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Treatment of chronic spontaneous urticaria with an inadequate response to H_1-antihistamines: an expert opinion

Chronic spontaneous urticaria (CSU) is characterized by the sudden, continuous or intermittent appearance of pruritic wheals (hives), angioedema, or both for six weeks or more, with no known specific trigger. The international EAACI/GA^{2}LEN/EDF/WAO urticaria guideline advises standard-dose, second-generation H_1-antihistamines as first-line therapy. However, H_1-antihistamine treatment leads to absence of symptoms in fewer than 50% of patients. Updosing of second-generation H_1-antihistamines (up to fourfold) as recommended by the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline as second-line therapy, can improve response, but many patients remain symptomatic. Definitions of response are often subjective and a consensus is needed regarding appropriate treatment targets. There is also an unmet need for biomarkers to assess CSU severity and activity and to predict treatment response. The EAACI/GA^{2}LEN/EDF/WAO urticaria guideline recommends add-on omalizumab, ciclosporin A (CsA), or montelukast third-line treatment in patients with an inadequate response to high-dose H_1-antihistamines. Omalizumab is currently the only licensed systemic biologic for use in CSU. Both omalizumab and CsA are effective third-line CSU treatments; montelukast appears to have lower efficacy in this setting. Omalizumab carries a label warning for anaphylaxis, although no cases of anaphylaxis were reported in the phase III trials of omalizumab in CSU and it is generally well tolerated in patients with CSU. Omalizumab arguably has a better safety profile than CsA.

Key words: chronic spontaneous urticarial, H_1-antihistamines, omalizumab, response, treatment

Urticaria is a manifestation of a heterogeneous group of diseases, characterized by the sudden appearance of pruritic wheals (hives) and/or angioedema [1-5]. The lifetime prevalence rate is 8.8% for all types of urticaria [6]. Chronic urticaria (CU) is characterized by the continuous or intermittent eruption of short-lived hives, angioedema, or both for six weeks or more [2]. The lifetime prevalence for CU is 1.8% [6], with a point prevalence of approximately 0.1% in Sweden [7] and 0.6% in Spain [8]. Approximately 79% of patients with CU are female [9].

CU can be classified as chronic spontaneous urticaria (CSU) (66-93% of patients), or chronic inducible urticaria (CIndU). CSU is the spontaneous development of signs and symptoms with no known specific trigger [2]. CSU and CIndU may co-exist in the same patient [1,2]. CSU is a frequently debilitating disease that can have a profound effect on patients' quality of life (QoL) [2, 10-12], with the presence of angioedema often leading to further impairment [10, 13].

While CSU is considered a self-limiting illness with a variable time course, a systematic review of studies describing the disease's natural time course showed variability between publications; this heterogeneity may be due to differing populations and definitions of remission [14]. Five-year remission rates (from diagnosis or symptom onset) have been shown to be 34-86% [15-17]. The current guideline-recommended first-line therapy for CSU is licensed doses of second-generation H_1-antihistamines [2]. Second-generation H_1-antihistamines at up to four-times the licensed dose are recommended second line, and add-on omalizumab, ciclosporin A (CsA) or montelukast are third-line options [2].

To gain insight and recommendations around the treatment options for patients with CSU with an inadequate response to H_1-antihistamines and the comparative efficacy and safety of available third-line treatment options, a meeting was held in Zurich, Switzerland, on 6 May, 2015. The meeting hosted nine CU expert physicians. Here, we

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report the topics discussed during the meeting and evidence-based consensus about inadequately controlled CSU and third-line treatment approaches.

Inadequately controlled CSU

Barriers relating to pharmacological treatment

Periods of increased disease activity, including periods of the disease being inadequately controlled by H_1-antihistamines, can occur unpredictably within the same patient with CU. In randomized controlled trials, therapy with H_1-antihistamines leads to an absence of symptoms in fewer than 50% of patients with CSU [3, 18]. Patients' CSU may be inadequately controlled by H_1-antihistamines for many reasons. While histamine is a major factor in the development of CSU, allergic-like disorders characterized by a prominent cellular infiltrate often require additional treatment approaches [19]. In extremely rare cases, H_1-antihistamines were reported to induce urticaria and lead to worsening of CSU [20-22]. Importantly, different responses can occur in the same patient but in different periods of the disease [3]. Each patient must be re-evaluated over time for control of their CSU, and changes in pharmacological treatment regimens may be necessary [2, 23].

Barriers relating to healthcare systems

ASSURE-CSU (an observational study of the economic and humanistic burden of CSU in 673 patients across seven countries, in 64 centres) assessed disease impact and healthcare resource utilization due to CSU [24]. The study reported a mean delay between CSU symptom onset and diagnosis of two years (1.5 years in Germany and 2.9 years in the UK and Canada) [25], highlighting the suboptimal patient journey; a clear additional barrier to controlling CSU symptoms.

Patients with inadequately controlled CSU are often treated by specialists rather than general practitioners. In many healthcare systems, patients with CSU initially present to primary care practitioners. Studies suggest that patients will see an average of two physicians before being referred to a specialist [26]. Moreover, some of these specialists are not experts in CU; fewer than one-third of physicians report being familiar with the international urticaria guideline [27]. Prior to specialist review, only 11% of CSU patients receive EAACI/GA^{2}LEN/EDF/WAO guideline-recommended first-line treatment [28]. This suggests that there is still a need for education regarding the existence and use of the international urticaria guideline.

Guideline-based management resulted in a good outcome in 78% of a cohort of Northern Irish patients who were severely affected with CSU [28]. Following specialist review, second-generation H_1-antihistamines were found to be the main pillar of specialist management and were used at higher than the licensed dose in 67% of cases, with 29% of patients requiring therapy in addition to high-dose, second-generation antihistamines [28]. These data indicate specialist compliance with stepwise EAACI/GA^{2}LEN/EDF/WAO guideline-based management. However, it should be noted that country-specific differences in treatments used are an important consideration when trying to understand the journey of a patient whose disease is inadequately controlled by H_1-antihistamines.

Barriers relating to patients with CSU

Some patients withdraw from treatment when their CSU is asymptomatic. As treatment for CSU is often necessary over long periods of time (months to years), patient compliance tends to be difficult to achieve, especially when high doses of H_1-antihistamines are combined with third-line treatment. Patients may not want to take more than the licensed dose of H_1-antihistamines or may not be suitable for other treatment regimens (such as CsA, which may be unsuitable for patients with hypertension, hepatic or renal impairment, or a history of malignancy). The EAACI/GA^{2}LEN/EDF/WAO urticaria guideline advises that CSU is managed by obtaining complete symptom control as fast as possible, and that patients should be treated until the disease is gone [2].

Possible solutions

Possible solutions to an inadequate response to H_1-antihistamines include updosing, switching H_1-antihistamines, or combining H_1-antihistamines, although only updosing is recommended in the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline. In our clinical experience, updosing H_1-antihistamines beyond the product licence can have benefits for some individuals, but may increase side effects such as drowsiness. Patients need to be counselled accordingly. Increasing the dose of second-generation H_1-antihistamines has been shown to improve treatment responses [28], but every third to fourth patient will still remain symptomatic. The international urticaria guideline recommends updosing H_1-antihistamines up to fourfold, but not to further increase the dose [2].

It is known that different H_1-antihistamines exhibit different pharmacokinetic and pharmacodynamic properties, so it cannot be excluded that switching H_1-antihistamines might lead to different disease outcomes [29, 30]. Patients may be offered a choice between two or more second-generation H_1-antihistamines, as differences in response and tolerance have been reported [2, 31, 32]. A multicentre study is needed to compare effectiveness of different second-generation H_1-antihistamines in CSU and against histamine-induced wheal and flare responses in the same patients [33]. A Cochrane analysis of 73 randomized clinical studies with H_1-antihistamines reached the same conclusion, as it was not possible to directly compare different therapies [34].

Combining H_1-antihistamines is unlikely to be effective in the treatment of inadequately-controlled CSU, as increased plasma concentrations of H_1-antihistamines may force the compounds to compete for the same receptors [35, 36]. The EAACI/GA^{2}LEN/EDF/WAO urticaria guideline recommends updosing second-generation H_1-antihistamines up to fourfold instead of combining different H_1-antihistamines, although more data are needed [2].

Definition of treatment response

The EAACI/GA^{2}LEN/EDF/WAO guideline recommends aiming for complete symptom control in urticaria [2]. As treatment of CSU is commonly over a long period of time and CSU should be treated until the present active episode (or the disease) is gone, the best treatment should be effective and well-tolerated.

Patient-reported outcome (PRO) measures of CSU activity and treatment response

Different PRO measures are available, and can be used either alone or in combination, to assess disease activity and guide assessment of treatment efficacy in CSU patients. These include the seven-day Urticaria Activity Score (UAS7) and the Urticaria Control Test (UCT) [37-39].

The UAS7 is a validated scoring system based on the once-daily recording by patients of both itch severity and the number or area of hives, over a period of seven days. The potential total score ranges from 0 (no itch/no hives) to 42 (most severe disease activity) [2,40]. The UAS7 has been transculturally translated and validated in various languages, for example Spanish [41].

The UCT comprises four questions regarding urticaria symptoms and impact on the patient's life, and these questions should be asked every four weeks. A score of $\geq$12 indicates the patient's symptoms are well-controlled [39]. Since June 2015, the UCT is available in English, German, Spanish, and Russian, among other languages [42, 43].

Recommendations for assessing CSU activity and treatment response

The international urticaria guideline recommends the use of UAS7 to measure disease activity and monitor response to treatment [2]. For patients with recurrent angioedema, the Angioedema Activity Score (AAS) is also available [44]. National Institute of Health and Care Excellence (NICE) guidelines (UK) recommend that "objective" disease activity assessment is undertaken (*e.g.* using UAS7) [45]. Ideally, UAS7 should be considered every week across the entire relevant treatment period. From a clinical point of view, knowing how the UAS7 was modified during the whole treatment period is useful and more accurate for assessment of efficacy.

In reality, the definition of complete response to treatment can be subjective, with differences between different physicians and countries. Typically, UAS7 = 0 represents no active disease and UAS7 = 1-6 "well-controlled disease" (low disease activity) [12]. Increasing disease activity, as measured by UAS7, has been shown to be associated with increased impact on patients' health-related QoL [12]. The UCT has no definition of complete response, although a UCT score of $\geq$12 represents well-controlled disease and a UCT score $\leq$11 poorly-controlled disease [39]. While "0" would be an ideal post-treatment UAS7 response, few individuals with CSU remain itch-free for seven consecutive days and the course of CSU can be unpredictable. Hence, this target may be difficult to achieve. A number of different definitions for "response" have been used in the literature (*table 1* table 1), but generally physicians consider a score of UAS7$\leq$6 (two standard deviations below mild activity) or UCT $\geq$12 [39] to be an adequate objective. It is important to empower patients and consider their opinion regarding their current disease activity and the risk of treatment-related adverse events they are willing to accept, particularly when considering a change in treatment strategy.

It should be noted that scores such as the UAS7 may not have been used previously in routine clinical practice by all physicians. Instead, they may have chosen to rely on assessing response based on prior clinical experience, particularly in patients with less severe disease. This is perhaps reflected in greater use of clinical judgement to define treatment response in real-world studies compared with clinical trials (*table 1*). We consider the routine use of UAS7 or UCT symptom scores to be best practice when monitoring CSU activity and treatment responses, and recommend their use by all physicians, as advised by the international guideline [2].

Biomarkers of CSU activity

There is an unmet need for biomarkers to assess CSU severity and predict treatment response. Plasma levels of

Table 1. Response data and definition of response for clinical trials and real-world studies of omalizumab in inadequately-controlled CSU [53, 57, 58, 62, 63, 68, 69, 95-97].

Clinical trials	Dose	Responders	Definition of response	Treatment duration
X-CUISITE	75-375 mg	70%	UAS7 = 0	24 weeks
MYSTIQUE	300 mg	40%	UAS7-90%	4 weeks
	300 mg	36%	UAS7 = 0	4 weeks
ASTERIA I+II	300 mg	59%	UAS7$\leq$6	12 weeks
	150 mg	41%	UAS7$\leq$6	12 weeks
GLACIAL	300 mg	52%	UAS7$\leq$6	12 weeks
Real-world evidence				
Metz *et al*. (2014) [69]	150-300 mg	83%	UAS7-90% + no Ahs	NS
Rottem *et al*. (2014) [96]	300 mg	77%	Clinical judgement	NS
	150 mg	36%	Clinical judgement	NS
Sussman *et al*. (2014) [97]	150 mg	69%	UAS7 = 0	Various
Labrador-Horillo *et al*. (2013) [68]	150-300 mg	82%	Clinical judgement	NS

Ahs: antihistamines; NS: not specified; UAS7: 7-day Urticaria Activity Score; UAS7-90%: 90% improvement in UAS7.

D-Dimer (a marker of fibrinolysis, which may be increased as a result of eosinophil activation in CU) have been proposed as a candidate prognostic marker [46]. Other candidate biomarkers include substance P, interleukin-6, C-reactive protein, metalloproteinase-9, and basophil CD203c [47, 48]. However, these have yet to be validated as biomarkers for CU and their predictive capacity is not yet defined [36, 47-49].

First-line treatment

The 2013 EAACI/GA^{2}LEN/EDF/WAO urticaria guideline recommends second-generation H_1-antihistamines at licensed doses for the first-line treatment of CSU [2]. These medications should be taken continuously at the lowest necessary dose rather than on demand [2]. As mentioned previously, this treatment with licensed doses of H_1-antihistamines leads to an absence of symptoms in fewer than 50% of patients with CSU [3].

Second-line treatment

If CSU symptoms persist after two weeks of treatment with licensed doses of second-generation H_1-antihistamines, the use of these medications at up to four times the licensed dose is recommended second line [2]. This dose increase results in a higher degree of efficacy in some, but not all, patients, with up to one third of patients remaining symptomatic [3]. Patients should be counselled regarding potential side effects, such as drowsiness.

Third-line treatment

If a patient's CSU symptoms persist after 1-4 weeks of second-line treatment, add-on omalizumab, CsA, or montelukast are recommended as third-line options [2]. It should be noted that some physicians have argued for timelines leading up to the introduction of third-line treatments to be more flexibly formulated. Short courses (maximum 10 days) of corticosteroids may be used at any time if disease exacerbations require this [2].

Omalizumab

Omalizumab is a recombinant, humanized, anti-IgE monoclonal antibody that targets the C3 domain of the Fc region of IgE, reducing the levels of free IgE by sequestration [1, 50, 51]. This reduction in IgE decreases mast cell activities and inflammatory mechanisms mediated by these cells [52]. Omalizumab has been shown to be efficacious in clinical studies of patients with CSU, as well as investigator-led trials and case studies in patients with CIndU [53-61]. ASTERIA I, ASTERIA II, and GLACIAL were phase III clinical studies designed to assess the efficacy and safety of omalizumab. In ASTERIA I and II, patients received omalizumab at doses of 75, 150 or 300 mg or placebo every four weeks for six doses (ASTERIA I) or three doses (ASTERIA II). Patients were observed for an additional 16 weeks after treatment. In the GLACIAL study, 300 mg omalizumab or placebo were administered every four weeks for six doses, followed by a 16-week observation period [53, 58, 62].

Efficacy

At Week 12 in ASTERIA II, 44% of CSU patients in the omalizumab arm (300 mg) were itch- and hive-free (UAS7 = 0), compared with only 5% of subjects in the placebo arm [58]. In GLACIAL (omalizumab 300 mg), 52% of patients demonstrated UAS7 $\leq$6 at 12 weeks compared with 12% in the placebo arm; additionally, 34% of omalizumab-treated patients were itch- and hive-free (UAS7 = 0) at 12 weeks as compared with 5% of placebo-treated patients [53]. Pooled data from ASTERIA I and ASTERIA II demonstrated similar efficacy and safety for omalizumab in CSU to that seen in the GLACIAL study, suggesting that background therapy in patients with inadequately-controlled disease does not affect response to omalizumab [63]. Patterns of response to omalizumab were also similar in the three studies [64]. Responses, which occurred in a dose-dependent manner and were highest with the 300-mg dose, were observed early (before four weeks) and persisted to 24 weeks [64]. At Week 12, the number of omalizumab-treated patients with UAS7 $\leq$6 in all three studies ranged between 52% and 66%, as compared with 11-19% in placebo-treated patients [64]. In patients receiving 300 mg of omalizumab for 24 weeks of treatment, median time to achieve a UAS7 $\leq$6 was six weeks (ASTERIA I and GLACIAL) and median time to achieve UAS7 = 0 was 12 or 13 weeks (ASTERIA I and GLACIAL, respectively) [64]. Some patients who achieved well-controlled urticaria or a complete response sustained this throughout the treatment period [64]. Omalizumab has also been shown to markedly improve health-related QoL in patients with CSU, as measured using PROs, such as the Chronic Urticaria Quality of Life questionnaire (CU-Q$_2$oL) [65]. Omalizumab was approved in the EU and the USA in 2014 as add-on therapy for the treatment of CSU in adult and adolescent ($\geq$12 years) patients with inadequate response to H_1-antihistamine treatment [66, 67].

In the real-world setting, responder rates for omalizumab are often >80% [68, 69]. Results from different trials are difficult to compare due to the aforementioned lack of a standard definition of response. In a retrospective analysis of 110 patients with CSU treated in nine hospitals with omalizumab (compassionate use), 93 patients (81.8%) had a significant or complete response (minimal symptoms with no need for rescue medication, or disappearance of hives and pruritus), 12 patients (10.9%) had a partial response (reduction of more than one level of therapy compared with baseline), and eight patients (7.2%) showed no response [68]. Forty-one patients (37.3%) stopped omalizumab (after 1-18 months) because of a good response. Twenty patients (47.5%) were retreated with omalizumab due to recurrence of symptoms and 18 (90%) of these regained well-controlled disease. Twenty-one (19.1%) of the patients were asymptomatic [68]. In another analysis, the most striking feature of omalizumab treatment for CSU was its rapid onset of action (57% of responders showed complete response [defined as reduction of >95% in UAS7]

within one week of the first injection; and a further 29% within four weeks) [69]. Data from UK specialist centres prescribing omalizumab (five centres) or CsA (three centres) for CSU reported changes in disease severity, with over three quarters (77%) of evaluable omalizumab-treated patients achieving a 75% reduction or more in UAS7 score, and 68% achieving UAS7 = 0 [5]. In the same study, a greater proportion of omalizumab-treated patients achieved ≥75% or ≥90% improvement in Dermatology Life Quality Index (DLQI) compared with CsA-treated patients (≥75% DLQI improvement achieved by 79% with omalizumab *vs* 41% with CsA; ≥90% DLQI improvement: 64% *vs* 18%; no statistical comparisons reported) [5]. These findings suggest that omalizumab treatment may be more effective than CsA in improving patient QoL.

In many clinical studies, the response rate is determined using UAS7, and scores are often lower than in real-world studies. This may be due to off-label dosing periods in the real world (such as three-weekly rather than monthly administration of omalizumab), which may allow symptoms to be controlled more effectively. More real-world data regarding the rate of failure of omalizumab therapy are needed, and an examination of existing data with regard to responders in sub-populations (such as "super-early responders") would also be useful. When examining response, the observation period between UAS7 assessments should be noted as symptoms return in some patients as they reach the four-week dosing interval. It should be noted that the definition of response to omalizumab treatment using UAS7 can differ from one clinical study to the next and has included UAS7 hives component only, UAS7-90%, UAS7 = 0, or UAS7≤6. A consensus definition of response/non-response is required.

Safety

Omalizumab has a well-established safety profile [1, 57, 69]. The most common adverse events include headache (6.1%), sinusitis (4.9%), arthralgia (2.9%), and injection-site reaction (2.7%) [1]. No events of anaphylaxis were reported in ASTERIA I and II or GLACIAL in the CSU population (note: anaphylaxis reactions have been observed in 0.2% of patients with asthma) [1, 63]. When recording side effects, awareness that some supposed side effects may actually represent delayed onset of efficacy is required for greater accuracy.

Summary

Despite there being some outstanding knowledge gaps for omalizumab (including its efficacy in patients with angioedema but no hives; mode of action, long-term use, efficacy and safety in children with CSU; definition of responders/non-responders; and predictors of response to treatment and time to response), there is already a considerable amount of high-quality data supporting the safety and use of omalizumab for treatment of CSU in the third-line setting [1, 61, 70, 71]. Retreatment with omalizumab can be effective and well-tolerated in patients with CSU who had previously benefited from this treatment, but who had stopped receiving it [68, 72]. Omalizumab has also been shown to be an effective treatment for inducing and maintaining long-term remission in patients with severe CSU [73-75]. The ongoing phase III OPTIMA (efficacy of optimized retreatment and step-up therapy with omalizumab in CSU patients) and phase IV XTEND-CIU (Xolair® treatment efficacy of longer duration in chronic idiopathic urticaria) studies will help address some of the knowledge gaps outlined above. In the OPTIMA study, CSU patients whose disease was clinically well-controlled with their initial 24-week treatment of omalizumab (150 or 300 mg) will receive retreatment with 150 or 300 mg of omalizumab on relapse (NCT02161562). The XTEND-CIU study aims to evaluate omalizumab treatment efficacy after 48 weeks compared with 24 weeks (NCT02392624). Given the high level of evidence and its license for use in CSU, omalizumab should be the preferred option.

Ciclosporin A

CSU is an immune-mediated disorder that is driven by mast cells and may involve activated T-cells. In CU skin biopsies, there is increased infiltration of CD4+ T-cells, monocytes, neutrophils, and eosinophils [76]. As such, CsA could be a suitable drug for the treatment of CSU as it directly inhibits mast cell degranulation as well as targeting T-cells [77, 78]. Similarly, CsA directly inhibits part of the basophil histamine release assay (BHRA) [79, 80]. Response of autoreactive CSU to CsA has been associated with disappearance of autoantibodies [80] and CsA may be disease-modifying in these patients [81].

Efficacy

Low-dose CsA treatment (3 mg/kg per day or less) has been shown to cause full remission of symptoms in a number of different randomized controlled trials and real-world studies [77, 80, 82, 83]. After 12 weeks' treatment with low-dose CsA for severe CSU, 13/19 (68%) patients were in full remission, while the remaining six (32%) had mild urticaria, as assessed by an urticaria scoring system, and required only antihistamine treatment. Most responders showed beneficial effects after one week of treatment. However, in one patient, a mild rise in serum creatinine was detected at the end of treatment (returning to normal within two weeks) and another complained of agitation and sleeplessness, which disappeared when medication was reduced to 2 mg/kg per day [77]. In a separate trial, full remission or moderate benefit was documented in 62/100 (62%) patients with CSU after three months of low-dose CsA treatment [82]. In the same study, 38% of patients discontinued CsA therapy (16.5% due to severe side effects) [82].

UK specialist centres prescribing omalizumab (five centers) or CsA (three centres) for CSU reported 10 (17%) patients who were symptom-free, improved symptoms in 33 (55%) patients, and no response in 17 (28%) patients receiving CsA. At that time, the UAS7 was not used to assess response to CsA. Potential adverse events were documented during CsA treatment for 28 (39%) patients: 24 (53%) of the 45 events were rated mild, 16 (36%) episodes were moderate, three (7%) episodes were rated severe, and two (4%) were considered not to be applicable (due to pregnancy). Thirty adverse events (61%) were judged to be "possibly related" to CsA treatment [5].

A positive Autologous Skin Serum Test (ASST) result can be associated with, but is not necessarily predictive of, successful CsA treatment [77, 84]. A positive BHRA may similarly be a marker of CsA response [81]. D-Dimer may also be a marker of response for CsA treatment as patients with severe CU have elevated D-Dimer levels [85, 86], although further investigation is required.

Safety

Potential side effects associated with CsA treatment necessitate that physicians monitor blood pressure and renal function in patients receiving it for CSU [19]. Commonly reported adverse events with CsA include hypertension, fatigue/tiredness, gastrointestinal problems, and headache [5]. With CsA use in transplant patients there is a concern regarding possible non-melanoma skin cancer. However, patients with CU may differ in their intensity and length of exposure to CsA [82].

Summary

Overall, despite the side effects, CsA treatment is supported by data from several clinical studies and is therefore also recommended by the EAACI/GA^{2}LEN/EDF/WAO urticaria guideline as third-line treatment. Our suggestion is to retain CsA as a short-term treatment option for use in omalizumab non-responders. CsA is not currently licensed for the treatment of CSU.

Leukotriene receptor antagonists

Histamine is a key mediator of mast cell degranulation, but leukotrienes, cytokines, and prostaglandins also play important roles. Cysteinyl leukotrienes are potent proinflammatory mediators, the effects of which can be blocked by leukotriene receptor antagonists (LTRAs), such as montelukast, zafirlukast, and pranlukast [87].

Efficacy

LTRAs alone are not superior to antihistamine therapy, although most trials have demonstrated that LTRAs alone generally have greater efficacy than placebo [87]. Combination therapy of LTRAs and antihistamines appears to be more efficacious for the treatment of CSU than antihistamines alone [87]. However, overall, the picture for LTRAs as add-on therapy for CSU is not clear. Some studies show no added benefit for montelukast as an add-on to H_1-antihistamines [88], while some show only marginal benefits: for example, desloratadine plus montelukast was shown to have no significant effect on the number of episodes of urticaria whilst improving symptoms and QoL in one small study [89]. Overall, the addition of LTRAs to H_1-antihistamines is a useful treatment option, especially if omalizumab is not available in the relevant country or if CsA is contraindicated or not tolerated [90].
Combination therapy of antihistamines plus LTRAs may be more effective in patients with aspirin and other non-steroidal anti-inflammatory drug-exacerbated CSU and in patients with a positive ASST [91]. There are some possible biomarkers for treatment efficacy of montelukast, including the levels of blood eosinophils or reduction of blood basophil levels [92]. Although these biomarkers could be a useful indicator of low-level inflammation, simple treatment regimens with licensed doses of H_1-antihistamines would reduce the level of inflammation to below detection levels and, consequently, they may not be suitable for severe disease where third-line treatments are required. As seen with the other third-line treatments for CSU, there is a continued need for validated biomarkers for treatment efficacy.

Safety

LTRAs appear to be well-tolerated, with a good side-effect profile [87].

Summary

The level of evidence to support the use of LTRAs is low. Given their good tolerability profile and cost, the panel would recommend LTRAs as a third-line add-on treatment in cases where omalizumab is not available, although they may not be effective in all cases. It should be noted that UK NICE guidance requires LTRAs to be evaluated in an individual with CSU before proceeding to omalizumab [45]. Montelukast is not currently licensed for the treatment of CSU.

Other potential treatments

Other possible third-line options for the treatment of CSU are supported by low levels of evidence as defined by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (see EAACI/GA^{2}LEN/EDF/WAO guideline for more details) (*table 2*) [2, 93, 94].

Table 2. Quality of evidence and strength of recommendation for use of intervention in CSU, based on the GRADE system [93].

Drug	Quality of evidence	Strength of recommendation
H_2-antihistamines	Moderate	Weak (+)
Oral corticosteroids (short course)	Low	Weak (+)
Oral corticosteroids	Very low	Strong (-)
Anti-inflammatory agents (dapsone, sulfasalazine, hydroxychloroquine, colchicines, mycophenolate mofetil)	Low-very low	Weak (+)
Immunosuppressive agents		
Methotrexate	Very low	Weak (+)
Cyclophosphamide	Very low	Weak (+)
Intravenous Ig	Low	Weak (+)

(+) recommendation for medication; (-) recommendation against medication.; Ig: immunoglobulin.

Table 3. Profiles of omalizumab, CsA, and LTRA as add-on third-line treatment for CSU [2, 5, 70, 94].

Drug	Efficacy	Safety	Quality of evidence
Omalizumab	High	Good	High (+)
CsA	High	Moderate	Moderate (+)
LTRA	Low	Good	Low (+)

(+) recommendation for medication. Quality of evidence and strength of recommendation for use of intervention are based on the GRADE system. CsA: ciclosporin A; LTRA: leukotriene receptor antagonist.

Issues for the future

The treatment of different subtypes of CSU should be explored further. It will also be interesting to determine whether third-line treatments can be stratified according to CSU disease severity or response versus non-response to treatment. To aid this, the rate of non-response should be compared between different third-line treatments. While CSU is the most likely diagnosis in patients with recurrent hives and/or angioedema, differential diagnoses are possible [2]. A key reason for non-response is misdiagnosis and, as such, the diagnosis of treatment non-responders should be reviewed [2].

In conjunction with ASSURE-CSU study data, results from the phase IV AWARE study (NCT02435238) will be of benefit regarding the pool of knowledge for CSU. This is a prospective, observational, non-interventional study with the aim of assessing the burden of disease in patients with CU and recording the therapies used in daily clinical practice, as well as the impact they have on the QoL and work productivity of individual patients. Primary outcome measures for AWARE are responses to PRO questionnaires (QoL, work productivity, and changes in disease) from patients receiving different treatments.

Conclusions

There is a need for validated biomarkers for CSU activity. In the absence of such biomarkers, changes in PRO measures, such as UAS7, are useful, and can be recommended for monitoring treatment efficacy and responses.

Both omalizumab and CsA have been shown to be highly effective in treating CSU (*table 3* table 3), with the efficacy of omalizumab supported by stronger evidence [70, 94]. Clinician-documented assessment of response to treatment suggests that more omalizumab-treated than CsA-treated patients achieve a complete absence of symptoms [5].

Guideline-driven management of CSU is recommended, although this may be impacted by considerations relating to reimbursement, availability, and experience. Where appropriate or in the absence of definitive local guidelines, the strength and level of available evidence indicate that omalizumab should be selected for the treatment of CSU in the third-line setting.

In conclusion, omalizumab, the only drug currently approved for use in H_1-antihistamine-refractory CSU, is an effective and well-tolerated third-line option for CSU. Omalizumab may have favourable efficacy and tolerability to CsA and montelukast in this setting; prospective, head-to-head studies would be informative. ■

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