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REVIEW

Chronic Spontaneous Urticaria: How to Measure It and the Need to Define Treatment Success

April W. Armstrong · Weily Soong · Jonathan A. Bernstein

ABSTRACT

Chronic spontaneous urticaria (CSU) is a complex skin disease characterized by the spontaneous appearance of wheals, angioedema, or both, for more than 6 weeks. Many patients experience a relapsing–remitting disease course for years. Owing to the unpredictability of wheal recurrence and the severity of pruritis, patients suffer considerable impairment in their quality of life. Physicians face multiple challenges, not least of which is a lack of clear guidance on what constitutes "treatment success". There is a lack of awareness of which measures should be used to best assess the various aspects of CSU, including disease activity, disease control, and quality of life—which themselves each comprise multiple components—and how to apply the results of each score to treatment decision-making. Although the overarching aim of treatment is for patients to be completely free of signs and symptoms of CSU, a more realistic definition of "treatment success" is needed to guide ongoing, long-term disease management for each individual patient. In this review, we consider what lessons can be learned from the current evidence base to provide further direction toward a universal definition of "treatment success".

Keywords: Medical dermatology; Outcome measurement; Patients; Quality of life; Urticaria

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a skin disease characterized by the spontaneous appearance of wheals, angioedema, or both, for more than 6 weeks [1]. Urticaria is a common complaint within dermatology and allergy/immunology practices, with 0.6–1.0% of the population suffering from CSU [2]. Average time from symptom onset to diagnosis has been reported as 2 years [3]; the diagnostic process includes assessment of cofactors, comorbidities, predictive measures of disease activity, and treatment response [1, 4].

Although the pathogenesis of CSU is not fully understood, it is thought to be caused by autoimmune mechanisms of mast cell activation and subsequent release of immune mediators such as histamine [4]. Current evidence indicates three subtypes of CSU: type I (autoallergic), which is mediated through immunoglobulin (Ig)E; type IIb (autoimmune), which is mediated primarily through IgG autoantibodies; and CSU due to unknown causes [4]. Although the clinical profile of these endotypes remains to be fully characterized, evidence suggests that patients with type IIb CSU have higher disease activity [5, 6].

Disease duration is typically 1–5 years [7] and likely longer for patients with more severe disease, especially those with a relapsing–remitting disease course [7, 8]. Although certain clinical characteristics and biomarkers have been associated with disease activity, disease duration, and treatment response [9], none have been validated; this means considerable variability in managing patients with CSU both across and within specialties, emphasizing the need for additional biomarker research.

The most recently updated guidelines for urticaria management are the international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines [1], which were developed in conjunction with, and are endorsed by, the American Academy of Allergy, Asthma & Immunology, the American Academy of Dermatology, and the American College of Allergy, Asthma, and Immunology, among other organizations. The treatment algorithm for CSU includes first-line, standard-dose, second-generation H$_1$-antihistamines (H$_1$-AH); subsequent treatments include up-dosed H$_1$-AH, omalizumab, and cyclosporine [1]. However, it remains unclear how broadly this treatment algorithm is implemented in practice, with many physicians solely relying on their clinical experience [10]. Treating patients with additional therapies such as leukotriene antagonists (montelukast) and H$_2$-antagonists, which have limited evidence relating to their efficacy [1, 11], delays the use of more effective treatments and prolongs patients' suffering. This problem may be especially prevalent in patients seen by multiple physicians, with many presenting initially in the primary or urgent care setting before eventually being referred to allergists and/or dermatologists [3, 10, 12].

Physicians are currently faced with many challenges in managing patients with CSU.

There is a lack of clarity concerning the clinical importance of several objective (i.e., biomarkers) and subjective (i.e., patient-reported outcome [PRO]) measures used to assess the activity, control, and impact of this multifaceted disease.

For physicians and patients, the treatment aim is to achieve and maintain a state of remission. However, with a large proportion of patients unable to achieve this [8, 13], there is a need for structured, practical, and realistic guidance of progress towards remission, i.e., "treatment success". In this article, we evaluate the most common treatment targets in published literature and clinical trials to provide further direction toward a universal definition of "treatment success".

METHODS

This article is based on previously conducted studies and does not contain any new studies with human participants or animals that were performed by any of the authors. Initial searches were performed in PubMed using the terms "chronic spontaneous urticaria" and "treatment" in the title or abstract. Papers published within the past 5 years were included in the initial screen. Searches were extended and supplemented as needed on the basis of the initial literature review, author expertise, and relevance. The figures have been reproduced with permission from Zuberbier T, et al. The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77:734–766. © 2022. John Wiley & Sons.

What Measures Are Used in the Literature?

An extensive range of PROs are used to determine disease activity, disease control, and the impact of CSU on a patient's quality of life (QoL). These measures include the weekly Urticaria Activity Score (UAS7), weekly Angioedema Activity Score (AAS7), Urticaria Control Test (UCT), Angioedema Control Test (AECT), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), Dermatology Life Quality Index (DLQI), and Angioedema Quality of Life Questionnaire (AE-QoL) (Table 1) [2]. This section aims to evaluate the PROs recommended by the EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines, those frequently used by physicians, and the measures most prevalent in clinical trials.

Treatment Targets Set by International Guidelines

Currently, there is no curative therapy for CSU; existing treatments purport to control disease activity and prevent symptom recurrence [8, 14, 15]. Guidelines provide more clarity on achieving disease control than predicting recurrence [1], which is a major clinical question.

The measures described in the EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines include UAS7 and/or AAS7 for disease activity, UCT and/or AECT for disease control, and CU-Q2oL and/or AE-QoL for the impact of CSU on a patient's QoL (Table 1). Guidance is given on which measures should be used in particular patient populations (e.g., patients who develop wheals, with or without angioedema). The usability of measures in different settings (i.e., clinical trials, routine clinical practice) is also considered, e.g., use of the four-item UCT as a measure of disease control in routine clinical practice due to ease of administration and a clearly defined cutoff for patients with "well-controlled" versus "poorly controlled" disease [1].

Treatment targets in CSU entail complete symptom control (UAS7 = 0) and normalizing QoL. A UAS7 = 0 score is defined as "complete control", yet many patients do not reach this target [3, 16]; should we be asking whether this is an appropriate target for all patients with CSU? Moreover, a paradigm of "adjust, assess, and act" involves continuously assessing a patient's disease status (using UCT) to determine whether treatment adjustments are required (Figs. 1, 2) [1], but recommendations

Table 1 Patient-reported outcomes

PRO	Format (time span)	Domain	Scoring system[a]	Scoring range	Correlating response	MCID
Disease activity						
UAS7 [23, 43]	Diary (based on the last 7 days)	Pruritus intensity and number of hives	0–3	0–42[b]	0 = Itch and hive free 1–6 = Well-controlled 7–15 = Mild activity 16–27 = Moderate activity 28–42 = Severe activity	9.5–10.5
AAS7 [53, 54]	Diary (based on the last 7 days)	Severity of physical discomfort, ability to perform daily activities, cosmetic impact, and global assessment of severity	0–3	0–105[b]	–	8
Disease control						
UCT [44, 45]	4-item questionnaire (based on the last 4 weeks)	Physical symptoms, impact on QoL, treatment effectiveness, symptom control	0–4	0–16	16 = Completely controlled 12–15 = Well-controlled < 12 = Uncontrolled	3
AECT [55]	4-item questionnaire (based on the last 4 weeks)	Frequency of angioedema, angioedema-related QoL impairment, the unpredictability of angioedema attacks, and angioedema control by current treatment	0–4	0–16	0–9 = Poorly controlled 10–16 = Controlled disease	–
QoL impairments						
CU-Q2oL [56, 57]	23-item questionnaire (based on the last 2 weeks)	Pruritus, swelling, daily life activities, sleep, appearance, and limitations	1–5	0–100	–	15
AE-QoL [58, 59]	17-item questionnaire (based on the last 4 weeks)	Functioning, fatigue/mood, fear/shame, and food	1–5	0–100	–	6

Table 1 continued

PRO	Format (time span)	Domain	Scoring system[a]	Scoring range	Correlating response	MCID
DLQI [60, 61]	10-item questionnaire (based on the last 7 days)	Symptoms/feelings, daily activities, leisure, work or school, personal relationships, and treatment side effects	0–3	0–30[b]	0–1 = No impact 2–5 = Little impact 6–10 = Moderate impact 11–20 = Very high impact 21–30 = Extremely high impact	4

Validated PROs to measure CSU symptom severity, disease control, and impact on QoL

AAS7 weekly Angioedema Activity Score, *AECT* Angioedema Control Test, *AE-QoL* Angioedema Quality of Life Questionnaire, *CSU* chronic spontaneous urticaria, *CU-Q2oL* Chronic Urticaria Quality of Life Questionnaire, *DLQI* Dermatology Life Quality Index, *QoL* health-related quality of life, *HSS7* weekly Hives Severity Score, *ISS7* weekly Itch Severity Score, *MCID* minimal clinically important difference, *PRO* patient-reported outcome, *QoL* quality of life, *UAS7* weekly Urticaria Activity Score, *UCT* Urticaria Control Test

[a]Each question is scored between the range

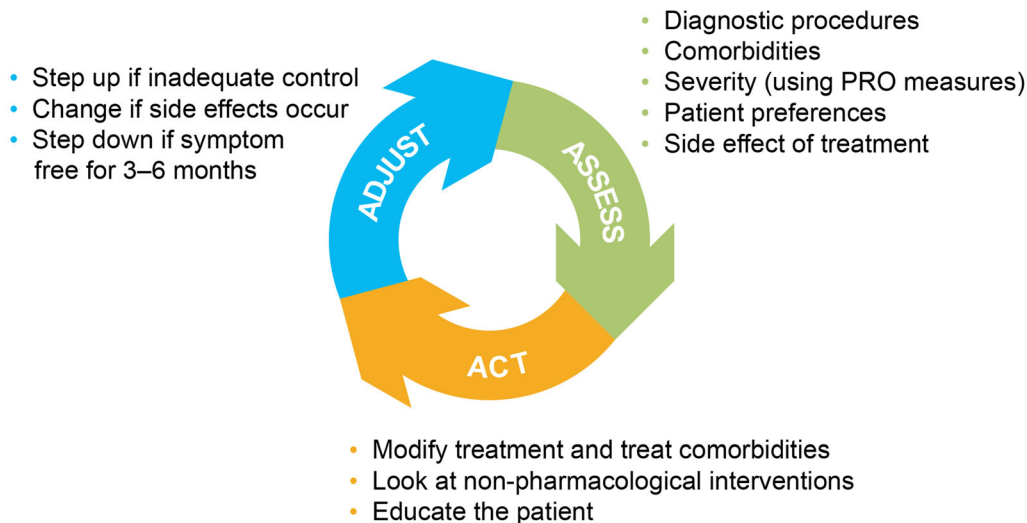[b]Higher scores for the PRO indicate a worse outcome

Fig. 1 The adjust, assess, and act paradigm [1]. A clinical decision-making aid for treatment adjustments for patients with urticaria. PRO, patient-reported outcome. Reproduced with permission from Zuberbier T, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77:734–766. © 2022. John Wiley & Sons
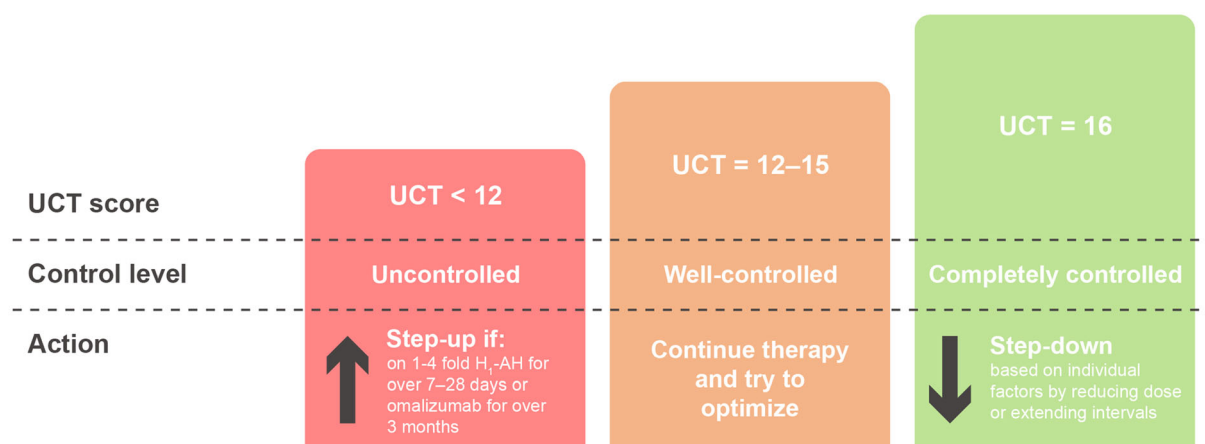
Fig. 2 UCT score [1]. The UCT is a four-item tool with a defined cutoff for patients with "completely controlled", "well-controlled", and "uncontrolled" disease, with a recall period of 4 weeks. Reproduced with permission from Zuberbier T, et al. The international EAACI/GA^{2}LEN/ EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77:734–766. © 2022. John Wiley & Sons. H$_1$-AH, second-generation H$_1$-antihistamines; UCT, Urticaria Control Test

for the continuous assessment of disease status are not well defined [1]. A comprehensive set of targets and frequency of monitoring must be defined for all relevant PROs to define treatment success.

Treatment Targets: Physician and Patient Perspectives

A key feature of CSU is the unpredictability of recurring hives and itch intensity; this profoundly affects a patient's QoL: their physical comfort, daily activities, and sleep [1, 3]. Consequently, reduction of itch/burning and resolution of visible hives/wheals are top treatment aims for patients [17]. The DERMLINE online survey reported that approximately half of patients were "not at all satisfied", "not satisfied", or "mildly satisfied" with their current medication, due to lack of response or side effects [18]. Patients have also reported that their physician did not understand the true emotional and physical burden of CSU [7]. These findings raise the question of whether physician and patient treatment aims align.

Choosing the correct treatment and when to switch treatments is a multifaceted decision. Inconsistencies in patient care have been attributed to physicians not relying on the guidelines in their decision-making [19]. Physicians have reported that guideline recommendations oversimplify the complex nature of CSU [10]. Furthermore, patients can present with comorbid disorders such as Hashimoto's thyroiditis, type I diabetes, and rheumatoid arthritis, which share a common pathogenic mechanism based on the presence of autoantibodies and chronic inflammation [5, 20]. However, the pathophysiology of CSU is not fully understood, and its acceptance as an autoimmune disease is not universal among physicians, causing differences in treatment approaches.

A treat-to-target approach is used in several chronic diseases to improve outcomes [21], with a recently defined consensus for psoriasis [22]. Currently, there is no comprehensive treat-to-target approach for CSU that incorporates all the necessary PROs and associated targets to evaluate disease activity, disease control, and QoL. One recently proposed approach is to achieve and maintain symptom control (UAS7 $\leq$ 6) or symptom remission (UAS7 = 0) [21]. Although UAS7 is an effective measure of disease activity [23], PROs to determine disease control and QoL are required to encapsulate all aspects of CSU.

Clinical and Laboratory Biomarkers to Inform Treatment Decisions

Clinical characteristics and biomarkers are used increasingly within clinical practice to inform treatment decisions. Although these indicators have not been definitively established, some appear to be associated with patient outcomes. Prolonged disease duration is associated with an insufficient response to standard-dose H_1-AH, comorbid chronic inducible urticaria (CIndU)—which itself is often linked to lack of response to standard-dose H_1-AH—late disease onset (> 45 years), intolerance to non-steroidal anti-inflammatory drugs, presence of angioedema, and a relapsing–remitting disease course [1, 8]. With regard to laboratory biomarkers, severe disease has been associated with elevated C-reactive protein (CRP) and D-dimer [8, 24]. In a study of 549 patients with CSU, 20.2% had comorbid CIndU; this subgroup required higher doses of H_1-AH and more patients experienced persistent symptoms after 5 years of follow-up than patients with isolated CSU [24]. Despite our increasing understanding of biomarkers in CSU, their clinical application remains unclear. Providers still require guidance on the appropriate timing of biomarker evaluation and how this can inform treatment decisions.

Another consideration is using biomarkers for the differential diagnosis of type IIb CSU, which has been associated with more severe disease [5, 6]. Type IIb CSU is characterized by low IgE, elevated IgG-anti-thyroid peroxidase (TPO), positive basophil histamine releasing assay (BHRA), positive autologous serum skin test, presence of IgG anti-FcεRI autoantibodies, basopenia, and eosinopenia [4, 9, 25]. Poor response to H_1-AH is associated with elevated CRP and D-dimer; poor response to omalizumab is associated with a low IgE, a low peripheral blood eosinophil count, basopenia, elevated TPO, and positive BHRA; and a good response to ciclosporin is associated with positive BHRA [4, 8, 9]. The link between biomarkers and treatment response demonstrates the potential value of biomarkers in clinical practice.

Endpoints and Treatment Targets Used in Key Clinical Trials

Since the purpose of late-phase clinical trials is to inform clinical practice, the endpoints selected should measure meaningful patient outcomes [26]. We explored common measures (e.g., UAS7) and treatment targets (e.g., UAS7 ≤ 6) used in key trials of H_1-AH and biologics (Table 2).

The most commonly used primary and secondary endpoints were change from baseline to specified timepoints in UAS7 [27–33]. Other primary endpoints included change from baseline in weekly Itch Severity Score (ISS7) [32–35] and urticaria Total Severity Score [30, 36]. UAS7 was the most commonly used PRO, particularly in recent clinical trials of biologics [27–29, 31–33]. In contrast to the primary endpoints, secondary endpoints were numerous and varied widely between trials, including change from baseline in UAS7 [28, 31, 34, 35, 37] or DLQI [35, 37]; time to a minimal clinically important difference (MCID) (≥ 5-points) reduction of ISS7 [34, 35, 37]; and proportion of patients with UAS7 ≤ 6 [28, 31–35, 37, 38]. QoL measures are commonly included in clinical trials but used inconsistently, which belies their importance to patients. Across late-stage trials, DLQI was the main indicator of QoL, generally as a secondary endpoint [32–35, 37, 39]. Although CU-Q2oL is a urticaria-specific tool recommended in the guidelines [1, 40], DLQI may be used more frequently because of its familiarity [41].

Generally, endpoints used in CSU clinical trials focus on efficacy, with minimal use of QoL and angioedema-specific measures. Unsurprisingly, UAS7 (e.g., change from baseline and UAS7 ≤ 6) is the most frequently used PRO [28, 31, 34, 35, 37, 38]. A UAS7 ≤ 6 score is defined as "well-controlled urticaria", which indicates a good response to treatment [23]. Despite the guideline recommendation [1], UCT was not included as a primary or secondary endpoint in any key clinical trials. PRO use remains largely unchanged since the early H_1-AH trials and may benefit from being made more consistent between different specialties.

Table 2 Key clinical trial endpoints

Trial name	Investigated therapy	Phase	Primary endpoint	Key secondary endpoint(s)	NCT number
XTEND-CIU [39, 62]	Omalizumab	IV	Percentage of participants with CIU/CSU clinical worsening by UAS7 $\geq$ 12 for at least 2 consecutive weeks from W24–W48	Time to CIU/CSU clinical worsening by UAS7 $\geq$ 12 for at least 2 consecutive weeks Percentage of participants with CIU/CSU clinical worsening by UAS7 > 6 for at least 2 consecutive weeks Change from W24–W48 in UAS7	NCT02392624
OPTIMA [38, 63]	Omalizumab	III	Number of participants with UAS7 $\leq$ 6 after the initial dosing period, relapsed (UAS7 $\geq$ 16) when treatment was discontinued and who achieved UAS7 $\leq$ 6 at W44	The difference in UAS7 between the start and end of the second dosing period Number of participants with UAS7 $\leq$ 6 after the second dosing period Time to relapse (UAS7 $\geq$ 16) after drug withdrawal in participants who responded to the initial dosing period	NCT02161562
X-ACT [64, 65]	Omalizumab	III	Change from baseline to W36 in the CU-Q2oL	Number of angioedema-burdened days from baseline to W36 Change from baseline to W36 in the AAS7 Change from baseline to W36 in the AE-Q2oL Change from baseline to W36 in the DLQI	NCT01723072

Table 2 continued

Trial name	Investigated therapy	Phase	Primary endpoint	Key secondary endpoint(s)	NCT number
ASTERIA I [34]	Omalizumab	III	Change from baseline to W12 in the ISS7	Change from baseline to W12 in the UAS7	NCT01287117
				Change from baseline to W12 in the weekly number of hives score	
				Time to MCID response ($\geq$ 5-point decrease) in ISS7 by W12	
				Percentage of participants with UAS7 $\leq$ 6 at W12	
ASTERIA II [35]	Omalizumab	III	Change from baseline to W12 in the ISS7	Change from baseline to W12 in the UAS7	NCT01292473
				Change from baseline to W12 in the weekly number of hives	
				Time to achieve MCID ($\geq$ 5-point decrease) in the ISS7	
				The proportion of participants with UAS7 $\leq$ 6	
GLACIAL [37]	Omalizumab	III	Safety	Change from baseline to W12 in the ISS7	NCT01264939
				Change from baseline to W12 in the UAS7	
				Change from baseline to W12 in the weekly number of hives	
				Time to achieve MCID ($\geq$ 5-point decrease) in ISS7	
				The proportion of participants with UAS7 $\leq$ 6	
N/A [66]	Ligelizumab	IIb	The proportion of participants with HSS7 = 0 at W12	The proportion of participants with HSS7 = 0 at W12 and W20	NCT02477332
				Change from baseline in HSS7, ISS7, UAS7 and AAS7	

Table 2 continued

Trial name	Investigated therapy	Phase	Primary endpoint	Key secondary endpoint(s)	NCT number
N/A [27, 67]	Benralizumab	IV	Change from baseline to W20 in the UAS7	Safety and tolerability	NCT03183024
N/A [28]	Fenebrutinib	II	Change from baseline to W8 in the UAS7	The proportion of participants with UAS7 ≤ 6 at W8	NCT03580369 NCT03580356
				Change from baseline to W4 in the UAS7	
N/A [31]	Remibrutinib	IIb	Change from baseline to W4 in UAS7	Change from baseline to W12 in UAS7	NCT03926611
				The proportion of participants with UAS7 = 0	
				The proportion of participants with UAS7 ≤ 6	
				Safety and tolerability	
REMIX-1 [33]	Remibrutinib	III	Change from baseline to W12 in UAS7	The proportion of participants with UAS7 ≤ 6 at W12	NCT05030311
			Absolute change in ISS7 at W12	The proportion of participants with UAS7 = 0 at W12	
			Absolute change in HSS7 at W12	The proportion of participants with UAS7 ≤ 6 at W2	
				The proportion of participants with DLQI = 0–1 at W12	
				The proportion of participants with AAS = 0 at W12	
REMIX-2 [32]	Remibrutinib	III	Change from baseline to W12 in UAS7	The proportion of participants with UAS7 ≤ 6 at W12	NCT05032157
			Absolute change in ISS7 at W12	The proportion of participants with UAS7 = 0 at W12	
			Absolute change in HSS7 at W12	The proportion of participants with UAS7 ≤ 6 at W2	
				The proportion of participants with DLQI = 0–1 at W12	
				The proportion of participants with AAS = 0 at W12	

Table 2 continued

Trial name	Investigated therapy	Phase	Primary endpoint	Key secondary endpoint(s)	NCT number
N/A [29]	Bilastine/ levocetirizine	III	Change from baseline to W6 in the UAS7	Change from baseline to W6 in the DLQI	N/A
				Change from baseline to W6 in the VAS	
MUCIS [68, 69]	Methotrexate	III	Number of participants with complete urticaria remission at W18	Safety and tolerability	NCT01960283
				Number of participants with pruritus at W18 and W26	
				Number of participants with complete remission at W26	
N/A [30]	Levocetirizine	IV	Change from baseline to W4 in the UAS and TSS	Change from baseline to W4 in the patient's global assessment of disease activity	N/A
				Change from baseline to W4 in the physician's global assessment of disease activity	
N/A [36]	Bilastine	II/III	Change from baseline to W2 in the TSS	Change from baseline to days 1–3 in the TSS	N/A
				Change from baseline to W1 in the TSS	

AAS7 weekly Angioedema Activity Score, *AE-QoL* Angioedema Quality of Life Questionnaire, *CIU* chronic idiopathic urticaria, *CSU* chronic spontaneous urticaria, *CU-Q2oL* Chronic Urticaria Quality of Life questionnaire, *DLQI* Dermatology Life Quality Index, *HSS7* weekly Hive Severity Score, *ISS7* weekly Itch Severity Score, *MCID* minimal clinically important difference, *N/A* not applicable, *TSS* urticaria Total Severity Score, *UAS* Urticaria Activity Score, *UAS7* weekly Urticaria Activity Score, *VAS* Visual Analog Scale, *W* week

DO TREATMENT TARGETS USED IN CURRENT LITERATURE AND CLINICAL TRIALS TRANSLATE INTO CLINICAL PRACTICE?

The treatment targets described in current literature and clinical trials indicate a lack of consensus between the guidelines and clinical trial design, but what is the picture in clinical practice?

A systematic review of real-world evidence of omalizumab in CSU ($N = 1507$) provided valuable insights into PRO use in clinical practice [15]. Overall, treatment response was reported in 76.2% of studies. UAS was the most commonly used PRO in clinical practice, with 26.2% and 11.9% of studies using UAS7 and UAS, respectively [15]. UCT was used infrequently in only 1.2% of studies [15]. DLQI and CU-Q2oL were reported in 7.1% and 6.0% of studies, respectively [15].

AWARE and ASSURE-CSU are observational studies conducted to investigate disease burden and treatment schedules for patients with CSU [3, 19]. Both studies indicate that PROs recommended in the guidelines are increasingly common in clinical practice.

In the AWARE study, disease burden was determined by monitoring symptom control (UAS7 and Angioedema Activity Score [AAS]), disease control (UCT), QoL (DLQI, CU-Q2oL, and AE-QoL), and work productivity (Work Productivity and Activity Impairment Questionnaire [WPAI]) [19]. Of note, UAS7 and AAS scoring tools measure disease activity [1] but were described as measures of symptom control [19]. At baseline, 22.0% of patients had a score of UCT $\geq$ 12, compared to 71.3% after 24 months [19]. However, in a sub-analysis, less than 1 in 3 patients who should have been switched to a more effective third-line treatment were actually switched [42]. These findings indicate either guideline recommendations may not be integrated into practice or there may be a lack of concise guidance on when patients should escalate treatment.

The ASSURE-CSU study reviewed PROs, including CU-Q2oL, AE-QoL, UAS7, DLQI, European Quality of Life Five Dimensions, Urticaria Patient Daily Diary, and WPAI [3]. Overall, AWARE and ASSURE-CSU demonstrated the practical value of UAS7 and UCT, and that DLQI and CU-Q2oL were the most common PROs for QoL [3, 19].

Most measures used in clinical trials are not used in clinical practice, likely due to feasibility challenges. The lack of standardization of treatment targets in clinical trials is also reflected in clinical practice. This heterogeneity in approach highlights the need to reach a consensus in implementing a definition of "treatment success".

CHALLENGES IN TRANSLATING DEFINITIONS OF "TREATMENT TARGETS" AND "TREATMENT SUCCESS" INTO CLINICAL PRACTICE

With a large proportion of physicians relying on their clinical experience to inform clinical decision-making [10], the variation in patient outcomes is unsurprising. How, then, can we define "treatment success"?

Based on current guidelines, the treatment target is to achieve UAS7 = 0, complete control (UCT = 16), and normalize QoL [1]. However, the targets of UAS7 = 0 and UCT = 16 do not reflect the realities of clinical management nor the complexity of CSU. In addition, the guidelines do not specify a target to determine a "normalization of QoL". To facilitate the long-term management of patients with CSU, PROs need to be accurately defined and implemented correctly into clinical practice: this definition would include a list of PROs that measure disease activity, disease control, QoL, and angioedema, alongside targets and any associated actions.

The PRO scores are all associated with disease status levels, which give physicians a good understanding of a patient's disease progression over time. Using the MCID, the smallest change in score that can be considered clinically relevant, may be informative here (Table 1). For example, to determine disease activity and control, a target of UAS7 $\leq$ 6, defined as well-controlled urticaria, or the MCID (9.5–10.5), is a good indicator of treatment response [23, 43]. In addition, a target of UCT $\geq$ 12, defined as well-controlled, or a change from baseline of 3 points, could be of equal clinical value to aid a decision to step down treatment [44, 45]. A choice between the PRO score or MCID should ideally be practical, i.e., whichever is easiest to determine.

With 43–59% of patients with CSU experiencing angioedema [3, 18, 19], the lack of angioedema-specific measures is surprising. The impact of angioedema on QoL, productivity, and healthcare utilization is considerable [46]. PROs, such as AAS, AECT, and AE-QoL, are used infrequently, perhaps indicating that physicians deem other PROs adequate in measuring angioedema. More widespread use of angioedema-specific PROs is a clear area for improvement.

Clinical characteristics and laboratory measures have been associated with predicting disease duration and severity, and response to treatment. Many tests offer little or no predictive value for the individual patient during the diagnostic process [4]. Informing physicians of updates in clinically informative biomarkers

should be a priority in the coming years. As the evidence base grows, predictive biomarkers may be utilized alongside specific treatment targets, which could significantly impact clinical decision-making.

MOVING TOWARD A UNIVERSAL DEFINITION OF "TREATMENT SUCCESS": REMAINING QUESTIONS

Current literature includes minimal guidance about what constitutes "treatment success". In this review, we have identified several unanswered questions that should guide us toward a definition of "treatment success" and provide practical insights to support its implementation.

"Remission" remains the aim of treatment but can mean many things. Previously reported definitions of "remission" have included the absence of hives and angioedema in the last 3 months while patients were not undergoing therapy; the proportion of patients completely or fully cleared of CSU based on a self-assessment of disease symptoms, with no information provided about whether treatment is ongoing [13]; absence of urticaria for at least 4 weeks without medication [47]; and absence of urticaria treatment from any medical services for at least 1 year [48]. Many questions remain for healthcare professionals: is remission classified as permanent or temporary; for how long do patients need to be without medication; can biologic therapies lead to permanent remission; does an extended treatment course, and having neither symptoms nor active disease for a longer period, increase the chances of being in permanent remission? A recent consensus report defined remission as "the total absence of disease signs or symptoms in the absence of treatment" for 2 weeks with standard H_1-AH, 4 weeks with up-dosed H_1-AH, and 3–6 months with biological therapy [49]. Still, the implementation of this definition remains a challenge. For example, early evidence from omalizumab clinical trials demonstrated that patients might experience clinical worsening

following treatment discontinuation after up to 6 months [50], or patients may need continuous treatment [51].

Another challenge healthcare providers face is deciding when and how to step down treatment. In the guidelines, UCT score is the only measure that informs treatment switching (Fig. 2), which poses various clinical questions: should all medications stop once disease activity has subsided; before stepping down, how long should patients be monitored if they respond; how does management change for patients predisposed to chronic spontaneous "indefinite" hives, analogous to thyroid issues, and do these patients need to be on chronic "suppression" therapy?

An understanding of recurrence is equally important. Recurrence has been defined as symptom recurrence "at least 6 months after cessation of controller therapy and resolution of prior chronic urticaria symptoms" [52]. Yet, in a recent consensus report, a definition of "recurrence" could not be agreed upon [49]. If a patient's symptoms recur after an undefined period, do physicians treat this as a recurrence of CSU and continue treatment considering prior therapies, or consider it new acute urticaria?

Insights into improved long-term clinical management can likely be gained from comparing biomarkers and clinical features of patients with a rapid and complete response versus treatment-refractory patients; this may allow more tailored treatment approaches.

Finally, to what extent is QoL a factor in treatment success and what is the most important aspect of treatment for the patient? The reduction of itching/burning and healing of all visible skin alterations have been reported as two principal treatment aims for patients [17]; however, treatment side effects, the burden of multiple medications, and preventing recurrence may be of utmost importance to an individual patient. Accurate measurement of these factors and their incorporation into shared decision-making can help patients feel confident in their treatment plan and reach true treatment success. Although we acknowledge that completion of multiple PROs may burden the patient and clinical team, incorporating

QoL and other PRO measures would help identify treatment success.

CONCLUSION

Prior to the development of a universal definition of "treatment success", several questions need to be answered. A universal definition of "remission" and "recurrence" is needed, alongside research into predictors for achieving these states. Further guidance is needed on when to step down treatment. PROs should be associated with treatment targets, timepoints to determine whether current treatment is effective, and actions linked to these outcomes. Lastly, the impact CSU has on a patient's QoL needs to be assessed, ideally over time.

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