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Review

Current and future therapies for treating chronic spontaneous urticaria

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Declaration of interest

M Maurer is or recently was a speaker and/or advisor for FAES Farma, Almirall Hermal, Genentech, GlaxoSmithKline, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, Merck Sharp & Dohme, Merck, Moxie, Takeda, UCB Pharma, and Uriach.

G A. Vena has been a speaker and/or a scientific consultant and/or an advisory board member for Astellas, Abbvie, Janssen-Cilag, Leo Pharma, Merck-Serono, Merck Sharp & Dohme, Novartis, Pfizer, and UCB Pharma.

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T Zuberbier is a consultant for the following companies: Ansell, Bayer Schering, DST, FAES Farma, Fujisawa, HAL Allergy, Henkel, Kryolan, Leti, Menarini, Merck, Merck Sharp & Dohme, Novartis, Procter and Gamble, Ranbaxy, Sanofi-Aventis, Schering Plough, Stallergenes, and UCB Pharma. He has the following organizational affiliations: Scientific Advisory Board, German Society for Allergy and Clinical Immunology (DGAKI); Head, European Centre for Allergy Research Foundation (ECARF); Committee member, WHO-Initiative Allergic Rhinitis and its Impact on Asthma (ARIA); Member, World Allergy Organisation Communications Council (WAO); Secretary General, Global Allergy and Asthma European Network (GA²LEN). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

List of abbreviations

AH= antihistamine

ASST= autologous serum skin test

CRTH2= Chemoattractant Receptor-Homologous Molecule expressed on Th2 cells

CsA= ciclosporin A

CSU= chronic spontaneous urticaria

EAACI= European Academy of Allergy and Clinical Immunology

EAACI/GA²LEN/EDF/WAO= European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization

GP= general practitioner

RCT= randomized controlled trial

sg-AH= second-generation H₁-antihistamine

UAS= urticaria activity score

Abstract

Introduction: Chronic spontaneous urticaria (CSU) is a disabling condition that causes deterioration of quality of life.

Areas covered: The international EAACI/GA²LEN/EDF/WAO guidelines have provided a stepwise treatment algorithm for CSU management. Second-generation H₁-antihistamines are the first-line treatment, and the second step is the up-dosing of the same drugs. In refractory patients, the guidelines recommend the addition of omalizumab, ciclosporin A or montelukast. Systemic corticosteroids can be used as a short course during acute exacerbations. A plethora of alternative treatments has been evaluated, although the overall level of evidence for such treatments is low. Future treatment options may include inhibitors of skin mast cells and antagonists to mast cell-activating signals that are relevant for the induction of CSU signs and symptoms.

Expert opinion: The only licensed options included in the guidelines algorithm are standard-dosed second-generation H₁-antihistamines and omalizumab. High-quality evidence has documented a rapid and strong symptomatic effect of omalizumab in CSU, although the optimal long-term regimens should be further investigated. The role of alternative drugs deserves additional studies. The potential of the existing treatments for inducing remission of CSU is unknown, and this is an important area of research, as is the evaluation of predictors of response, prognostic factors, and pathomechanisms.

Keywords: alternative drugs, antihistamines, chronic spontaneous urticaria, ciclosporin, montelukast, omalizumab.

Article highlights

- The EAACI/GA²LEN/EDF/WAO guidelines recommend second-generation H₁-antihistamines as the mainstay of treatment of chronic spontaneous urticaria, and up-dosing of these drugs as second-line treatment.
- In refractory patients, the third-line treatment suggested by the guidelines consists of the addition of one of the following drugs: omalizumab, ciclosporin A or montelukast.
- Omalizumab is the only drug approved for treatment of chronic spontaneous urticaria in patients with inadequate response to H₁-antihistamines.
- Long-term use of systemic corticosteroids should be avoided, while a short course can be tried to manage acute exacerbations.
- Several alternative therapies have been evaluated in severe recalcitrant cases, but the level of evidence for such approaches is low and their role deserves further studies.
- Novel agents are under investigation and future options may include inhibitors of skin mast cells and antagonists to mast cell activating signals.

1. Introduction

Chronic spontaneous urticaria (CSU) is a common disease characterized by the presence of wheals, angioedema or both, repeated episodes for more than six weeks, and the spontaneous occurrence of lesions, i.e. lesions that are not specifically triggered by physical-environmental factors as is the case in inducible chronic urticarias [1]. Even if generally devoid of life-threatening consequences, CSU is a disabling condition that causes a marked deterioration of the quality of life of affected patients, with a significant impact on ordinary daily activities, sleep, work capacity, social functioning, psycho-emotional aspects, and carries substantial direct and indirect health care costs [2-6].

There is a paucity of data regarding the natural history and prognostic factors in CSU. It is believed that 10% to 50% of patients have CSU for more than 5 years and that CSU duration might be predicted by disease severity [7].

The rational treatment of urticaria consists in the elimination of causal agents, but the identification of an etiology in CSU is unfortunately unsuccessful in most cases. In other words, the underlying cause of CSU in most patients remains unknown despite intensive efforts towards an etiological diagnosis. The mainstay of CSU treatment is therefore based on pharmacological interventions aimed at providing symptomatic relief and improvement of the quality of life, although the management of underlying and exacerbating factors is a desirable goal, whenever possible [8].

Autoimmune mechanisms have been implicated in the pathogenesis of CSU, at least in subgroups of patients, based on the presence of functional histamine-releasing autoantibodies and IgE antibodies to autoantigens. A screening test capable of disclosing the autoreactive nature of CSU is the autologous serum skin test (ASST), whose positivity suggests the presence of circulating histamine-releasing factors including autoantibodies [9].

Recent data support other possible pathogenic mechanisms, involving dysregulation of intracellular signaling pathways in basophils and mast cells, disturbed innate immunity response, and the activation of the extrinsic coagulation pathway [10-13]. Interestingly, consistent observations have documented the inflammatory nature of CSU with a significant increase of circulating inflammatory markers, in apparent correlation with disease severity [10,14].

This article focuses on the treatment of CSU in adult patients with special attention to standard well-established treatment approaches. These treatments are commonly used in clinical practice and recommended by the international European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA²LEN/EDF/WAO) guidelines [1], which provide a stepwise treatment algorithm for CSU management (Table 1). A brief mention will be devoted to alternative treatments as well as to future drugs in development.

The treatment of physical and other inducible urticarias is excluded from this review, as well as that of other conditions linked to urticaria for historical reasons that should not be considered true urticarial variants anymore as they are not histamine-mediated (e.g., bradykinin-mediated angioedema, urticarial vasculitis, and autoinflammatory disorders like cryopyrin-associated periodic syndromes and Schnitzler's syndrome). Moreover, this review does not deal with phototherapy, plasmapheresis, autologous whole blood or serum

therapy, herbal treatment, psychotherapy, acupuncture, diets or other non-pharmacological types of intervention.

2. **H₁-Antihistamines**

The signs and symptoms of CSU are, by and large, the result of the interaction of histamine with H₁-receptors on target structures. H₁-antihistamines (AHs) are, therefore, fundamental medications for urticaria in general, and also for CSU. AHs act as inverse agonists that interact with the H₁-receptor favouring its inactive conformation, and are traditionally distinguished into first-generation sedating drugs and second-generation AHs (sg-AHs), which are minimally or non-sedating because of their poor penetration of the blood–brain barrier. Compared to the first-generation AHs, sg-AHs are highly selective for the H₁-receptor and have a better side-effect profile. Moreover, no clinically significant cardiac effects have been reported for most sg-AHs, even at high doses [15].

Many AHs, especially the most recent ones, have been found to exert direct or indirect anti-inflammatory effects [16,17], which are more evident at high dosages in some experimental studies. This is held to be one of the effects possibly underlying the effectiveness of AH up-dosing in refractory cases [17].

The first-line therapeutic approach to CSU is the use of the modern sg-AHs, because of high-quality evidence for efficacy and safety from numerous randomized controlled trials (RCTs) [1,8,18], and because of their low cost. Modern sg-AHs should be taken continuously rather than on-demand, in order to achieve an optimal control of symptoms and prevent urticarial episodes [19].

On the contrary, the international guidelines discourage the use of first-generation AHs as they can cause sedation, have anticholinergic effects, impair cognitive and psychomotor functions and show drug interactions [1]. Nevertheless, despite these recommendations,

sedating AHs continue to be frequently prescribed in clinical practice. In fact, in a recent cross-sectional survey study among dermatologists, paediatricians and general practitioners (GPs) in Germany [20], 23% of the respondents declared to use first-generation AHs as first-line treatment for CSU (19.2% of dermatologists, 25.3% of paediatricians, and 27.8% of GPs).

A double-blind, cross-over RCT in 24 patients with difficult-to-treat CSU compared monotherapy with levocetirizine 20 mg/day and combined therapy with levocetirizine 15 mg/day plus hydroxyzine 50 mg at night for periods of 5 days [21]. Treatments were equally effective in improving urticaria activity score (UAS), night-time sleep disturbances and quality of life scores, whereas only treatment with levocetirizine plus hydroxyzine increased daytime somnolence.

Unfortunately, AHs at licensed doses are estimated to relieve symptoms effectively in less than 50% of CSU patients [2].

In patients refractory to standard doses of sg-AHs, the second step in the guidelines' therapeutic algorithm consists of a trial of up to 4-fold dosed modern sg-AHs [1], although this step corresponds to an off-label approach.

Ever-growing evidence suggests that higher doses of sg-AHs increase the rate of responders without relevant changes in the safety profile [22,23], although positive results have not been uniformly observed. In this regard, the effect of up-dosing might also be related to the *in vivo* receptor occupancy of the drug, that has been proposed as a more reliable predictor for human pharmacodynamics and antihistamine potency [23].

The efficacy and safety of up-dosing up to 4 times the conventional dose have not been systematically evaluated for all the existing sg-AHs. A few RCTs have been conducted so far, and, at present, the most convincing results have been attained with cetirizine, levocetirizine, desloratadine, and rupatadine. In a double-blind RCT [24], 80 CSU patients

were randomized to receive levocetirizine or desloratadine, starting each treatment at the conventional daily dose of 5 mg and then increased weekly to 10 mg and 20 mg, with nonresponders subsequently crossed over to 20 mg of the other drug. Approximately three quarters of patients obtained benefit from higher than conventional AH doses, without experiencing any safety problems.

The analysis of the pooled data from two RCTs in 538 CSU patients treated with different doses of rupatadine showed that rupatadine 20 mg/day resulted in a higher percentage of patients with at least 75% symptom reduction than rupatadine at the licensed dose of 10 mg/day [25]. However, in an RCT in CSU patients, rupatadine caused somnolence in 5.4% and 21.4% at daily doses of 10 mg and 20 mg, respectively (vs 2.9% in the placebo group) [26].

3. Common, recommended and established treatments for refractory cases

Patients who remain refractory to sg-AHs at standard and higher dosages require alternative treatments. CSU resistant to AH therapy has been shown to be associated with a higher incidence of angioedema and concomitant physical urticaria, more positive ASST results, higher baseline severity, and laboratory features indicative of low-grade inflammation and platelet activation [27].

The third-line treatment suggested in the therapeutic algorithm is one of the following three agents: omalizumab, ciclosporin A (CsA) or montelukast (Table 1) [1].

3.1. Omalizumab

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that has initially been licensed for the use in severe allergic asthma, and more recently received approval for the treatment of CSU in patients aged 12 years and above, who remain symptomatic despite AH

treatment. Omalizumab selectively binds to the C3 domain of the IgE heavy chain and thereby reduces serum levels of free IgE and downregulates the expression of membrane FcεRI expression on mast cells and basophils. In CSU, the mode of action of omalizumab is likely to be more complex and multifaceted [28].

The quality of evidence documenting the efficacy of omalizumab in CSU is particularly high and, in fact, it is the best-studied drug in CSU from a clinical viewpoint, together with AHs. Several studies indicated the very good safety and efficacy profile of omalizumab, but unfortunately it is very expensive like all biologicals. The results of the three pivotal phase III RCTs with omalizumab in CSU, ASTERIA I and II and GLACIAL, are summarized in Table 2 [29-31]. These RCTs did not show any new safety issue or concern for omalizumab and consistently suggested a safety profile comparable to placebo [32]. However, the majority of serious adverse events registered throughout the ASTERIA II study occurred in the group receiving the highest dose (300 mg) of omalizumab [30], and in the ASTERIA I study the proportion of patients with adverse events reported as suspected to be drug-related increased as the dose increased, without however identifying any specific event typology [29]. The GLACIAL study was designed with the primary objective to evaluate the safety of omalizumab 300 mg compared with placebo and disclosed that the overall incidence and severity of adverse events were similar between omalizumab and placebo recipients [31]. No results of long term studies of omalizumab in CSU are available as of yet, but reasonable clues that long term omalizumab is safe can be derived from the experience in allergic asthma.

A recent systematic review analyzed the cumulative results from 5 RCTs with omalizumab, which were categorized as having a low risk of bias, in a total of 1,116 CSU patients [32]. There was a statistically significant improvement in multiple measures of disease activity and quality of life following treatment with omalizumab when compared with placebo. As

compared to placebo, treatment with omalizumab was more frequently associated with both complete response (risk ratio 6.44, 95% confidence interval 3.95-10.49) and partial response ($UAS \leq 6$; risk ratio 4.08, 95% confidence interval 2.98-5.60). In dose-ranging studies, the improvement of most efficacy outcomes, including the primary endpoint, appeared to be dose-dependent, with significant and clinically meaningful effects seen with either 150 mg or 300 mg of omalizumab and with the highest response rates achieved with 300 mg [33]. A post-hoc analysis of ASTERIA II results revealed that, at week 12, patients who were completely free of hives and itching ($UAS7 = 0$) were 5% in the placebo group, and 16%, 22%, and 44% with omalizumab 75 mg, 150 mg, and 300 mg, respectively [30].

CSU studies provided interesting aspects of the activity of omalizumab in CSU, with a rapid onset of action, often evident within 1-2 weeks, and a symptomatic effect, expressed by a gradual re-occurrence of symptoms after treatment discontinuation in most patients without an apparent rebound. Clinical experience of long-term treatment beyond 6 months in CSU is limited [34,35], and prescribers are advised to periodically reassess the need for continued therapy. It is remarkable to underline that, in some case series, re-treatment with omalizumab has proved to be safe and effective [36,37]. Of note, omalizumab can help control of symptoms also in inducible urticarias [34,37], which can be associated to CSU in some cases.

3.2. Ciclosporin

Clinical experience, two RCTs, and several non-controlled studies and case series support the efficacy of CsA in severe AH-resistant CSU. The rational basis for the use of CsA in CSU is provided by the drug's multifaceted mode of action that encompasses not only its well-known immunomodulating activity but also many intrinsic anti-inflammatory effects, such as the inhibition of the release of histamine and neoformed mediators from mast cells and basophils [38]. The efficacy of CsA over placebo in CSU has been confirmed by the results of two

RCTs performed with two different CsA formulations in patients with severe unremitting refractory CSU responding poorly to AHs.

In the first study [39], 30 ASST-positive patients were randomized to receive CsA 4 mg/kg/day (n= 20), supplied as the old oral formulation, or placebo (n= 10) for 4 weeks, in combination with cetirizine 20 mg/day. A significantly greater decrease in UAS between weeks 0 and 4 was observed with CsA as compared to placebo, and 42% of patients on active treatment but none on placebo had responded at 4 weeks. The ASST response to post-treatment serum was also significantly reduced. Open-label CsA was administered to 17 non-responders and 11 responded after 4 weeks. Of the responders to randomized and open-label CsA, 26% had not relapsed over a 20-week follow-up period.

A double-blind multicenter RCT investigated the response to CsA microemulsion in 99 CSU patients, who were allocated to receive 16-week CsA, 8-week CsA + 8-week placebo, and 16-week placebo [40]. CsA was administered at the daily dose of 5 mg/kg on days 0-13, 4 mg/kg on days 14-27, and 3 mg/kg from day 28. All patients received cetirizine 10 mg/day. Fewer therapeutic failures occurred with 16-week CsA (n= 3) than with placebo (n= 11) and 8-week CsA (n= 8). After 8 weeks, the severity score was significantly improved by CsA, and patients experienced significantly greater improvement in quality of life scores with CsA compared with placebo. A significantly greater reduction in symptom scores versus placebo was still present at 16 weeks in both CsA groups. Fewer patients resorted to rescue medication in the 16-week CsA group compared with the other two treatment groups. Adverse events were reported more frequently in the CsA groups than in the placebo group, and two CsA-treated patients discontinued because of hypertension.

3.3. Leukotriene inhibitors

Montelukast has been the most studied among leukotriene antagonists, and is the most used and the only representative of this drug class included in treatment guidelines. Montelukast has the advantages of a low cost and favorable safety profile, but low-quality evidence in CSU has shown equivocal data, with an overall low efficacy [1]. Clinical experience seems to indicate that leukotriene inhibitors can be useful in patients intolerant to aspirin or to food additives or in those with positive ASST [41]. Table 3 summarizes the most important studies of montelukast in CSU [42-45].

As pointed out in a recent systematic review [46], most of the data available in CSU suggested that leukotriene inhibitors are not superior to placebo or AHs, while combination therapy with AHs appears to be more efficacious compared to AH alone. According to results obtained by Di Lorenzo et al [42] in patients with moderate CSU, however, the regular combined therapy of desloratadine plus montelukast did not seem to offer a considerable advantage over desloratadine monotherapy.

3.4. Systemic corticosteroids

There is consensus to not use systemic corticosteroids long term in CSU, because of the risk of relevant adverse effects, while a short course (max 10 days) of systemic corticosteroids can be tried to manage acute exacerbation [1].

As of today, in clinical practice, the most common drugs used to treat CSU unresponsive to AHs, especially in the event of severe flare, are systemic corticosteroids, as also mentioned by Kaplan [47]. Recent results obtained from a large US database highlighted this finding in CSU patients, with 54.7 % of them documented to have filled at least one prescription of oral corticosteroids [4]. In a cross-sectional survey involving dermatologists, paediatricians and GPs in private practice in Germany [20], oral corticotherapy was reported as the first-choice modality of CSU management by 17.9% of respondents. Of note, physicians who were aware

of the international guideline recommendations were significantly less likely to use systemic steroids.

In a retrospective analysis, the effect of a short course of oral prednisone (25 mg/day for 3 days, then 12.5 mg/day on days 4-6, and 6.25 mg/day on days 7-10) was evaluated in 86 CSU pts with little or partial response to AHs [48]. Treatment was considered effective if it resulted in the control of CSU (= minimal or no symptoms) achieved with AHs only at licensed doses for at least 1 month following the discontinuation of corticosteroid therapy. A single short course of prednisone reportedly induced remission in nearly 50% of patients, and a second course for patients with a temporary response induced remission in a further 9%, whereas less than 15% of patients did not respond at all.

A recent study in 641 CSU patients demonstrated that the initial use of oral corticosteroids did not influence the disease course as the time required to reach stable, long-term control was not decreased by adding oral corticosteroids to a single AH in the initial treatment, as well as by combining different AHs [49].

4. Alternative agents

The inconstant response of CSU to conventional AH therapy has led to the search of alternative treatments to be considered in severe refractory cases.

H₂-receptor antagonists have long been included in the traditional armamentarium for CSU treatment with the aim of reaching a stronger suppression of histamine at multiple receptor sites. Actually, the use of H₂-antihistamines in combination with old-generation AHs might result in increased serum AH concentrations, as demonstrated for cimetidine with hydroxyzine [50], but has no therapeutic rationale for the co-administration with sg-AHs that are without the risk of this pharmacokinetic interaction. A review of the existing data mostly

derived from few old and small studies concluded against a therapeutic role of H₂-antihistamines in urticaria and judged the evidence as weak [51].

The inflammatory nature and the autoimmune/autoreactive mechanisms that appear to be relevant in some patients with CSU have prompted the use of several systemic medications with anti-inflammatory and/or immunomodulating/immunosuppressive properties in patients with severe, unremitting CSU refractory to AHs, such as dapsone, sulfasalazine, hydroxychloroquine, tacrolimus, methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, intravenous immunoglobulin, and biologicals targeting tumor necrosis factor [38,41,52]. However, the overall quality of evidence to support the use of these drugs is low, because of the low number, design, size and methodological characteristics of the controlled studies performed so far [52]. For many treatments, only case reports and uncontrolled studies are available.

The demonstration of the activation of the coagulation cascade in CSU has opened new treatment perspectives and deserves more research. As of now, reports documenting the successful use of anticoagulants in CSU are limited to sporadic cases [41].

Preliminary data from a few small studies have suggested a potential role of vitamin D in CSU, based on the observation of decreased serum vitamin 25 hydroxyvitamin D levels in CSU patients and the possible adjuvant benefit of oral supplementation [53,54].

Preliminary clinical results exist for miltefosine [55], an alkylphosphocholine approved for the treatment of breast cancer metastasis and leishmaniasis. As a lipid raft modulator, this drug can inhibit mast cell activation and degranulation. The results obtained from an RCT in 76 randomized CSU patients who did not respond to standard-dosed AHs indicated that, after 4 weeks of treatment, there was a substantial reduction in UAS levels and number of wheals in miltefosine-treated patients as compared to the placebo group, even if no significant differences were observed in the intensity of pruritus.

5. Novel and future agents

Ongoing or recently completed phase I/II and phase II studies in CSU are examining the feasibility of different biologics that are licensed and used for the treatment of other chronic inflammatory conditions such as canakinumab, rituximab, and abatacept [56]. In addition, several novel agents are under investigation in CSU (Table 4). These include the IgE targeting biologics quilizumab and ligelizumab, the Syk inhibitor GSK2646264, and the Chemoattractant Receptor-Homologous Molecule expressed on Th2 cells (CRTH2) antagonist AZD1981.

Quilizumab is a humanized monoclonal antibody that specifically targets the M1 prime epitope of membrane IgE. Preclinical studies indicate that targeting membrane IgE-positive cells with antibodies against M1 prime can prevent IgE production in humans and significantly reduce the levels of serum IgE [57]. Quilizumab was assessed for its safety and efficacy in AH-refractory CSU patients in a multicenter, double-blind study. Patients received placebo or 450 mg quilizumab subcutaneously twice, four weeks apart, which was well-tolerated. While the detailed publication of the results of the study is still pending, the authors reported, at the annual meeting of the EAACI in 2015, an average reduction of approximately 25% in serum total IgE by week 20 in quilizumab-treated CSU patients, and an improvement in itch scores and urticaria activity, which, however, was not statistically significantly different from that in placebo-treated patients.

No results are available, as of yet, from the clinical trials on ligelizumab, GSK2646264, and AZD1981. Ligelizumab (QGE031B), like omalizumab, is an antibody that binds free IgE. It has shown an almost 50-fold increased affinity for human IgE as compared to omalizumab [58,59]. GSK2646264 inhibits Syk, a critical component of the mast cell activation pathway, and is currently under investigation in CSU and cold urticaria. The aim of this first in human

placebo-controlled study is to characterize the safety, local tolerability, pharmacokinetics and pharmacodynamics and efficacy of topical GSK2646264. In another ongoing placebo-controlled study, the CRTH2 antagonist AZD1981 is assessed for its safety and efficacy in the treatment of CSU patients refractory to AHs. CRTH2 is a receptor for prostaglandin D₂, which is released by activated mast cells and a recruitment signal for infiltrating leukocytes.

6. Possible future targets

Currently mast cells become an increasingly interesting area of research and many novel functions and receptors have been described. Mast cell mediator release plays a key role also in CSU and after decades of concentrating on the IgE-induced mast cell activation, a broad range of other ways of activation of mast cell degranulation has been identified. Those other ways of inducing degranulation may also explain the phenomenon of pseudoallergic reactions. These are known to play an important role in urticaria with patients reacting to drugs, e.g. nonsteroidal anti-inflammatory drugs or pseudoallergens in food, which can be both artificial additives as well as naturally occurring aromatic compounds [60,61]. Only last year the role of the MRGPRX2-receptor has been described to play a role in these reactions although this was shown in LAD-2 cells [62].

Table 5 lists a number of ligands and receptors which are now known to be involved in mast cell degranulation and could serve as targets for future drug development.

7. Expert opinion

CSU is a complex clinical entity with extreme variability in disease activity and duration, as well as response to conventional treatments. The knowledge on predictors of response and prognostic factors is limited, as is that regarding the exact pathogenesis. The identification of autoimmune mechanisms has been a great advance and has provided convincing arguments

supporting the usefulness of immunosuppressive treatments. However, the understanding in such a context is still incomplete. For instance, one of the relevant open questions is linked to the occurrence of spontaneous stable resolution of CSU symptoms in the majority of patients. CSU might be a multifactorial disease and the clinical expression results from multiple different pathomechanisms, and this can explain the divergent response to conventional and alternative treatments among CSU patients in clinical practice.

Further research on pathogenesis could promote the identification of novel therapeutic agents. Future advances in understanding the pathogenic mechanisms, including intracellular signaling leading to histamine release in mast cells and basophils, may create a rationale for targeted therapeutics. Nevertheless, the clinical experience with novel treatments and the elucidation of their mode of action in CSU might help to recognize other unidentified mechanisms.

In general, CSU management is widely heterogeneous in clinical practice and often relies upon empirical data and physician's specific clinical experience and skills. The availability of the international EAACI/GA²LENEDF/WAO guidelines for the management of urticaria has been a useful contribution for a comprehensive description of classification, diagnosis, and management options, providing a set of recommendations according to an evidence-based approach. Concerning the treatment algorithm proposed by the international guidelines in CSU, good quality evidence is available only for sg-AHs, CsA, and omalizumab. Of note, neither montelukast nor CsA are approved for the treatment of CSU. Therefore, their use in CSU, despite the recommendation made by the guidelines, is off-label, as is the use of sg-AHs at doses higher than those licensed. The interest in the up-titration of sg-AHs is, in part, related to the need to obtain further information on this approach, also for medico-legal issues.

The possible refractoriness of CSU to conventional treatments has prompted the endless search for alternative effective agents. Omalizumab has recently been added to the

armamentarium for CSU treatment, and seems to be a rapid and effective treatment, although duration of remission is variable, with some patients requiring maintenance treatment. Therefore, the optimal regimens and treatment strategies with omalizumab in the long-term should be further investigated and are likely to be tailored on an individual basis in clinical setting.

As concerns other therapeutic alternatives investigated for CSU treatment, evidence for most agents is restricted to anecdotal reports, open label studies and retrospective analyses. Furthermore, considering the available RCTs, a marked heterogeneity exists in terms of outcomes, methodology, patient populations (e.g., selection criteria, definition of CSU, definition of refractoriness), which prevents direct comparison of results from different studies.

The use of alternative agents in clinical practice has to take into account a careful assessment of the risk/benefit ratio. All these alternative agents are not approved for CSU treatment, and their long-term safety in patients with CSU is unclear. Regardless of the efficacy in the short-term, some alternative agents (e.g., anticoagulants or immunosuppressants) show a safety and tolerability profile that makes them unsuitable for protracted treatment periods.

Common limitations in many RCTs conducted in CSU patients include small sample size, short treatment duration, and absence of post-treatment follow-up.

Research on long-term treatment using standardized outcome measures and validated patient-reported measures of disease severity and quality of life is needed.

The real potential for inducing remission of CSU is unknown for the existing therapeutic agents [38], and this is an important area of research.

Novel treatments are under development and in clinical testing. More and better treatment options are needed, for CSU and chronic inducible urticaria.

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Table 1. Recommended treatment algorithm for CSU proposed by the EAACI/GA²LENEDF/WAO guidelines [1].

Step	Intervention	Considerations
First	Modern sg-AHs	Strong recommendation High-quality evidence Low cost and worldwide availability, very good safety profile, good efficacy
Second	<i>If symptoms persist after 2 weeks</i> Increase dosage up to fourfold of modern sg-AHs	Strong recommendation High-quality evidence Low cost, good safety profile, good efficacy
Third	<i>If symptoms persist after 1–4 further weeks</i> Add on to modern sg-AHs one of the following:	
	Ciclosporin	Strong recommendation High-quality evidence Medium to high cost, moderate safety profile, good efficacy
	Montelukast	Weak recommendation Low quality evidence Low cost, good safety, low efficacy
	Omalizumab	Strong recommendation High-quality evidence High cost, very good safety profile, very good efficacy
Short course (max 10 days) of corticosteroids may also be used at all times for acute exacerbations		Weak recommendation Low-quality evidence Low cost, worldwide availability, good safety profile (for short course only),

good efficacy during intake, but very low for lasting efficacy

CSU= chronic spontaneous urticaria; EAACI/GA²/LENEDF/WAO= European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization; sg-AHs= second-generation H₁-antihistamines

Table 2. Pivotal randomized placebo-controlled phase III studies with omalizumab in CSU.

Study (ClinicalTrials.gov Identifier)	Patients	Treatment	Main efficacy results
ASTERIA I (NCT01287117) [29]	319 pts aged 12–75 years with symptomatic CSU despite treatment with approved doses of AHs (one randomized patient was not treated)	Six SC injections of placebo or omalizumab 75 mg, 150 mg, or 300 mg every 4 weeks, followed by 16 weeks of follow-up	At week 12, mean weekly ISS decreased from baseline by 6.4, 6.6, and 9.4 points in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively, vs the placebo group (3.6 points). The difference between omalizumab and placebo was significant in favor of each omalizumab group. Significant improvements compared with placebo in all nine endpoints with omalizumab 300 mg, six of nine endpoints with omalizumab 150 mg, and two of nine endpoints with omalizumab 75 mg.
ASTERIA II (NCT01292473) [30]	323 pts aged 12–75 years (18–75 years in Germany) with persistent CSU despite treatment with AHs at licensed doses	Three SC injections of placebo or omalizumab 75 mg, 150 mg, or 300 mg every 4 weeks, followed by a 16-week follow-up period	Mean changes from baseline in weekly ISS at week 12 significantly improved with 150 mg (−8.1±6.4) and 300 mg of omalizumab (−9.8±6.0) but not with 75 mg of omalizumab (−5.9±6.5), as compared with placebo (−5.1±5.6). Significant difference between either 150 mg or 300 mg of omalizumab and placebo with respect to all prespecified secondary endpoints.
GLACIAL (NCT01264939) [31]	336 pts aged 12–75 years (18–75 years in Germany) with persistent CSU despite use of AHs at up to four times the approved dose plus H ₂ -antihistamines, antileukotrienes, or both	Six SC injections at 4-week intervals of placebo or omalizumab 300 mg, followed by a 16-week observation period.	The mean change from baseline in weekly ISS at week 12 was significantly improved with omalizumab compared with placebo (8.6 vs 4.0). Significant improvements were seen in all additional efficacy endpoints at week 12; these benefits were sustained

(one randomized patient was not treated).	to week 24.
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AHs= H₁-antihistamines; CSU= chronic spontaneous urticaria; ISS= itch severity score; SC= subcutaneous
The primary endpoint in the three studies was the change of weekly ISS at week 12 from baseline

Table 3. Randomized placebo-controlled studies with montelukast alone or in combination with second-generation AHs in CSU.

Study design and patients	Treatment	Efficacy measures	Main results
DB, double-dummy, parallel-group 160 pts with moderate CSU [42]	- desloratadine 5 mg/d - desloratadine 5 mg/d + montelukast 10 mg/d - montelukast 10 mg/d - placebo Duration: 6 weeks	Daily reflective and instantaneous assessment of individual items (pruritus, number of hives, size of largest hive, interference with sleep, and interference with daily activities), using 4-point scales	Early discontinuation in 27 pts in the montelukast group and 35 pts in the placebo group (0 in the other two groups). Significant superiority of all groups over placebo in terms of TSS, number of hives, and hive size (reflective evaluation). No differences between desloratadine and desloratadine + montelukast in both the reflective and instantaneous assessments. Montelukast superior to placebo with regards to TSS and number of hives (instantaneous assessment), but not different from placebo in pruritus and hive size (instantaneous evaluation), and in interference with sleep and the use of rescue medication (reflective evaluation).
SB, cross-over 30 pts with CSU refractory to AHs alone or combined with other drugs [43]	- montelukast 10 mg/d - placebo Cetirizine in each group on an "as needed" basis Two 6-week treatment periods with a 2-week washout interval	UAS Use of AHs	All pts completed the study. More significant decreases in UAS with montelukast vs placebo. AH use significantly less frequent during the montelukast period.
DB, cross-over 24 pts with CSU not controlled by AHs [44]	- montelukast 10 mg/d - placebo Addition to the usual AH therapy Two 2-week treatment periods with a 1-week washout interval	Symptom scores (number and size of wheals, angioedema). In-house severity scale (sum of pruritus, wheal number and sleep disturbance scores), Post hoc analysis with conversion into the validated UAS	Two pts excluded due to noncompliance. No difference in TSS and medication scores between the two periods. Superiority of montelukast over placebo in most severe pts (only 5!) detected by the in-house severity scale but not by UAS assessment.

DB	- desloratadine 5 mg/d + placebo	Pruritus, number of separate episodes, size and number of wheals, and patients' QoL	76 Evaluable pts. Desloratadine alone and with montelukast superior to placebo. Desloratadine + montelukast improved symptoms and QoL significantly more than desloratadine alone, without effect on the number of urticarial episodes.
81 pts with mild CSU [45]	- desloratadine 5 mg/d + montelukast 10 mg/d - placebo Duration: 6 weeks		

AH= H₁-antihistamine; CSU= chronic spontaneous urticaria; DB= double-blind; QoL= quality of life; SB= single-blind; TSS= total symptom score; UAS= urticaria activity score

Table 4. Possible novel and future treatments of CSU currently under investigation [56].

Intervention	ClinicalTrials.gov Identifier	Trial status	Last information verification	Sponsor (Collaborator)	Comments
AZD1981	NCT02031679	currently recruiting pts	Jan 2014	Johns Hopkins University (AstraZeneca)	AZD1981 is an oral, selective, reversible CRTH2 receptor antagonist
QGE031	NCT02477332	not yet open for patient recruitment	June 2015	Novartis Pharmaceuticals	QGE031 (ligelizumab) is a high-affinity humanized IgG1κ anti-IgE mAb
Quilizumab	NCT01987947	ongoing, but not recruiting pts	Sept 2014	Genentech	Quilizumab is a humanized mAb targeting specifically the M1 prime epitope of membrane IgE
Canakinumab	NCT01635127	unknown	July 2012	University of Zurich	Canakinumab is a human anti-IL-1β mAb
Rituxumab	NCT00216762	terminated	Aug 2015	Johns Hopkins University (Genentech)	Rituximab is a chimeric anti-CD20 mAb
Abatacept	NCT00886795	unknown	Apr 2013	Johns Hopkins University (Bristol-Myers Squibb)	Abatacept is a soluble CTLA-4-Ig dimeric fusion protein targeting the interaction between CD80/CD86 and CD28

Accessed December 13, 2015

The list does not include studies withdrawn prior to enrollment

CRTH2= Chemoattractant Receptor-Homologous Molecule expressed on Th2 cells; CSU= chronic spontaneous urticaria; CTLA= Cytotoxic T-Lymphocyte Antigen; IL= interleukin; mAb= monoclonal antibody

Table 5. Possible future targets

Stimulus	Receptor	Action on mast cells
IgG	Fc γ RI	degranulation
C3a	C3aR	degranulation chemotaxis
C5a	C5aR	degranulation chemotaxis
<i>S. aureus</i> protein A	Fc-receptor	degranulation
Antimicrobial peptides	GPCR	degranulation
NGF	TrkA	growth differentiation degranulation
Substance P	MRGPRX2/NK1R	degranulation
SCF	C-kit	proliferation differentiation histamine release
IL-3	IL-3R	enhances histamine and LTC ₄ release
IL-4	IL-4R	enhances IgE-induced Th2 cytokine production
Endothelin-1	ET _A	degranulation
Histamine	H4R	degranulation production of various proinflammatory cytokines and chemokines
Pseudoallergens	MRGPRX2	degranulation

IL= interleukin; LT= leukotriene; NGF= nerve growth factor; SCF= stem cell factor