



Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

**Recherche und Synopse der Evidenz zur Bestimmung der
zweckmäßigen Vergleichstherapie nach § 35a SGB V**

und

**Schriftliche Beteiligung der wissenschaftlich-medizinischen
Fachgesellschaften und der Arzneimittelkommission der
deutschen Ärzteschaft (AkdÄ) zur Bestimmung der
zweckmäßigen Vergleichstherapie nach § 35a SGB V**

Vorgang: 2024-B-042 Garadacimab

Stand: April 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Garadacimab
routinemäßige Prophylaxe von Attacken des hereditären Angioödems (ab 12 Jahren)**

Kriterien gemäß 5. Kapitel § 6 VerfO

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.

Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.

Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.

nicht angezeigt

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V im Anwendungsgebiet:

- Lanadelumab (neues Anwendungsgebiet; *laufendes Verfahren*)
- Berotralstat (Beschluss vom 02.12.2021)
- Lanadelumab (Neubewertung nach Überschreitung der 50 Mio. € Umsatzgrenze; Beschluss vom 04.11.2021)
- Lanadelumab (Beschluss vom 01.08.2019, *aufgehoben*)

Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.

Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Garadacimab	Geplantes Anwendungsgebiet laut Beratungsanforderung: Garadacimab is indicated for the routine prophylaxis of recurrent attacks of hereditary angioedema (HAE) in patients 12 years of age and older.
C1-Esterase-Inhibitor B06AC01 Cinryze, Berinert	Behandlung und vor einem medizinisch indizierten Eingriff durchgeführte Prophylaxe von Angioödem-Attacken bei Erwachsenen, Jugendlichen und Kindern (2 Jahre und älter) mit hereditärem Angioödem (HAE). Routineprophylaxe gegen Angioödem-Attacken bei Erwachsenen, Jugendlichen und Kindern (6 Jahre und älter) mit schweren und wiederkehrenden Attacken eines hereditären Angioödems (HAE), bei denen orale prophylaktische Behandlungen nicht vertragen werden oder keinen ausreichenden Schutz bieten, oder bei Patienten, die sich mit wiederholten Akutbehandlungen nur unzureichend therapieren lassen. [...] <i>[Cinryze, Stand FI: 09/2022]</i> Hereditäres Angioödem Typ I und II (HAE), Therapie und vor einem Eingriff durchgeführte Prophylaxe des akuten Schubes <i>[Berinert 500/1500, Stand FI: 04/2022]</i> Berinert zur subkutanen Injektion wird zur Prävention von rezidivierenden hereditären Angioödemattacken (HAE) bei jugendlichen und erwachsenen Patienten mit C1-Esterase-Inhibitor-Mangel angewendet. <i>[Berinert 2000/3000, Stand FI: 04/2022]</i>
Tranexamsäure B02AA02 Cyklokapron	[...] Zur Vorbeugung des Auftretens von Ödemen bei hereditärem Angioödem (Schwellungsneigung im Unterhautgewebe an verschiedenen Körperstellen sowie Schleimhäuten, einschließlich Kehlkopf und Rachen). <i>[Cyklokapron® 500 mg Filmtabletten, Stand FI: 10/2022]</i>
Lanadelumab B06AC05 Takhzyro	TAKHZYRO wird bei Patienten ab 2 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) angewendet. <i>[Stand FI 11/2023]</i>
Berotrastat B06AC06 Orladeyo	Orladeyo wird angewendet bei erwachsenen und jugendlichen Patienten ab einem Alter von 12 Jahren zur routinemäßigen Prävention wiederkehrender Attacken des hereditären Angioödems (HAE). <i>[Stand FI 12/2022]</i>

Quellen: AMIce-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-042 (Garadacimab)

Auftrag von: Abt. AM
Bearbeitet von: Abt. FB Med
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Inhaltsverzeichnis

Abkürzungsverzeichnis	3
1 Indikation	4
2 Systematische Recherche	4
3 Ergebnisse.....	5
3.1 Cochrane Reviews.....	5
3.2 Systematische Reviews	8
3.3 Leitlinien.....	8
4 Detaillierte Darstellung der Recherchestrategie.....	26
Referenzen	29
Anhang	30

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Bei Personen ab 12 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation hereditäres Angioödem durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (<https://www.google.com/>) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 08.02.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 93 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Beard N et al., 2022 [1].

Interventions for the long-term prevention of hereditary angioedema attacks

Fragestellung

To assess the benefits and harms of interventions for the long-term prevention of HAE attacks in people with Type I, Type II or Type III HAE.

Methodik

Population:

- Children or adults with Type I, Type II or Type III HAE (HAE nC1-INH)

Intervention:

- avoralstat, berotralstat, subcutaneous C1-INH, plasma-derived C1-INH, nanofiltered C1-INH, recombinant human C1-INH, danazol, and lanadelumab

Komparator:

- placebo or any active comparator, or both.

Endpunkte:

Primary outcomes:

- HAE attacks (number of attacks per person, per population) and change in number of HAE attacks
- Mortality
- Serious adverse events, such as hepatic dysfunction, hepatic toxicity and deleterious changes in blood tests (e.g. glucose tolerance, thyroid hormones, lipids, lipoproteins)

Secondary outcomes:

- Quality of life (measured by any validated measure, such as Angioedema Quality of Life Questionnaire (AE-QoL), HealthRelated Quality of Life Questionnaire for HAE (HAEQoL), 12-Item Short Form Health Survey (SF-12))
- Severity of breakthrough attacks as reported by individual studies
- Disability (measured by any validated measure, such as Work Productivity and Activity Impairment Questionnaire). This includes any outcome that measures changes in the ability of people to attend and function well in the workplace and in recreational activities
- Adverse events, such as weight gain, mild psychological changes (irritability, nervousness, mood changes), increased body hair, gastrointestinal health, nausea, vomiting and flushing

Recherche/Suchzeitraum:

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 3 August 2021);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 7) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (1946 onwards) (searched 3 August 2021);

- Embase Ovid (from 1974 onwards) (searched 3 August 2021); • CINAHL EBSCO (from 1982 onwards) (searched 3 August 2021).

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

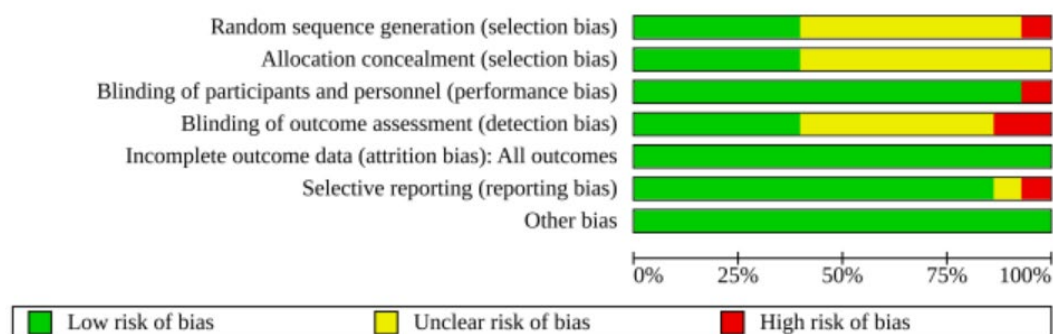
- 15 studies (912 participants)

Charakteristika der Population/Studien:

- children or adults with Type I, Type II or Type III HAE (HAE nC1-INH) who were treated for the prevention of HAE attacks.
- We defined Type I HAE as HAE caused by insufficient amounts of C1-INH; Type II HAE as HAE presenting with sufficient amounts of C1-INH, but subfunctional or non-functional C1-INH; and Type III HAE as HAE with normal C1-INH concentrations and function (US HAE Association 2018).
- If the justification for designating the type of HAE is not specifically given, we accepted the diagnosis stated by the study authors.

Qualität der Studien:

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

- Risk of hereditary angioedema attacks
 - Five studies comparing intervention with placebo reported on risk of HAE attacks (APeX-1; COMPACT; Gelfand 1976; OPuS-1; OPuS-2).
 - All interventions except avoralstat decreased the risk of HAE attacks; however, there were few studies for each drug.
 - At approved doses, C1-INH compared with placebo showed fewer HAE attacks than berotralstat (Analysis 1.2) (COMPACT).
 - The RR for C1-INH versus placebo was 0.29 (95% CI 0.16 to 0.50, 1 study, 85 participants; $P < 0.001$) and for berotralstat versus placebo was 0.63 (95% CI 0.39 to 1.00; 1 study, 37 participants; $P = 0.05$).
- Mortality
 - There were no deaths in any study; therefore analyses were not possible.

- Adverse events
 - including serious adverse events, did not occur at a rate higher than placebo.
 - However, serious adverse event data and other adverse event data were not available for danazol, which prevented us from drawing conclusions about the absolute or relative safety of this drug.
 - No deaths were reported in the included studies.
- Quality of life
 - The most common measure of quality of life for people with HAE is the Angioedema Quality of Life (AE-QoL) scale.
 - Meta-analysis of the studies that measured the AE-QoL revealed a clinically significant improvement in quality of life for three of the four drugs (avoralstat (OPuS-1; OPuS-2), berotralstat (APeX-1; APeX-2; APeX-J), and lanadelumab (HELP)).
 - Avoralstat reduced the AE-QoL by 6.78 points (95% CI –11.61 to –1.95; 2 studies, 117 participants). Berotralstat reduced the AE-QoL by an average of 15.28 points (95% CI –29.42 to –1.14; 3 studies, 130 participants), and lanadelumab reduced the AE-QoL by 14.91 points (95% CI –21.89 to –7.92, 1 study, 117 participants), more than twice the cut-off for clinical significance.
 - In the SAHARA trial, there was no clear difference with pdC1-INH in the first cross-over period (MD –3.49, 95% CI –10.86 to 3.88; 1 study, 60 participants), but in the second period there was an improvement in quality of life (MD –16.87, 95% CI –22.79 to –10.95; 1 study, 53 participants).
- Severity of breakthrough attacks Continuous outcomes
 - Only two studies reported severity of breakthrough attacks on a continuous scale (COMPACT; NCT01005888); both studies used C1INH as the intervention and placebo as the control.
 - The COMPACT trial reported breakthrough attack severity for 40 IU/kg and 60 IU/kg; both doses were superior to placebo, with reductions in severity of around 0.3 points on a 0 to 3 scale (representing no symptoms ('0'); mild symptoms ('1'); moderate symptoms ('2'); or severe symptoms ('3')).
 - NCT01005888 compared C1-INH-nf 1000 IU to placebo, and also showed a reduction in attack severity compared with placebo.

Anmerkung/Fazit der Autoren

The available data suggest that berotralstat, C1-INH (subcutaneous, plasma-derived, nanofiltered and recombinant), danazol and lanadelumab are effective in lowering the risk or incidence (or both) of HAE attacks. In addition, C1-INH and lanadelumab decrease the severity of breakthrough attacks (data for other drugs were not available). Avoralstat, berotralstat, C1-INH (all forms) and lanadelumab increase quality of life and do not increase the risk of adverse events, including serious adverse events. It is possible that danazol, subcutaneous C1-INH and recombinant human C1-INH are more effective than berotralstat and lanadelumab in reducing the risk of breakthrough attacks, but the small number of studies and the small size of the studies means that the certainty of the evidence is low. This and the lack of head-to-head trials prevented us from drawing firm conclusions on the relative efficacy of the drugs.

Kommentare zum Review

Siehe Summary of Findings im Anhang. Im Anhang wurde auf die Studienergebnisse von Avoralstat und Danazol aufgrund der fehlenden Zulassung verzichtet.

3.2 Systematische Reviews

Es wurden keine systematischen Reviews im AWG identifiziert.

3.3 Leitlinien

Maurer M et al., 2022 [3,4].

World Allergy Organization (WAO) in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI)

The international WAO/EAACI guideline for the management of hereditary angioedema—
The 2021 revision and update

Leitlinienorganisation/Fragestellung

The goal of this guideline is to provide clinicians and their patients with guidance that will assist them in making rational decisions in the management of HAE, primarily HAE type 1 and type 2 (HAE-1/2).

Methodik

Grundlage der Leitlinie

- Update der WAO/EAACI guideline 2017
- Repräsentatives Gremium;
- Finanzielle Interessenkonflikte dargelegt; Finanzierung der LL: „Funding and support of the development of this update and revision of the guideline came from WAO and EAACI. This revision and update of the guideline benefitted from the help and support of the GA2LEN/HAEi network of Angioedema Centers of Reference and Excellence (ACARE, <https://acare-network.com>)“;
- Systematische Suche der Literatur und Bewertung der Evidenz dargelegt; systematische Auswahl der Literatur: unklar
- Formaler Konsensusprozess dargelegt
- externes Begutachtungsverfahren: keine Angaben
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum

- For the update and revision of recommendations from the previous version of the guideline, a systematic search of the literature from 1 June 2016 was performed. For new and additional recommendations (recommendations 3, 11, 13, 16, 17, 19, and 25), as well as for pre-existing recommendations with a revised wording (recommendations 1, 2, 4, 5, 7, 9, 10, 12, 14, 18, 21, 22, and 28), a complete search from 1 January 1985 was performed.
- literature search and evaluation process continued during the review process and manuscript development and was continuously updated until 19 July 2021.

LoE

TABLE 1 Evidence grades

- A. Randomized, double-blind clinical trial of high quality (eg, sample size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis and sufficient sample size)
- B. Randomized clinical trial of lesser quality (eg, only single-blind, limited sample size: at least 15 patients per study arm)
- C. Comparative trial with severe methodological limitations (eg, not blinded, very small sample size and no randomization) or large retrospective observational study, large open-label-study, registry data
- D. Adapted from existing consensus document or statement based on expert opinion voting during consensus conference, evidence non A–C

GoR

The recommendations provided by this guideline use standardized wording, ie, “we recommend” or “we suggest”.

- “We recommend” reflects a strong recommendation, implying:
 - (1) that all or almost all informed people would make that choice,
 - (2) that less time is needed for health care providers to make decisions and more time is available for overcoming barriers to their implementation and adherence, and
 - (3) that, in most clinical situations, the recommendation may be adopted as policy.
- “We suggest” reflects a weak recommendation implying:
 - (1) that most informed people would make that choice, but a substantial number would not,
 - (2) that health care providers and patients will need to devote more time on the process of decision making as compared to strong recommendations, and
 - (3) that policy making may require the use of further resources. Importantly, this guideline acknowledges and aims to mitigate the disparity in healthcare resources for the management of HAE between countries.

Empfehlungen

7 On-demand treatment of HAE attacks

RECOMMENDATION 7

We **recommend** that attacks are treated with either intravenous C1 inhibitor, ecallantide or icatibant

96% agreement, evidence level A

7.1 On-demand treatment with C1 inhibitor

[...] The safety and tolerability of all available pdC1-INH are good, and few adverse events have been reported. The risk of allergic reactions is negligible. Modern pdC1-INH use has neither been associated with transmission of hepatitis B or C nor human immunodeficiency viruses.¹³⁹⁻¹⁴²

Ruconest (Pharming) is the only available recombinant human C1-INH (rhC1-INH). [...] RhC1-INH is indicated for on-demand treatment of all types of HAE attacks in adults and children (2 years or older).^{125,143} [...] Safety data from controlled and uncontrolled studies with rhC1-INH support a favorable safety profile. Transmission of human viruses is not a concern.¹⁴⁷⁻¹⁴⁹

7.2 On-demand treatment with the kallikrein inhibitor ecallantide

The kallikrein inhibitor ecallantide (Kalbitor; Takeda) is licensed only in the United States and a few Latin American countries for the on-demand treatment of all types of HAE attacks in HAE-1/2 patients aged 12 years and older.^{118,150} [...] The main safety concern is potentially serious hypersensitivity reactions, including

anaphylaxis, which was reported in 3% - 4% of treated patients. The drug, therefore, should only be administered by a health care professional with appropriate medical support to manage anaphylaxis.^{118,123,151,152}

7.3 On-demand treatment with the bradykinin B2 receptor antagonist icatibant

[...] The safety and tolerability of icatibant are good, although transient local injection site reactions (erythema, wheal, pruritus and burning sensation) may occur. Allergic reactions have not been reported.^{121,157-159}

118. Takeda. Kalbitor prescribing information. 2020. https://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf. Accessed August 16, 2021.

121. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363(6):532-541.

123. Levy RJ, Lumry WR, McNeil DL, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104(6):523-529.

125. Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2010;126(4):821-827 e814.

139. De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. *Transfus Apher Sci*. 2003;29(3):247-254.

140. Gröner A, Nowak T, Schäfer W. Pathogen safety of human C1 esterase inhibitor concentrate. *Transfusion*. 2012;52(10):2104-2112.

141. Simon TL, Kalina U, Laske R, Mycroft S, Widmer E, Roth NJ. Manufacturing of plasma-derived C1-inhibitor concentrate for treatment of patients with hereditary angioedema. *Allergy Asthma Proc*. 2020;41(2):99-107.

142. Terpstra FG, Kleijn M, Koenderman AH, et al. Viral safety of C1-inhibitor NF. *Biologicals*. 2007;35(3):173-181.

143. Reshef A, Grivcheva-Panovska V, Kessel A, et al. Recombinant human C1 esterase inhibitor treatment for hereditary angioedema attacks in children. *Pediatr Allergy Immunol*. 2019;30(5):562-568.

147. Moldovan D, Bernstein JA, Cicardi M. Recombinant replacement therapy for hereditary angioedema due to C1 inhibitor deficiency. *Immunotherapy*. 2015;7(7):739-752.

148. Moldovan D, Reshef A, Fabiani J, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: european open-label extension study. *Clin Exp Allergy*. 2012;42(6):929-935.

149. Riedl M. Recombinant human C1 esterase inhibitor in the management of hereditary angioedema. *Clin Drug Investig*. 2015;35(7):407-417.

150. DyaxCorp. Withdrawal of Kalbitor at EMA. 2011.

151. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363(6):523-531.

152. Craig TJ, Li HH, Riedl M, et al. Characterization of anaphylaxis after ecallantide treatment of hereditary angioedema attacks. *J Allergy Clin Immunol Pract*. 2015;3(2):206-212. e204.

157. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol*. 2007;119(6):1497-1503.

158. Farkas H. Icatibant as acute treatment for hereditary angioedema in adults. *Expert Rev Clin Pharmacol*. 2016;9(6):779-788.

159. Farkas H, Kóhalmi KV. Icatibant for the treatment of hereditary angioedema with C1-inhibitor deficiency in adolescents and in children aged over 2 years. *Expert Rev Clin Immunol*. 2018;14(6):447-460.

LONG -TERM PROPHYLACTIC TREATMENT OF HAE

Plasma-derived C1-INH

RECOMMENDATION 15

We **recommend** the use of plasma-derived C1 inhibitor as first-line long-term prophylaxis

87% agreement, evidence level A

Plasma-derived C1-INH is currently a preferred LTP agent for the prevention of HAE attacks, and we recommend its use as first-line long-term prophylaxis (Recommendation 15).^{126,197,205,213–216} Approved product indications vary around the world. Dosing should be twice a week based upon the half-life of pdC1-INH. Dose and/or frequency may need adjustment for optimum efficacy.^{126,217–220}

Recent studies show that subcutaneous twice-weekly administration of pdC1-INH at a dose of 60 U per kilogram bodyweight provided very good and dose-dependent preventive effects on the occurrence of HAE attacks.²⁰⁵ The subcutaneous route may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1-INH compared to LTP with intravenous C1-INH, allowing for better symptom control.^{221–224}

Appropriate vaccination for hepatitis A and B should be generally considered for patients in regular/repeated administration of human plasma-derived products including C1 inhibitor.^{140,141} Routine prophylaxis with pdC1-INH has been shown to be safe and effective, and it improves quality of life in patients with relatively frequent HAE attacks compared with acute treatment of individual HAE attacks.^{210,222,223,225–227}

Thromboembolic events due to C1-INH concentrate use in HAE are rare, and patients who experience such events often have underlying thromboembolic risk factors (eg, implanted central venous catheters).^{228–233} There are no known interactions with other medicinal products. Tachyphylaxis seems rare with only one report of increasing doses required to prevent attacks when C1-INH concentrate is used regularly for prophylaxis.²³⁴

Lanadelumab

RECOMMENDATION 16

We **recommend** the use of lanadelumab as first-line long-term prophylaxis

89% agreement (strong recommendation), evidence level A

Lanadelumab is a subcutaneously injectable, fully human, antiactive plasma kallikrein monoclonal antibody (IgG1/ κ -light chain). It is a preferred LTP agent for the prevention of HAE attacks due to its efficacy and the fact it is administered subcutaneously. We, therefore, recommend the use of lanadelumab as first-line LTP (Recommendation 16).^{195,235–237}

It is typically administered as 300 mg every 2 weeks; however, a dosing interval of 300 mg every 4 weeks may be considered if a patient is well controlled (eg, attack free).^{196,238} It appears safe with the rate of adverse events not appreciably higher among patients who received lanadelumab than among those who received placebo.^{195,204}

Berotrastat

RECOMMENDATION 17

We **recommend** the use of berotrastat as first-line long-term prophylaxis

81% agreement, evidence level A

Berotrastat is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. It is a preferred LTP agent for the prevention of HAE attacks due to its efficacy and the fact it is an oral medication (Recommendation 17).^{206,239,240} It is typically administered as 150 mg orally with food with dose reductions to 110 mg in some regions where it is licensed based on if there is hepatic impairment, use of P-glycoprotein or BCRP inhibitors (drug interactions) or patients experience gastrointestinal symptoms on the 150-mg dose.²⁴¹ Berotrastat appears safe, with the most common side effects being gastrointestinal reactions, including abdominal pain, vomiting, and diarrhea, which occurred more frequently in patients receiving 150 versus 110 mg or placebo.²⁴⁰ These reactions generally occurred early after initiation of treatment with Berotrastat, became less frequent with time and typically self-resolved.^{242,243}

Summary: plasma-derived C1-INH, lanadelumab and berotrastat

Taken together, this guideline recommends any of the three medications for the first-line long-term prophylactic treatment of patients with HAE-1/2, ie, plasma-derived C1-INH, lanadelumab and berotrastat, based on the results of randomized controlled clinical trials.^{126,205,235,240} Where all three first-line LTP medications are available, the choice of which one to use should be made by shared decision

making.²⁴⁴ This guideline encourages studies that compare the efficacy and safety of first-line LTP medications and the identification of predictors of treatment responses. Currently, there is not enough evidence to recommend any of these three treatment options over each other. Where none of the three recommended first-line LTP treatments are available, efforts should aim to change this. Alternative options for LTP, in the absence of all three first-line LTP treatments, include the off-label use of intravenous recombinant C1-INH.²⁴⁵ Importantly, first-line LTP treatments should be initiated as approved. For lanadelumab, and to some extent for C1-INH, adapting the dose and/or treatment interval, after achieving complete response, can decrease treatment burden.^{196,219,220} Changes in the dose or the treatment intervals should be based on data obtained using patient-reported outcome measures. Poor control should prompt treatment optimization including consideration of switching LTP medication to improve efficacy.^{198,201,246,247}

Androgens

RECOMMENDATION 18

We recommend the use of androgens only as second-line long-term prophylaxis

89% agreement, evidence level C

Attenuated androgens have traditionally been used for long-term prophylaxis of HAE-1/2.^{248–252} Androgen derivatives have been demonstrated to be effective in HAE-1/2, and the oral administration facilitates their use.^{248,253} However, androgens must be regarded critically, especially in light of their adverse androgenic and anabolic effects, drug interactions, and contraindications. Side effects are numerous and involve most patients; in other words, the absence of side effects is exceptional.^{250,254} Side effects appear to be dose-related. Virilization is the most feared complication in women; menstrual disorders and even amenorrhea as well as diminished libido and hirsutism are also common,^{255–257} as are weight gain, headache, myalgia, depression, and acne. Androgens may lead to virilization of the female fetus and are, therefore, absolutely contraindicated during pregnancy.^{258,259} In children and adolescents, therapy with androgens may interfere with the natural growth and maturation process. In addition, androgens are subject to numerous contraindications and show interactions with many other drugs (eg, statins and antidepressants).^{211,260,261} Careful surveillance is imperative in long-term prophylaxis with androgens. In addition to clinical tests and examinations and questioning of the patient, semiannual blood and urine tests (standard urine test strip) are needed, and at least once a year, an ultrasound of the liver should be performed.^{211,260,262,263} Because of this, androgens should not be used as first-line LTP, and we recommend using them only as second-line long-term prophylactic treatment (Recommendation 18).^{252,264}

Long-term prophylaxis with antifibrinolytics

Antifibrinolytics such as tranexamic acid are not recommended for long-term prophylaxis.

Data for their efficacy are largely lacking, but some patients may find them helpful.^{270–274}

They are primarily used where first-line prophylactic treatment options are not available and androgens are contraindicated. The safety profile of antifibrinolytics is good. The most common side effect is gastrointestinal upset. Contraindications/ precautions include the presence of thrombophilia or increased thrombotic risk or acute thrombosis, eg, deep venous thrombosis and pulmonary embolism. The doses of tranexamic acid used range from 30 to 50 mg/kg body weight daily divided into two or three doses to a maximum of 6 g per day. Dose-ranging studies and comparisons with other prophylactic medications have not been performed.^{6,7,272,275,276}

10 | MANAGEMENT OF HAE- 1/2 IN CHILDREN

10.3 | Therapy of HAE in children

RECOMMENDATION 21 (evidence level A; 94% agreement)

- We recommend C1 inhibitor or icatibant be used for the treatment of attacks in children under the age of 12 94% agreement, evidence level A

Hintergrundinfos:

Like adults, all pediatric HAE-1/ 2 patients need to have a treatment action plan (see below) and on-demand therapy (Recommendation 21).^{143,214,307–309} C 1-INH and i catibant a re t he only approved

on-demand treatments for children with HAE-1/ 2.^{116,117,119,120} Both are effective, well tolerated and show a good safety profile. For abdominal attacks, parenteral fluid replacement may be required as children are more susceptible to hypovolemia and dehydration, and extravasation into the peritoneal cavity and the intestinal lumen can be substantial. When C1-INH and icatibant are not available, SDP is preferred over FFP, but both are considered second-line treatment. Ecallantide is licensed for the use in adolescents in the United States.¹¹⁸

As in adults, preprocedural prophylaxis is recommended for medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract.^{165,166} Plasma- derived C1INH is the first- line preprocedural prophylactic option, and short courses of attenuated androgens should only be used second line, when C1- INH concentrate is not available. With either option, ondemand therapy should be available because short- term prophylaxis is not 100% effective.¹⁶⁸ The indications for long- term prophylaxis in adolescents are the same as in adults (see above). The preferred therapy in children younger than 12 years of age for long- term prophylaxis is pdC1- INH. The dosing interval and dose may need to be adjusted according to the individual response. When C1- INH concentrate is not available for long- term prophylaxis, antifibrinolytics (ie, tranexamic acid 20– 50 mg/kg) are preferred to androgens because of their better safety profile; however, efficacy is questioned by many, and data in support of its use are not available. Epsilon aminocaproic acid is less well tolerated than tranexamic acid. Androgens are not recommended for long- term prophylaxis in children and adolescents prior to Tanner Stage V. The administration of androgens requires careful safety monitoring. The continued need for regular prophylaxis with androgens and the dosing should be reviewed on a regular basis. Initial danazol dose for children is 2.5 mg/kg per day with subsequent adjustment, until symptom suppression or the maximum tolerated, or maximum recommended dose is reached, with a maximum single dose of 200 mg per day. Androgens result in masculinization and hypogonadism in boys and menstruation irregularities in girls. Unfavorable effects on behavior are possible. Reduction in ultimate body height may occur owing to the premature closure of epiphyseal growth plates.^{6,7,297– 299,310,311}

10.4 | Primary prevention and other management considerations in children with HAE

Es werden folgende Informationen bei Kindern/Jugendlichen zur Verfügung gestellt (Keine konkrete Empfehlung verabschiedet):

As in adults, most attacks in children with HAE- 1/2 occur without an obvious trigger.³¹² Infections seem to be more common triggers of attacks in childhood. Compulsory and recommended vaccinations for children are safe, and the prevention of infections (eg, throat infections) may reduce the frequency of attacks. Medicinal products that can cause edema as an adverse effect are less frequently used in children. Treatment with an ACE inhibitor is less often necessary during childhood. However, early initiation of oral estrogen- containing contraceptives is increasingly common, may trigger attacks and should be avoided. Hormonal contraception with progesterone- only pills may benefit many young women with HAE- 1/2.^{275,313,314} or at least should not increase attack frequency. Other triggers like strenuous physical activities involving mechanical trauma and emotional challenges (stress) are essential elements of childhood and adolescence.³¹⁵ Restrictions of suspected triggers should be individualized and sensibly applied, along with the use of prophylaxis where necessary, with the aim of avoiding any limitations in activities and lifestyle. The aim of HAE- 1/2 management at all ages is to normalize the lives of patients.^{297,316} Providing pediatric patients and their families with appropriate information is indispensable to support them to adopt a suitable lifestyle and to avoid complications. Educators, teachers, and health care personnel responsible for the child at day care or school should receive written information on the disease, with advice on the management of HAE attacks, including the urgency of treatment for airway attacks. C1- INH or icatibant for emergency use should be available at home, school, and travel including school field trips. An action plan is necessary, and the family and local hospital should have therapies available for emergency treatment, and this should be included in the treatment plan. All HAE patients have a potential for receiving human blood products. Vaccinations for hepatitis A and B are recommended by many experts.^{295,297} All patients should be considered to receive influenza vaccine and other routine vaccinations.

Referenzen für die Therapy of HAE in children (RECOMMENDATION 21):

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The International/Canadian Hereditary Angioedema Guideline

Fragestellung

The objective of this guideline is to provide evidence-based recommendations for the management of patients in Canada and internationally with HAE-1, HAE-2, and HAE nC1-INH. This includes the treatment of attacks, STP, LTP, and recommendations for self-administration, individualized therapy, QoL and comprehensive care.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse beschrieben; kein externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Keine Angaben zur Gültigkeit und Überprüfung der Aktualität

Recherche/Suchzeitraum:

- systematic search using Ovid MEDLINE on June 27, 2018 and November 4, 2018

LoE / GoR

- Criteria for determining Levels of Evidence and Strength of Recommendation were adapted from the GRADE system, and the process was based primarily on the Journal of Clinical Epidemiology's 2011–2013 series of articles describing the GRADE methodology.

Empfehlungen

Acute treatment of HAE-1 and HAE-2

Recommendation 3

Effective therapy should be used for the acute treatment of attacks of angioedema to reduce duration and severity of attacks.

Level of Evidence: High (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

We emphasized the importance of healthcare professionals only using effective therapies supported by evidence, specifically not using non evidence-based therapies such as antihistamines, corticosteroids and epinephrine, which treat histamine-mediated angioedema. In addition to acute therapy, patients should discontinue and avoid any known triggers such as estrogen-containing oral contraceptives or replacement therapy, dipeptidyl peptidase IV (DPP-IV) inhibitors, neprilysin inhibitors, and ACE inhibitors [39–46].

Recommendation 4

Intravenous pdC1-INH is an effective therapy for the acute treatment of attacks.

Level of Evidence: High (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Plasma-derived (pd) C1-INH is a human blood product. Treatment with pdC1-INH replaces the deficient protein in patients with HAE-1/2. It has been shown to effectively treat attacks of HAE-1/2 in adults and children [31], and is administered either by healthcare professionals or by patients and their caregivers who have been trained in its administration.

The recommended dose for acute treatment of attacks is derived from clinical trials. There have been no head to head trials comparing products so it cannot be concluded that they all have equivalent efficacy. The pdC1-INH products are safe and well tolerated when used as indicated, with no documented transmission of infectious agents.

Recommendation 5

Icatibant is an effective therapy for the acute treatment of attacks.

Level of Evidence: High (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Bradykinin is a key mediator in inducing angioedema through activation of the bradykinin B2 receptor [8]. Icatibant is a synthetic decapeptide and acts as a selective bradykinin B2 receptor competitive antagonist. It is administered as a single 30 mg subcutaneous (SC) injection. It is generally systemically well tolerated, although 97% of patients experience transient local pain, swelling, and erythema at the injection site.

Recommendation 6

Ecallantide is an effective therapy for the acute treatment of attacks.

Level of Evidence: High (96.77% Agree, 3.23% Disagree)

Strength of Recommendation: Strong (96.77% Agree, 3.23% Disagree)

Clinical considerations

Plasma kallikrein generates bradykinin through cleavage of high-molecular-weight kininogen [8, 47, 48]. Ecallantide is a 60-amino acid recombinant protein that selectively and reversibly inhibits kallikrein. It is administered as three 10 mg SC injections for a total dose of 30 mg [49]. It has been shown to effectively treat attacks in adolescent and adult patients with HAE-1/2 [35]. Hypersensitivity reactions have been described with this agent in 5% of administrations, of which approximately 50% were possible anaphylactic reactions. It should only be administered by a healthcare practitioner in a location where anaphylaxis can be appropriately managed.

Recommendation 7

Intravenous rhC1-INH is an effective therapy for the acute treatment of attacks.

Level of Evidence: High (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Recombinant human (rh) C1-INH (conestat- α) is generated in the mammary glands of transgenic rabbits, and is identical to pdC1-INH except for the degree of protein glycosylation [50]. This difference in glycosylation results in shorter plasma mean half-life of the recombinant product [51, 52], however the effect this has on physiologic activity is not known [53]. It has been shown to effectively treat attacks in children 13 years of age and older and adults with HAE-1/2 [37]. Because of an isolated anaphylactic reaction after administration of rhC1-INH to a rabbit-allergic person, those known or suspected of having a rabbit allergy should not receive rhC1-INH.

Recommendation 8

Attenuated androgens should not be used for the acute treatment of attacks.

Level of Evidence: Low (96.97% Agree, 3.03% Disagree)

Strength of Recommendation: Strong (96.97% Agree, 3.03% Disagree)

Recommendation 9

Tranexamic acid should not be used for the acute treatment of attacks.

Level of Evidence: Low (96.97% Agree, 3.03% Disagree)

Strength of Recommendation: Strong (96.97% Agree, 3.03% Disagree)

Clinical considerations

Attenuated androgens such as the 17 α -alkylated anabolic androgen danazol and anti-fibrinolytic drugs such as tranexamic acid have not been shown to be efficacious in the acute treatment of attacks of HAE-1/2. Given the lack of evidence for these agents in the acute treatment of HAE, we strongly agreed that they should not be used for the treatment of acute HAE attacks.

Recommendation 10

Frozen plasma could be used for the acute treatment of attacks if other recommended therapies are not available.

Level of Evidence: Low (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Frozen plasma (FP) is a blood product, which contains C1-INH in association with other plasma proteins. FP is not as safe as solvent detergent plasma (SDP) with respect to pathogen inactivation, and the level of evidence that FP is effective in the acute treatment of attacks of HAE-1/2 is low. It also contains potential substrates for the generation of additional bradykinin and in theory could worsen attacks of angioedema. There may be a significant delay in getting FP and/or SDP in a timely manner—in some cases up to 24 h.

Therefore, we felt strongly that frozen plasma products, although potentially beneficial, should only be used if other recommended therapies are not available, and that every effort should be made to ensure timely and appropriate therapy for HAE attacks [54, 55]. A decision to use FP will depend on local and patient factors and will require risk/benefit assessment of the respective merits of local FP treatment versus symptomatic relief only. Thus the threshold for treating when only FP is available would usually be limited to life-threatening or severely painful attacks.

Recommendation 11

Attacks should be treated early to reduce morbidity and mortality.

Level of Evidence (morbidity): Moderate (100% Agree)

Level of Evidence (mortality): Consensus (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Early treatment leads to more rapid symptom resolution. Observational studies have suggested that early treatment can be efficacious in reducing the duration of an HAE attack in some patients [56–62]. Therefore, despite the absence of a high level of evidence, we strongly endorsed early treatment in an attempt to reduce morbidity and likely mortality. Interestingly, early treatment with C1-INH might also reduce the overall severity of an attack in addition to reducing the time to symptom relief [63]. Because of the potential barriers in accessing therapy in a timely manner, patients should be trained on how to self-administer therapies appropriate for the acute treatment of HAE attacks. If patients are not able to self-administer, efforts should be made to ensure that this therapy is made available to them without a significant delay.

Recommendation 12

All attacks of angioedema involving the upper airway are medical emergencies and must be treated immediately.

Level of Evidence: Low (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Attacks of HAE are unpredictable and potentially life threatening. Mortality due to laryngeal angioedema is well recognized [1]. All attacks of laryngeal angioedema should be considered medical emergencies, and therapies that have been shown to be effective in the treatment of HAE should be readily available and given immediately. It is also recommended that all patients with laryngeal edema, even following self-therapy, be assessed in the emergency department in the event that the angioedema does not respond to therapy and expertise in airway management is required [64].

Acute treatment of HAE in paediatric patients

Recommendation 14

All paediatric patients diagnosed with HAE should have access to acute treatment, including those that are symptom free.

Level of Evidence: Consensus (94.59% Agree, 5.41% Disagree)

Strength of Recommendation: Strong (94.59% Agree, 5.41% Disagree)

Clinical considerations

Symptom-free is in reference to those patients who have been diagnosed with inherited C1-inhibitor deficiency, but who have yet to demonstrate any symptoms of the disease. Due to the risks associated with the disease, all diagnosed patients should have ready access to acute treatment either on site or at a

nearby medical facility. The following are drug-specific recommendations for the acute treatment of HAE attacks in paediatric patients.

Recommendation 15

Intravenous pdC1-INH is an effective therapy for the acute treatment of HAE-1/2 attacks in paediatric patients.

Level of Evidence: Moderate (85.29% Agree, 11.76% Disagree, 2.94% Abstain)

Strength of Recommendation: Strong (94.87% Agree, 2.56% Disagree, 2.56% Abstain)

Clinical considerations

When children are treated with pdC1-INH for HAE attacks, responses are consistent with that of adults [83]. Studies have demonstrated that the intervention is safe and well tolerated [31] in the paediatric population and effective in reducing time to symptom relief [32, 84, 85]. Also similar to adults, data suggest that early treatment with pdC1-INH leads to more rapid symptom resolution [59, 62]. Dosing for pdC1-INH is 20 units (U)/kg IV Berinert® (CSL) [31, 83, 86, 87], 500 U IV Cinryze® (Takeda) for children 10–25 kg, or 1000 U IV Cinryze® for children > 25 kg [88–90].

Recommendation 16

Icatibant is an effective therapy for the acute treatment of HAE-1/2 attacks in paediatric patients.

Level of Evidence: Consensus (97.3% Agree, 2.7% Disagree)

Strength of Recommendation: Strong (92.31% Agree, 2.56% Disagree, 5.13% Abstain)

Clinical considerations

Icatibant has been approved to treat patients ≥ 2 years of age in some countries [91]. Depending on the age of the patient, the single SC dose of 0.4 mg/kg (to a maximum dose of 30 mg) injected into the abdomen can be self-administered, or given by a caregiver particularly in children. It does not require intravenous access, which can be challenging in paediatric patients [91–93].

Recommendation 17

Intravenous rhC1-INH is an effective therapy for the acute treatment of HAE-1/2 attacks in paediatric patients.

Level of Evidence: Consensus (100% Agree)

Strength of Recommendation: Strong (97.37% Agree, 2.63% Disagree)

Clinical considerations

Intravenous rhC1-INH is a recombinant form of C1-INH that has been studied in adolescents and adults for the acute treatment of HAE attacks [37]. Dosing is weight based, 50 U/kg (unless a patient is ≥ 84 kg, then the dose is 4200 U), and delivered intravenously [94].

Recommendation 18

Ecallantide is an effective therapy for the acute treatment of HAE-1/2 attacks in adolescent patients.

Level of Evidence: Consensus (97.44% Agree, 2.56% Abstain)

Strength of Recommendation: Strong (89.74% Agree, 2.56% Disagree, 7.69% Abstain)

Clinical considerations

Ecallantide has been studied and approved for use in adolescents ≥ 12 year of age in the USA based on data from 4 clinical studies [49, 95]. This small pooled data set showed efficacy in children as young as 10 years of age. Ecallantide is administered as 3 SC injections for a total of 30 mg [49], but cannot be self-administered.

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Empfehlungen zur Langzeitprophylaxe für HAE-1 und HAE-2

Recommendation 26 (Empfehlungsgrad: siehe Kasten)

Recommendation 26

pdC1-INH is an effective therapy for long-term prophylaxis in patients with HAE-1/2.

Level of Evidence: High (100% Agree)

Strength of Recommendation: Strong (100% Agree)

Clinical considerations

Controlled clinical trials have demonstrated that both IV and SC pdC1-INH used for prophylaxis in HAE-1/2 reduces the number, duration, and severity of attacks of angioedema [36, 38, 114]. C1-inhibitor prophylaxis has traditionally been given intravenously [38]. More recent trials have shown higher levels of efficacy when C1-inhibitor is given as a higher dose subcutaneously. The subcutaneous route also reduces the inconvenience and medicalization associated with the intravenous route, and avoids hazards of repeated venipuncture and indwelling catheters [115], further improving QoL [116]. However, direct comparison between the IV and SC routes has not been subject to formal trial.

Recommendation 27 (Empfehlungsgrad: siehe Kasten)

Recommendation 27

Lanadelumab is an effective therapy for long-term prophylaxis in patients with HAE-1/2.

Level of Evidence: High (95% Agree, 5% Disagree)

Strength of Recommendation: Strong (92.5% Agree, 5% Disagree, 2.5% Abstain)

Clinical considerations

Lanadelumab is a subcutaneously injectable, fully humanized, anti-active plasma kallikrein monoclonal antibody (IgG1/κ-light chain). It is administered as 300 mg every 2 weeks, however a dosing interval of 300 mg every 4 weeks may be considered if a patient is well controlled (e.g., attack free) for more than 6 months [110].

Recommendation 28 (Empfehlungsgrad: siehe Kasten)

Recommendation 28

Subcutaneous C1-INH or lanadelumab should be used as first-line for long-term prophylaxis.

Level of Evidence: Consensus (90% Agree, 10% Disagree)

Strength of Recommendation: Strong (97.37% Agree, 2.63% Disagree)

Clinical considerations

Although there have not been any head-to-head comparisons of long-term prophylactic agents, hence a consensus level of evidence for efficacy, we strongly agreed that either subcutaneous pdC1-INH or lanadelumab are appropriate as first-line LTP.

Recommendation 29 und 30 (Empfehlungsgrad: siehe Kasten)

Recommendation 29

Attenuated androgens and anti-fibrinolytics should not be used as first-line prophylaxis in patients with HAE-1/2.

Level of Evidence: Consensus (89.47% Agree, 7.89% Disagree, 2.63% Abstain)

Strength of Recommendation: Strong (88.89% Agree, 5.56% Disagree, 5.56% Abstain)

Recommendation 30

Attenuated androgens are an effective therapy for long-term prophylaxis in some patients.

Level of Evidence: Moderate (90.32% Agree, 9.68% Disagree)

Strength of Recommendation: Strong (90.32% Agree, 9.68% Disagree)

Clinical considerations

Considerations when deciding to start prophylaxis are discussed below, in “Approach to individualized therapy” section. The decision to start LTP should be based on the efficacy of the therapy, its side effects and safety profile, and the patient’s preference. Although androgens and anti-fibrinolytics are not recommended as first line, these agents may be considered for LTP in those patients who have already obtained benefit from their use or who have difficulty obtaining first-line options. It should not be necessary for patients to fail other long-term prophylaxis therapies, such as androgens and anti-fibrinolytics, before using pdC1-INH or lanadelumab.

Controlled trials and observational studies have demonstrated that treatment with 17 α -alkylated anabolic androgens, such as danazol, reduces the frequency and severity of HAE attacks [117–122]. Although one of the trials was a randomized controlled trial, the level of evidence for the trial was not considered high as there were insufficient details on funding, sequence generation, and outcome reporting [120]. Historically, many patients have been controlled with androgen therapy and their use in some patients may be acceptable provided that the lowest effective dose is used to achieve efficacy and minimize adverse events. Expert opinion suggests the optimal dose for danazol, to minimize adverse events, is ≤ 200 mg/day [9, 98].

Androgens can affect serum lipid levels, can be hepatotoxic resulting in hepatitis, and have been associated with hepatocellular adenoma and, in very rare cases, carcinoma [118, 123, 124]. It is recommended that all patients on androgen therapy be monitored for hypertension and have a complete blood count, liver enzymes, urinalysis, serum α -fetoprotein, creatine phosphokinase and lipid profile performed every 6 months, and an annual liver ultrasound [17].

Virilising effects of androgen therapy can occur and include menstrual irregularities, masculinization, irreversible voice alteration, and hirsutism. Psychological side effects include emotional irritability and lability, aggressive behaviour and depression. Androgens interact with several medications. They are contraindicated in pregnancy and lactation, before puberty, and in patients with androgen-dependent malignancy and hepatitis [123, 124]. Patients need to be made aware of these side effects when considering and while on androgen therapy, and physicians should carefully consider the risks and benefits for the particular patient.

There is a moderate level of evidence showing the benefit of the anti-fibrinolytic agent tranexamic acid as an LTP agent. This benefit was demonstrated in a randomized placebo-controlled trial with 18 subjects ≥ 12 years taking 1 g of tranexamic acid three times a day [125], and a double-blind crossover study of ϵ -aminocaproic acid in 9 patients aged 7 to 40

years [126]. These data suggested that anti-fibrinolytic agents could be useful for LTP for HAE-1/2. However, their role in current LTP was felt to be justified only in certain patient groups due to the lack of efficacy and the potential side effects at the dosage studied. The recommended dosage for tranexamic acid is 30–50 mg/kg daily divided in 2 or 3 doses to a maximum of 6 g per day.

Langzeitprophylaxe in pädiatrischen Patienten

Recommendation 34 (Empfehlungsgrad: siehe Kasten)

Recommendation 34
When long-term prophylaxis is indicated in paediatric patients, pdC1-INH is the treatment of choice.
Level of Evidence: Consensus (100% Agree)
Strength of Recommendation: Strong (97.5% Agree, 2.5% Disagree)

Clinical considerations

The clinical studies assessing the use of prophylactic pdC1-INH in children have been of small sample size [84, 85, 131–134]. Pooled data from an RCT and its open-label extension study demonstrated that pdC1-INH was effective and well tolerated for routine prophylaxis in children with HAE. Patients received IV infusions of pdC1-INH 1000 U (500 U for children ages 6 to 11) or placebo every 3 to 4 days. During the placebo-controlled pivotal trial, pdC1-INH reduced the number of angioedema attacks by nearly twofold ($n = 4$). During the open-label extension, pdC1-INH significantly decreased the pre-enrolment median monthly attack rate ($n = 23$). Adverse events during the studies were minimal (1 patient with pyrexia in the pivotal trial, and 1 patient with headache and nausea and another with infusion-site erythema considered related to pdC1-INH in the openlabel extension) [85]. Lanadelumab and SC pdC1-INH are indicated for routine prevention of recurrent attacks of HAE in **patients aged 12 years and older** (see Table 3).

Recommendation 35 (Empfehlungsgrad: siehe Kasten)

Recommendation 35
Androgens should not be used for long-term prophylaxis in paediatric patients.
Level of Evidence: Moderate (87.18% Agree, 7.69% Disagree, 5.13% Abstain)
Strength of Recommendation: Strong (84.62% Agree, 12.82% Disagree, 2.56% Abstain)

Clinical considerations

Androgens are known to cause premature closure of the epiphyses [135, 136], among other significant side effects, and are therefore contraindicated as LTP in the paediatric population before Tanner stage 5. However due to their efficacy, as described above, and in the absence of other available options, androgens may be considered once patients have completed puberty. If androgen use is necessary, paediatric patients should start at the lowest effective dose. They should have regular monitoring for side effects.

Anti-fibrinolytics cannot be recommended for LTP in the paediatric population due to the lack of evidence. Where they have been studied in children, they have shown limited efficacy [133]. **Similar to adults, paediatric patients should not be required to fail other non-specific therapies, such as androgens or anti-fibrinolytics, before proceeding to more specific LTP agents.**

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2024) am 07.02.2024

#	Suchfrage
1	MeSH descriptor: [Angioedemas, Hereditary] explode all trees
2	((C1 AND inhibitor*) OR "C1 INH" OR C1INH OR SERPING*) AND deficien*):ti,ab,kw
3	(hereditary OR congenital* OR inborn OR inherited OR familial):ti,ab,kw
4	(angioedema* OR (angio NEXT edema*) OR angiooedema* OR (angio NEXT oedema*) OR (angioneurotic NEXT edema*) OR (angioneurotic NEXT oedema*) OR (giant NEXT urticaria*) OR HAE OR (quincke* AND (edema* OR oedema*))) :ti,ab,kw
5	("HAE-C1-INH" OR "HAE-C1INH" OR "HAE-nC1-INH" OR "HAE-nC1INH" OR "HAE-nl-C1-INH" OR "HAE-nl-C1INH"):ti,ab,kw
6	#1 OR #2 OR (#3 AND #4) OR #5
7	#6 with Cochrane Library publication date from Feb 2019 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 07.02.2024

verwendete Suchfilter:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	angioedema, hereditary[mh]
2	((C1[tiab] AND inhibitor*[tiab]) OR C1-INH[tiab] OR C1INH[tiab] OR SERPING*[tiab]) AND deficien*[tiab]
3	hereditary[tiab] OR congenital*[tiab] OR inborn[tiab] OR inherited[tiab] OR familial[tiab]
4	angioedema*[tiab] OR "angio edema*" [tiab] OR angiooedema*[tiab] OR "angio oedema*" [tiab] OR "angioneurotic edema*" [tiab] OR "angioneurotic oedema*" [tiab] OR "giant urticaria*" [tiab] OR "HAE" [tiab] OR (quincke*[tiab] AND edema*[tiab]) OR (quincke*[tiab] AND oedema*[tiab])
5	HAE-C1-INH[tiab] OR HAE-C1INH[tiab] OR HAE-nC1-INH[tiab] OR HAE-nC1INH[tiab] OR HAE-nl-C1-INH[tiab] OR HAE-nl-C1INH[tiab]
6	#1 OR #2 OR (#3 AND #4) OR #5
7	(#6) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews" [tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR (("evidence based" [tiab:~3]) OR evidence base[tiab]) AND

#	Suchfrage
	(review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data syntheses*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR syntheses*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
8	(#7) AND ("2019/02/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 07.02.2024

verwendete Suchfilter:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	angioedema[mh]
2	((C1[tiab] AND inhibitor*[tiab]) OR C1-INH[tiab] OR C1INH[tiab] OR SERPING*[tiab]) AND deficien*[tiab]
3	angioedema*[tiab] OR "angio edema*" [tiab] OR angioedema*[tiab] OR "angio oedema*" [tiab] OR "angioneurotic edema*" [tiab] OR "angioneurotic oedema*" [tiab] OR "giant urticaria*" [tiab] OR "HAE" [tiab] OR (quincke*[tiab] AND edema*[tiab]) OR (quincke*[tiab] AND oedema*[tiab])
4	HAE-C1-INH[tiab] OR HAE-C1INH[tiab] OR HAE-nC1-INH[tiab] OR HAE-nC1INH[tiab] OR HAE-nl-C1-INH[tiab] OR HAE-nl-C1INH[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2019/02/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 08.02.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Anhang

Abbildung 1: Beard N et al., 2022 [1]. Summary of findings

Summary of findings 2. Berotralstat compared with placebo or active control for preventing hereditary angioedema attacks

Berotralstat compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: berotralstat

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with berotralstat				

Risk of HAE attacks (during follow-up)	Study population		RR 0.63 (0.39 to 1.00)	37 (1)	⊕⊕⊕⊕ Low^a	—
	910 per 1000	573 per 1000 (355 to 910)				
Change in number of HAE attacks (per week)	Study population		—	130 (3)	⊕⊕⊕⊕ Low^a	—
	The number of HAE attacks per week ranged across control groups from 0.55 to 0.95	The number of HAE attacks per week in the intervention groups was 0.39 attacks lower (0.74 lower to 0.05 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 0.77 (0.02 to 24.03)	128 (3)	⊕⊕⊕⊕ Low^a	—
	45 per 1000	35 per 1000 (1 to 1000)				
Quality of life Angioedema Quality of Life scale (lower score is better) (during follow-up)	Study population		—	130 (3)	⊕⊕⊕⊕ Moderate^b	—
	The mean change in quality of life ranged across control groups from 3.18 points to -9.69 points	The mean change in quality of life in the intervention group was 15.28 points lower (29.42 lower to 1.14 lower)				
Disability Standardised mean difference (lower is better) (during follow-up)	Study population		—	50 (2)	⊕⊕⊕⊕ Low^a	—
	The mean change in disability ranged across control groups from 1.51 to -1.95	The mean change in disability in the intervention groups was 1.01 units lower (1.62 lower to 0.40 lower)				
Adverse events (during follow-up)	Study population		RR 1.03 (0.88 to 1.22)	128 (3)	⊕⊕⊕⊕ Moderate^b	—
	761 per 1000	784 per 1000 (670 to 1000)				

^aThe risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels for imprecision.

^bDowngraded one level for imprecision.

Summary of findings 3. C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

C1-INH compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: C1-INH(SC)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with C1-INH(SC)				
Risk of HAE attacks (during follow-up)	Study population		RR 0.29 (0.16 to 0.50)	43 (1)	⊕⊕⊕⊕ Low^a	—
	810 per 1000	24 per 1000 (0 to 162)				
Change in number of HAE attacks (per week)	Study population		—	45 (1)	⊕⊕⊕⊕ Low^a	—
	The mean number of HAE attacks per week in the control group was 0.93	The mean number of HAE attacks per week in the intervention group was 0.81 lower (0.98 lower to 0.64 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 0.34 (0.01 to 8.14)	44 (1)	⊕⊕⊕⊕ Very low^b	—
	23 per 1000	8 per 1000 (0 to 187)				

Quality of life standardised mean difference (lower is better) (during follow-up)	Study population		—	36	⊕⊕⊕⊕	—
	The mean change in quality of life in the control group was -0.87 units	The mean change in quality of life in the intervention groups was 0.29 units lower (0.76 lower to 0.18 higher)		(1)	Low^a	
Disability (any validated scale) (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	Study population		RR 1.03 (0.84 to 1.27)	44	⊕⊕⊕⊕	—
	663 per 1000	683 per 1000 (557 to 842)		(1)	Moderate^c	

^aThe risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

C1-INH(SC): subcutaneous C1 esterase inhibitor; **CI**: confidence interval; **HAE**: hereditary angioedema; **N/A**: not applicable; **RR**: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels for imprecision.

^bDowngraded three levels for imprecision.

^cDowngraded one level for imprecision.

Summary of findings 4. Plasma-derived C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

pdC1-INH compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: pdC1-INH

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pdC1-INH				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	71 (1)	⊕⊕⊕⊕ Low^a	—
	The number of HAE attacks per week in the control group was 0.9	The number of HAE attacks per week in the intervention group was 0.53 attacks lower (0.58 lower to 0.48 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 0.54 (0.09 to 3.10)	71 (1)	⊕⊕⊕⊕ Very low^b	—
	53 per 1000	29 per 1000 (5 to 164)				
Quality of life Angioedema Quality of Life Score (lower score is better) (during follow-up)	Study population		—	31 (1)	⊕⊕⊕⊕ Low^a	—
	The mean change in quality of life in the control group was -6.86	The mean change in quality of life in the intervention group was 3.49 points lower (10.86 lower to 3.88 higher)				
Disability (any validated scale) (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	Study population		RR 1.05 (0.78 to 1.42)	71 (1)	⊕⊕⊕⊕ Low^a	—
	561 per 1000	589 per 1000 (438 to 797)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; pdC1-INH: plasma-derived C1 esterase inhibitor; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded two levels for imprecision.

^bDowngraded three levels for imprecision.

Summary of findings 5. Nanofiltered C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

C1-INH-nf compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: C1-INH-nf

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with C1-INH-nf				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	22 {1}	⊕⊕⊕⊕ Very low^d	—
	The mean number of HAE attacks per week in the control group was 1.06	The mean number of HAE attacks per week in the intervention group was 0.53 lower (0.78 lower to 0.28 attacks per week lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events	Study population		N/A	N/A	N/A	Outcome not reported.

(during follow-up)	N/A	N/A				
Quality of life	Study population		—	16	⊕⊕⊕⊕	—
standardised mean difference				(1)	Very low^a	
(lower is better)	The mean change in quality of life in the control group was 4.85 units	The mean change in quality of life in the intervention group was 0.91 units lower (1.64 lower to 0.18 lower)				
(during follow-up)						
Disability	Study population		—	16	⊕⊕⊕⊕	—
standardised mean difference				(1)	Very low^a	
(lower is better)	The mean change in disability in the control group was -0.71	The mean change in disability in the intervention group was 0.84 units lower (1.57 lower to 0.12 lower)				
(during follow-up)						
Adverse events	Study population		N/A	N/A	N/A	Outcome not reported.
(during follow-up)	N/A	N/A				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

C1-INH-nf: nanofiltered C1 esterase inhibitor; **CI:** confidence interval; **HAE:** hereditary angioedema; **N/A:** not applicable; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded three levels for imprecision.

Summary of findings 6. Recombinant human C1 esterase inhibitor compared with placebo or active control for preventing hereditary angioedema attacks

rhC1-INH compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: rhC1-INH

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with rhC1-INH				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	32 (1)	⊕⊕⊕⊕ Very low^a	—
	The number of HAE attacks in the control group was 1.8 per week	The number of HAE attacks per week in the intervention groups was 0.92 attacks lower (1.31 lower to 0.53 lower)				
Mortality (during follow-up)	Study population		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events (during follow-up)	Study population		RR 1.50 (0.06 to 34.66)	29 (1)	⊕⊕⊕⊕ Very low^a	No events reported in the placebo group, 1 event reported in the rhC1-INH group.
	0 per 1000	0 per 1000 (0 to 0)				
Quality of life standardised mean difference (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Disability (any validated scale) (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	Study population		RR 1.39 (0.71 to 2.70)	29 (1)	⊕⊕⊕⊕ Low^b	—
	286 per 1000	398 per 1000 (203 to 772)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; rhC1-INH: recombinant human C1 esterase inhibitor; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded three levels for imprecision.

^bDowngraded two levels for imprecision.

Summary of findings 7. Lanadelumab compared with placebo or active control for preventing hereditary angioedema attacks

Lanadelumab compared with placebo or active control for preventing HAE attacks

Patient or population: children or adults with Types I or II HAE

Settings: outpatient setting

Intervention: lanadelumab

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with lanadelumab				
Risk of HAE attacks (during follow-up)	Study population		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Change in number of HAE attacks (per week)	Study population		—	83 (2)	 Low^a	—
	The number of HAE attacks per week ranged across control groups from 0.37 to 0.49	The number of HAE attacks per week in the intervention groups was 0.41 attacks lower (0.48 lower to 0.35 lower)				
Mortality	Study population		N/A	N/A	N/A	No deaths reported.

(during follow-up)	N/A	N/A				
Serious adverse events	Study population		RR 0.88 (0.08 to 10.39)	162		—
(during follow-up)	24 per 1000	73 per 1000 (7 to 765)		(2)	Low^d	
Quality of life	Study population		—	68		—
standardised mean difference (lower is better) (during follow-up)	The mean change in quality of life in the control group was -4.72 points	The mean change in quality of life in the intervention group was 0.91 units lower (1.43 lower to 0.40 lower)		(1)	Low^d	
Disability	Study population		—	64		—
Standardised mean difference (lower is better) (during follow-up)	The mean change in disability in the control group was -5.42	The mean change in disability in the intervention group was 1.38 units lower (1.94 lower to 0.82 lower)		(1)	Low^d	
Adverse events	Study population		RR 1.07 (0.77 to 1.47)	158		
(during follow-up)	1000 per 1000	840 per 1000 (710 to 980)		(2)	Low^d	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; HAE: hereditary angioedema; N/A: not applicable; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

^dDowngraded two levels for imprecision.

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: **2024-B-042**

Verfasser	
Name der Institution	<i>Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI), federführend</i> <i>Deutsche Dermatologische Gesellschaft (DDG)</i> <i>Gesellschaft für Pädiatrische Allergologie (GPA)</i>
Namen aller beteiligten Sachverständigen	Prof. Dr. med. Bettina Wedi (federführend, DGAKI) Prof. Dr. med. Matthias Augustin (DDG) Prof. Dr. med. Alexander Nast (DDG) Prof. Dr. med. Christian Vogelberg (GPA)
Datum der Erstellung	21. März 2024

Indikation
„... wird bei Patienten ab 12 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) angewendet.“
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? (Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)
Grundsätzlich kommen zwei verschiedene therapeutische Strategien beim hereditären Angioödem durch C1-INH-Mangel (HAE-C1-INH) zur Anwendung: Entweder werden die Attacken behandelt, sobald sie für den Patienten erkennbar sind (on-demand-Therapie, Bedarfstherapie) oder es wird eine Dauertherapie durchgeführt, deren Ziel die Vermeidung der Attacken ist (Prävention, Prophylaxe) (Bork et al. 2019, Leitlinie AWMF-Register-Nr. 061-029).
Zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) bei Patientinnen und Patienten ab 12 Jahren kommen in Frage:
1. Lanadelumab Lanadelumab ist ein voll humaner, monoklonaler Antikörper, der an Plasma-Kallikrein bindet und es hierdurch hemmt. Dadurch wird die Spaltung von HMWK inhibiert und damit auch die Freisetzung des vasoaktiven Bradykinins, das zur Ödembildung führt. In einer randomisierten, doppelblinden, Plazebo-kontrollierten Studie mit 125 Patienten zeigte sich eine signifikante Attackenreduktion bei den mit Lanadelumab behandelten Patienten (Banerji, Riedl et al. 2018). Die Studie lief über 26 Wochen. Weitere Analysen zeigten, dass die Wirkung frühzeitig einsetzt und über die gesamte Studienzeit anhielt (Riedl, Maurer et al. 2020). Eine Open-Label-Studie mit Lanadelumab zeigte ähnliche Resultate (Banerji, Bernstein et al. 2022). In der Open-Label Extension über 132 Wochen zeigte sich eine signifikante Verbesserung der

gesundheitsbezogenen Lebensqualität (HRQoL) sowie eine gute Krankheitskontrolle gemessen mit dem Angioedema Control Test (ACT) (C1 et al. 2023).

Lanadelumab wird subkutan appliziert. Die Dosierung beträgt 300 mg Lanadelumab alle 2 Wochen. Bei Attackenfreiheit kann eine Dosisreduktion auf 300 mg alle 4 Wochen Lanadelumab in Erwägung gezogen werden.

2. C1-INH-Konzentrat aus Plasma (intravenöse oder subkutane Therapie)

a) intravenöse Therapie

In einer randomisierten und kontrollierten cross-over-Studie (22 Patienten in 2 12-Wochen-Perioden) reduzierte das nanofiltrierte C1-INH-Konzentrat Cinryze® in einer Dosierung von 1000 IE zweimal wöchentlich die HAE-Attackenzahl von 12,7 auf 6,3. Die Schwere und Dauer der verbliebenen Attacken war signifikant geringer (Zuraw, Busse et al. 2010). Cinryze® wurde im Oktober 2008 für die Langzeitprophylaxe in den USA zugelassen und im Juni 2011 auch in Europa (Shire, UK). Seit 2017 ist Cinryze® auch für Kinder - ab dem 6. Lebensjahr - für die Prophylaxe des HAE-C1-INH in der EU zugelassen.

Die meisten Patienten, die eine Langzeitprophylaxe mit C1-INH-Konzentrat durchführen, injizieren sich das Medikament selbst oder erhalten es durch Angehörige bzw. durch Heimtherapie-Firmen. Patienten müssen für solch eine Therapie mit häufigen intravenösen Injektionen geeignet sein und geschult werden.

b) subkutane Prävention

Im Jahr 2017 wurde eine Studie mit subkutan applizierten C1-INH bei zur Prävention von HAE-Attacken publiziert (Longhurst, Cicardi et al. 2017). In einem Cross-over-Design erhielten die Patienten 40 oder 60 IU CSL830 (subkutan appliziertes volumenreduziertes C1-INH-Konzentrat) und Placebo zweimal pro Woche. Die Resultate zeigten eine hohe Attackenreduktion bei CSL830 gegenüber Placebo. Die Open-Label Extensionsstudie über bis zu 140 Wochen bestätigte die Ergebnisse (Craig et al. 2022). Ein großer Teil der Patientinnen und Patienten war während der Studie attackenfrei.

In den USA wurde CSL380 2017 unter dem Namen HAEGARDA zur Langzeitprophylaxe des HAE-C1-INH zugelassen. In Deutschland sind in Analogie hierzu „Berinert 2000 IE“ und „Berinert 3000 IE“ für die Prävention von HAE-Attacken bei jugendlichen und erwachsenen Patienten mit C1-INH-Mangel zugelassen.

3. Berotralstat

Berotralstat ist ein neuartiger Plasma-Kallikrein-Inhibitor. Er bindet an Kallikrein und hemmt dessen proteolytische Aktivität und damit die Entwicklung von HAE-Attacken. Er ist für die routinemäßige Prophylaxe von Schwellungsattacken beim HAE in Deutschland zugelassen. Eine besondere Eigenschaft des Berotralstat ist die Wirksamkeit bei oraler Applikation. In einer randomisierten, doppelblinden, Placebo-kontrollierten Phase-3-Studie zeigte sich Berotralstat bei einmal-täglicher, oraler Gabe signifikant wirksam (Zuraw, Lumry et al. 2020). Die Studiendauer betrug 24 Wochen. Die häufigsten unerwünschten Wirkungen waren gastrointestinale Symptome sowie Kopfschmerz. Die open-label Extension der Phase 2 zeigte eine gute Verträglichkeit über 48 Wochen (Farkas H et al. 2021). Langzeitdaten der Phase 3 Studie über 96 Wochen zeigten signifikante Verbesserungen der Attackenraten, des on-demand-Medikamentenverbrauchs sowie der Lebensqualität. 93% waren Attackenfrei (Kiani-Alikhan et al. 2024).

4. Gestagene

Gestagene können bei der Behandlung von Frauen mit einem HAE-C1-INH hilfreich sein. Eine Zulassung oder RCT-Studien hierzu gibt es nicht, jedoch Berichte über Therapieerfolge in Fallserien (Bouillet, Longhurst et al. 2008, Saule, Boccon-Gibod et al. 2013). Desogestrel ist eine „progesteron-only-pill“ (POP). Etwa zwei Drittel der Frauen berichteten unter Gestagen über eine Symptomverbesserung. Bei 7 Frauen kam es dagegen zu einer Verstärkung der HAE-C1-INH-

Symptomatik (Longhurst 2013). Die Dosierung entspricht derjenigen, wie sie bei Antikonception empfohlen wird. An Nebenwirkungen sind u.a. Gewichtszunahme und Zwischenblutungen möglich. Eine Progesterontherapie sollte nicht mit einer Androgentherapie oder Tranexamsäurebehandlung kombiniert werden. Der günstige Effekt einer Progesterontherapie ist allgemein deutlich geringer als der einer Prophylaxe mit Lanadelumab, C1-INH-Konzentrat oder mit abgeschwächten Androgenen.

4. Attenuierte Androgene

Seit 1976 werden abgeschwächte Androgenderivate für eine Langzeitprophylaxe eingesetzt, dementsprechend gibt es genügend Erfahrungen über Wirksamkeit und Sicherheit. Verwendet werden Danazol und Oxandrolon. Stanazolol ist nicht mehr verfügbar. Die Wirksamkeit der Androgene ist hoch. In einer doppelblinden, randomisierten Cross-over-Studie mit Danazol (600 mg pro Tag) versus Placebo an insgesamt 9 Patienten senkte Danazol die Attackenanzahl signifikant (2,2% versus 93,6%) (Gelfand, Sherins et al. 1976). Obwohl in dieser Studie alle Patienten an Gewicht zunahmten und alle 5 Frauen Menstruationsstörungen bis hin zur Amenorrhoe (4 von 5) beschrieben, wurden die Nebenwirkungen als „minimal“ beschrieben. Allerdings wird eine so hohe Dosis Danazol heute nicht mehr empfohlen, verwendet werden maximal 200 mg pro Tag.

Eine nicht-randomisierte Studie untersuchte unerwünschte Ereignisse, die durch Langzeitprophylaxe mit den abgeschwächten Androgenen Danazol und Stanazolol verursacht wurden, und verglich diese unerwünschten Ereignisse mit den Raten bei Personen mit HAE, die keines der beiden Medikamente erhalten hatten (Cicardi et al. 1997). Die Teilnehmer hatten die abgeschwächten Androgene im Median 125,5 Monate lang eingenommen (Spanne: 22 bis 273 Monate). Es zeigte sich eine dosisabhängige Inzidenz von Menstruationsstörungen bei 50% der prämenopausalen Frauen und eine dosisabhängige Zunahme des Körpergewichts bei 28% aller Teilnehmer. Hypertonie war auch häufiger bei Personen, die Danazol einnahmen, als bei unbehandelten Kontrollen.

In einer 2008 publizierten Studie waren 46% der Patienten unter Danazol vollkommen erscheinungsfrei oder hatten 1 oder weniger Attacken pro Jahr (Bork, Bygum et al. 2008). Nicht alle Patienten sprechen auf eine Androgen-Behandlung an. Bei einem Teil der Patienten kann die Wirksamkeit nach einigen Jahren nachlassen (Fust, Farkas et al. 2011). Die möglichen Nebenwirkungen sind zahlreich und umfassen u.a. Gewichtszunahme, Menstruationsstörungen und Virilisierung bei weiblichen Patienten sowie Hepatotoxizität, Depression, arterielle Hypertonie und hämorrhagische Zystitis bei langdauernder Anwendung. Vereinzelt sind Leberzelladenome aufgetreten, bei einigen wenigen Patienten auch Leberzellkarzinome. In einer Langzeit-Beobachtungsstudie waren nur 21 % der Danazol-Patienten frei von Nebenwirkungen und 30 von 118 Patienten beendeten die Danazol-Behandlung aufgrund von Nebenwirkungen (Bork, Bygum et al. 2008).

Attenuierte Androgene sind in Deutschland nicht zugelassen, sie müssen über die internationale Apotheke bezogen werden. Es ist empfehlenswert, eine solche Behandlung - wenn überhaupt erwogen - in einem HAE-Behandlungszentrum durchführen zu lassen. Die Anzahl der mit Danazol behandelten Patienten ist in Deutschland wesentlich zurückgegangen.

5. Tranexamsäure

Zwei antifibrinolytische Agentien haben sich beim HAE-C1-INH als wirksam erwiesen, Epsilonaminocaprönsäure (EACA) und Tranexamsäure. In einer doppelblinden Placebo-kontrollierten Cross-over-Studie mit 16 g EACA täglich versus Placebo zeigte sich bei 4 Patienten eine signifikante Wirksamkeit der EACA (Frank, Sargent et al. 1972). In einer weiteren Placebo-kontrollierten Cross-over-Studie mit Tranexamsäure zeigte sich bei den meisten Patienten eine deutliche Besserung des HAE-C1-INH durch Tranexamsäure (Sheffer, Austen et al. 1972). Seit 1972 wird Tranexamsäure zur Langzeitbehandlung des HAE-C1-INH eingesetzt (Blohme 1972), es ist besser verträglich als EACA. Die Wirksamkeit von Tranexamsäure (Cyklokapron®) ist bei

Erwachsenen im Allgemeinen deutlich geringer als die von attenuierten Androgenen. Bei der Langzeitprophylaxe ist die Tranexamsäure wegen Wirksamkeitsmangel praktisch verlassen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Es gibt keine Kriterien für unterschiedliche Behandlungsentscheidungen bei „Patienten ab 12 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE)“, die regelhaft berücksichtigt werden.

Die Einschätzung der Wirksamkeit beruht auf den Resultaten der RCTs. Head-to-head-Studien sind nicht vorhanden.

Ein Cochrane-Analyse randomisierter kontrollierter Studien zur medikamentösen Langzeitprophylaxe des HAE bei Kindern und Erwachsenen, die Daten bis zum 3. August 2021 umfasste, identifizierte 15 Studien mit 912 Teilnehmern (Beard N et al. 2022). Die Studien untersuchten Avoralstat (nicht in Deutschland zugelassen), Berotralstat sowie subkutane und intravenöse C1-INH-Konzentrate, Danazol und Lanadelumab. Studien zur prophylaktischen Anwendung von Tranexamsäure fanden sich nach den Autoren nicht *(Kommentar: die unter 5. Hier benannten Studien sind so alt, dass sie mit den Cochrane Suchmethoden nicht gefunden wurden)*. Das Fazit der Cochrane-Analyse-Autoren: Die verfügbaren Daten legen nahe, dass Berotralstat, C1-INH (subkutan, Plasmaderivat, nanofiltriert und rekombinant), Danazol und Lanadelumab effektiv sind, um das Risiko oder die Häufigkeit (oder beides) von HAE-Attacken zu verringern. Darüber hinaus verringern C1-INH und Lanadelumab die Schwere von Durchbruchattacken (Daten für andere Medikamente lagen nicht vor). Avoralstat, Berotralstat, C1-INH (alle Formen) und Lanadelumab steigern die Lebensqualität und erhöhen nicht das Risiko von Nebenwirkungen, einschließlich schwerwiegender Nebenwirkungen. Es ist möglich, dass Danazol, subkutanes C1-INH und rekombinantes menschliches C1-INH wirksamer sind als Berotralstat und Lanadelumab bei der Verringerung des Risikos von Durchbruchattacken pro Woche, aber die geringe Anzahl von Studien und die geringe Größe der Studien bedeuten, dass die Evidenzqualität gering ist. Dies und das Fehlen von Direktvergleichen ermöglichten keine konkreten Schlussfolgerungen über die relative Wirksamkeit der Medikamente.

Kürzliche Real-World-Daten in England zeigten verminderte Attackenraten unter 6-monatiger Anwendung von Berotralstat im Vergleich zu den drei Monaten vorher unter einer Langzeitprophylaxe mit attenuierten Androgenen bzw. Tranexamsäure (Ahuja M et al. 2023).

In Einzelfällen lässt die Venensituation eine intravenöse Langzeitprophylaxe nicht zu, so dass auf Medikamente mit anderer Applikationsform ausgewichen werden muss.

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