of our knowledge, a total of 8 patients with CSU reached a positive outcome and did not report side effects following dupilumab treatment (59).

Two RCTs are currently ongoing to investigate the efficacy and safety of dupilumab in treating CSU.

A phase III clinical trial was designed in 234 pediatric and adult subjects (age range, 6-80 years) to investigate the efficacy of 24-weeks of dupilumab treatment in study participants with CU who remain symptomatic despite the H1 antihistamine and/or omalizumab treatment. Improvement in disease status and severity, health-related quality of life, and need for rescue therapy (oral corticosteroid (OCS) have been adopted as endpoints (60). In parallel, a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two-arm clinical tri-

al, enrolling 72 adult subjects (age range, 18-75 years) is ongoing to investigate the efficacy of 16-weeks of dupilumab treatment in reducing CSU activity in participants who remain symptomatic despite the H1 antihistamine treatment (61).

Benralizumab

Benralizumab is a murine monoclonal antibody that binds to the isoleucine-61 of the domain 1 of human IL-5R α , causing eosinophils depletion and modulating eosinophils-associated proteins and/or genes (62). It is indicated as an add-on maintenance treatment of severe eosinophilic asthma inadequately controlled despite high-dosage inhaled corticosteroids and long-acting β 2-agonists in patients older than 12 years. Benralizumab is administered subcutaneously 30 mg every four weeks for the first three doses and every eight weeks after that (62). The benralizumab-mediated depletion of eosinophils and basophils could explain its efficacy in treating CSU.

In June 2017, a phase IV, non-randomized, single-blind, placebo-controlled, interventional clinical trial, enrolling 12 adult subjects (age range, 19-70 years) was started to investigate the efficacy of benralizumab when compared to placebo in patients with CSU who remain symptomatic despite the H1 antihistamine treatment (63). More recently, a phase II multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial was performed to investigate the use of benralizumab as a treatment for 160 adult patients (older than 18 years) with CSU who are symptomatic despite the use of antihistamines (64). Currently, no results are posted for both RCTs.

Tezepelumab

Tezepelumab is a human monoclonal antibody that inhibits the action of thymic stromal lymphopoietin (TSLP), an epithelial cytokine promoting the release of Th2 cytokines (65). Taking advantage of the evidence that shows that TSLP is increased in lesional but not non-lesional skin of CSU patients

(65), it has been postulated that anti-TSLP can prevent and treat CSU by blocking the release of pro-inflammatory cytokines by immune cells.

A phase II, multicenter, interventional, randomized, parallel-group, placebo-controlled, omalizumab-controlled clinical trial is ongoing to efficacy and safety of tezepelumab to treat 270 adult participants (older than 18 years) suffering from CSU. However, results are not yet published (66).

Anti-TNF alpha (TNF- α)

TNF- α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. It is responsible for several cellular signaling events, including releasing pro-inflammatory cytokines and adhesion molecules and T cell recruitment. Since the crucial role of mast cells in the pathogenesis of UC, their ability to release TNF- α as well as the high levels of TNF- α found in CSU lesions, the administration of anti-TNF- α (Etanercept, Infliximab, Adalimumab) have been tested in adult patients, with success (67, 68). Successively, the anti-TNF- α has been reported to be effective in 60% of 20 CSU patients, including some omalizumab non-responders, with CSU (69).

Abatacept

A phase I-II, interventional, single group, open-label clinical trial showed the safety and efficacy of 4 doses Abatacept, a monoclonal antibody that links the cluster differentiation (CD)80 and CD86, in 4 adult subjects with CSU who have had an inadequate response to anti-histamine therapy. Moreover, no serious adverse events were reported (70).

Rituximab

Rituximab is a chimeric monoclonal antibody that targets the CD20 on the surface of immature, mature, and memory B cells leading to a depletion of B cells. Rituximab is used in treating hematology malignancies and autoimmune diseases; however, thanks to the evidence that it inhibits B cells producing both

IgE and IgG autoantibodies against Fc ϵ RI, it has been postulated that its use also in treating CSU (71).

The first evidence of Rituximab use in CSU was described in a 12-year-old boy and in a 51-year-old white woman who experienced a significant improvement in CSU after four Rituximab injections, and they remained asymptomatic up to 12 9 months, respectively (72, 73).

In September 2005, a phase I/II, interventional, non-randomized, open-label, single-arm clinical trial was started. Fifteen patients, age range 18 to 70 years, suffering from CSU, defined as symptoms >50% of the days or three days per week for more than 12 weeks, were enrolled; however, currently, no data are posted (74). We are not aware of other ongoing clinical trials with Rituximab in treating CSU.

Conclusion

The use of omalizumab in adults and adolescents with CSU is well supported by high-quality data within the current literature. Other biologics are under investigation for the treatment of refractory CSU, including the high-affinity anti-IgE monoclonal antibody ligelizumab, the anti-IL-4 and IL-13 monoclonal dupilumab, the anti-IL-5 receptor alpha monoclonal antibody benralizumab, and several novel drugs that are still in development.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 1 September 2021

Accepted: 30 September 2021

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