Received: 10 December 2021 | Revised: 6 January 2022 | Accepted: 24 January 2022

DOI: 10.1111/all.15244

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTERS

Outcome measures in randomized controlled studies of acute therapy for hereditary angioedema: A systematic review

To the Editor,

Hereditary angioedema (HAE) is characterized by recurrent swellings of subcutaneous and mucosal tissue. Access to effective on demand medication to treat acute attacks is vital for every HAE patient. Clinical trials investigating new acute treatment options focus on increased efficacy, easier routes of administration, and reduced side effects.[1] The outcome measures that have been reported in these studies have been varied.[2] The existence of this range of efficacy outcomes is, at least partly, caused by the difficulty in developing an unique uniform outcome measure that captures the heterogeneity in attack location, symptoms, severity, and temporal patterns. In addition, these efficacy outcomes have to depend heavily on patient-reported outcomes, since sensations such as relief of discomfort, disability, and pain cannot be measured objectively by clinicians. The heterogeneity in outcome measures hinders trial comparison, leads to selective outcome reporting bias, and the large quantity of outcome measures used in a single trial puts a significant burden on participants. It is unclear which primary outcome parameters best reflect the efficacy of the investigated acute treatment options. These issues can be addressed with a Core Outcome Set (COS); "an agreed standardized collection of outcomes which should be measured and reported, as a minimum, in all trials for a specific clinical area."[3] This systematic review aims to summarize the efficacy outcome measures reported in studies evaluating acute treatment in HAE patients as a first step in the development of a COS.

The applied methods for this systematic review are described in the Supplementary. Eleven papers describing 13 eligible trials were identified (Figure S1, references in the Supplementary). Table S1 shows the definitions of all outcome measurement instruments used in the included trials. The 13 unique primary outcomes were collapsed into nine standardized outcome terms, representing outcomes with the same meaning but with differing wording (Table 1). Table 2 displays the standardized outcome terms used as secondary outcomes in the included trials. The majority (81%) of these standardized outcomes were not used as a secondary outcome in more than one trial. The exploratory outcomes are summarized in Table S2. Two outcome measures which were planned in the trial protocol were not mentioned in the full paper or supplementary material (Table S3).

We identified 72 standardized efficacy outcome terms reported in studies evaluating on demand treatment of acute attacks in HAE patients, of which nine were used as a primary outcome measure. No outcome measure was reported consistently in all 13 trials. Eleven instruments were utilized by 74% of the standardized outcomes, which can be broadly divided in instruments evaluating location-specific symptoms and instruments giving a general classification of overall attack severity. Outcomes measuring treatment response were predominantly either time-based (e.g., time to symptom relief) or symptom-based (e.g., change in severity at a predefined time point). Approaches to multi-sites attacks focused on an index symptom or made use of a composite score based on severity assessments of symptoms at multiple sites. Of all utilized instruments and reported outcome measures, only the Treatment Outcome Score and Mean Symptom Complex Score at 4 h and 24 h,[4] the Visual Analog Scale,[5] and "onset of symptom relief" measured without an

TABLE 1 Standardized primary outcomes

	n	Article reference in Supplementary
Time to onset of symptom relief, mean of multiple attacks	3	4–6
Time to onset of symptom relief with VAS–3	2	10
Time to onset of symptom relief with VAS–4	2	12
Improvement at primary attack location within 4 h	1	7
MSCS score after 4 h	1	9
Time to onset of symptom relief assessed by patient	1	3
Time to onset of symptom relief with TEQ	1	13
Time to 50% reduction in symptom severity with VAS–3	1	11
TOS after 4 h	1	8

Abbreviations: MSCS, mean symptom complex severity; *n*, number of individual trials that used this outcome; TEQ, treatment effect questionnaire; TOS, treatment outcome score; VAS-3, visual analog scale-3; VAS-4, visual analog scale.

TABLE 2 Standardized secondary outcomes

	n	Article reference in Supplementary
Proportion with onset of symptom relief within 4 h	3	6, 10
Time to onset of symptom relief assessed by patient	3	7, 10
Time to complete resolution with VAS−3	2	10
Time to complete resolution with VAS−4	2	12
Time to complete resolution, mean of multiple attacks	2	5, 6
Time to onset of symptom relief assessed by investigator	2	10
MSCS score after 4 h	1	8
MSCS score after 24 h	1	8
Time to any reduction in LSS assessed by patient	1	11
Time to any reduction in LSS assessed by investigator	1	11
Time to any reduction in VAS−5	1	11
Time to complete resolution	1	8
Time to complete resolution with TEQ	1	13
Time to complete resolution of cutaneous and/or abdominal symptoms with VAS−3	1	11
Time to complete resolution of laryngeal symptoms with VAS−5	1	11
Time to onset of laryngeal symptom relief with VAS	1	11
Time to onset of relief of cutaneous and/or abdominal symptoms assessed by patient	1	11
Time to onset of relief of cutaneous and/or abdominal symptoms assessed by investigator	1	11
Time to onset of relief of cutaneous and/or abdominal symptoms with VAS	1	11
Time to onset of relief of laryngeal symptoms assessed by patient	1	11
Time to onset of relief of laryngeal symptoms assessed by investigator	1	11
Time to onset of abdominal pain relief with VAS−3	1	11
Time to onset of skin pain relief with VAS−3	1	11
Time to onset of skin swelling relief with VAS−3	1	11
Time to sustained improvement in overall response	1	8
Time to 50% reduction in CSS assessed by patient	1	11
Time to 50% reduction in CSS assessed by investigator	1	11
Time to 50% reduction in symptom severity with VAS−5	1	11
TOS after 4 h	1	9
TOS after 24 h	1	8
Vomiting episodes within 4 h	1	3
Worsening intensity	1	3

Abbreviations: CSS, composite symptom score; LSS, laryngeal symptom score; MSCS, mean symptom complex severity; *n*, number of individual trials that used this outcome; TEQ, treatment effect questionnaire; TOS, treatment outcome score; VAS, visual analog scale; VAS-3, visual analog scale-3; VAS-4, visual analog scale-4; VAS-5, visual analog scale.

instrument,[6] have been validated. The clear need for a COS in this field is also illustrated by the variability in clinical trials in definitions of severity of attacks and eligibility of attacks, and variability in the criteria for rescue medication use and timing of rescue medication and efficacy assessments.

KEYWORDS

efficacy, hereditary angioedema, outcomes, swelling, treatment

ACKNOWLEDGEMENTS

The authors thank Nerissa P. Denswil for her help with the construction of the search strategies.

CONFLICT OF INTEREST

LF and RP have no conflicts of interest. DC reports speaking and/or consultancy fees from BioCryst, CSL Behring, Intellia, Ionis Pharmaceuticals inc., KalVista, Pharming, Pharvaris, and Shire/Takeda.

REGISTRATION

PROSPERO https://doi.org/10.1016/j.jaci.2009.12.645.

Lauré M. Fijen
Remy S. Petersen
Danny M. Cohn

Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Lauré M. Fijen, Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: l.m.fijen@amsterdamumc.nl

ORCID

Lauré M. Fijen https://orcid.org/0000-0002-0834-8138
Remy S. Petersen https://orcid.org/0000-0003-4836-7349
Danny M. Cohn https://orcid.org/0000-0002-9036-3723

REFERENCES

1. Fijen LM, Bork K, Cohn DM. Current and prospective targets of pharmacologic treatment of hereditary angioedema types 1 and 2. *Clin Rev Allergy Immunol*. 2021;61(1):66-76.
2. Caballero T. Efficacy assessments in randomized controlled studies of acute therapy for hereditary angioedema. *J Clin Immunol*. 2012;32(6):1204-1212.
3. Williamson PR, Altman DG, Bagley H, et al. The COMET handbook: version 1.0. *Trials*. 2017;18(Suppl 3):280.
4. Vernon MK, Rentz AM, Wyrwich KW, White MV, Grienenberger A. Psychometric validation of two patient-reported outcome measures to assess symptom severity and changes in symptoms in hereditary angioedema. *Qual Life Res*. 2009;18(7):929-939.
5. McMillan CV, Speight J, Relan A, Bellizzi L, Haase G, Cicardi M. Content validity of visual analog scales to assess symptom severity of acute angioedema attacks in adults with hereditary angioedema: an interview study. *Patient*. 2012;5(2):113-126.
6. Bewtra A, Bernstein J, Ritchie B, et al. C1 esterase inhibitor: retrospective validation of a commonly used endpoint in hereditary angioedema studies, time to onset of relief, in a global, multicenter, randomized, placebo-controlled study (I.M.P.A.C.T.1). *J Allergy Clin Immunol*. 2010;125(2):AB165.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

DOI: 10.1111/all.15274

Adrenaline autoinjector is underprescribed in typical cold urticaria patients

To the Editor,

Intramuscular adrenaline is the first-line treatment for anaphylaxis and an adrenaline autoinjector (AAI) should be carried as a first-aid measure by patients at risk.[1] Cold-induced anaphylaxis (ColdA), which may result in fatality,[2] is common in typical cold urticaria (ColdU), and risk factors for ColdA have recently been identified for the first time.[3] As of now, it is largely unclear how often patients with ColdU (i) receive adrenaline treatment and (ii) are provided with an AAI.[2] A study by Gernez et al. in the USA showed that 48% of allergy and immunology specialists prescribe an AAI to ColdU patients less than 10% of the time.[4]

Here, we present further results of the COLD-CE (i.e., comprehensive evaluation of ColdU and other cold-induced reactions) study,[3] performed by the UCARE network.[5] The study included 412 ColdU patients with whealing in response to local cold stimulation testing (i.e., typical ColdU). Concomitant chronic spontaneous urticaria was found in 10% ($n = 40$) of them. Of 372 patients with stand-alone ColdU, 69% ($n = 258$) were females and 91% adults (i.e., ≥18 years; $n = 338$). Their median age was 36 years (IQR 26–48).

ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms.[3] It was diagnosed in 39% ($n = 145$) of patients. Physician collected data on baseline patient characteristics, clinical manifestations induced by different cold triggers, and answered the following: (i) "Did the patient ever receive adrenaline for the treatment of ColdU/ColdA by medical personnel or by AAI self-administration?" and (ii) "Was AAI prescribed before study enrollment?". Only 8% ($n = 12$) of ColdA patients had received treatment with adrenaline, and 37% ($n = 54$) of patients had an AAI (Table 1). Hypotension was experienced by 13% ($n = 48$) of patients, but only 17% ($n = 8$) of them received adrenaline and only 10% ($n = 5$) both adrenaline treatment and AAI prescription (Table S1). Patients were also categorized based on the climate of their residency (Table S2). ColdA was more common in temperate than cold climate countries (44% vs. 21%, $p < 0.001$) and AAI was more often prescribed in the former (30% vs. 15%, $p = 0.011$). The frequency of ColdA did not significantly differ between temperate and tropical countries (44% vs. 42%, $p = 1.000$), but AAI was more often prescribed in the former (30% vs. 12%, $p = 0.038$). ColdA triggered by complete cold water immersion (e.g., at beaches) was diagnosed in 29% ($n = 107$) of patients, but only 8% ($n = 8$) of them received adrenaline (Table 1). AAI was more often prescribed in patients with oropharyngeal/laryngeal symptoms than those without (37% vs. 20%, $p = 0.001$; Table 2).

Our findings suggest that ColdA is undertreated and they call for changes in ColdU management. ColdA should be approached