Gemeinsamer Bundesausschuss

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-312 Donidalorsen

Stand: März 2025

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

Donidalorsen
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; Beschluss 06.06.2024) - 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:	
Donidalorsen Dawnzera	Geplantes Anwendungsgebiet laut Beratungsanforderung: Donidalorsen ist indiziert für die routinemäßige Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) bei Erwachsenen und Jugendlichen ab 12 Jahren.
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. […] *[Cinryze, Stand FI: 09/2022]* Hereditäres Angioödem Typ I und II (HAE), Therapie und vor einem Eingriff durchgeführte Prophylaxe des akuten Schubes *[Berinert 500/1500, Stand FI: 04/2022]* Berinert zur subkutanen Injektion wird zur Prävention von rezidivierenden hereditären Angioödemattacken (HAE) **bei jugendlichen und erwachsenen Patienten** mit C1-Esterase-Inhibitor-Mangel angewendet. *[Berinert 2000/3000, Stand FI: 04/2022]*
Tranexamsäure B02AA02 Cyklokapron	[…] Zur Vorbeugung des Auftretens von Ödemen bei hereditärem Angioödem (Schwellungsneigung im Unterhautgewebe an verschiedenen Körperstellen sowie Schleimhäuten, einschließlich Kehlkopf und Rachen). *[Cyklokapron® 500 mg Filmtabletten, Stand FI: 10/2022]*
Lanadelumab B06AC05 Takhzyro	TAKHZYRO wird bei Patienten ab 2 Jahren zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) angewendet. *[Stand FI 11/2023]*
Berotralstat 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). *[Stand FI 12/2022]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-312 (Donidalorsen)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. Januar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
C1INH	C1 inhibitor
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
HAE	Hereditäres Angioödem
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	Intravenous
KI/CI	Konfidenzintervall
LoE	Level of Evidence
LTP	Long-term prophylaxis
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SC	Subcutaneous
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) bei Erwachsenen und Jugendlichen ab 12 Jahren.

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.

Die Erstrecherche wurde am 08.02.2024 durchgeführt, die folgende am 06.01.2025. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 97 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:

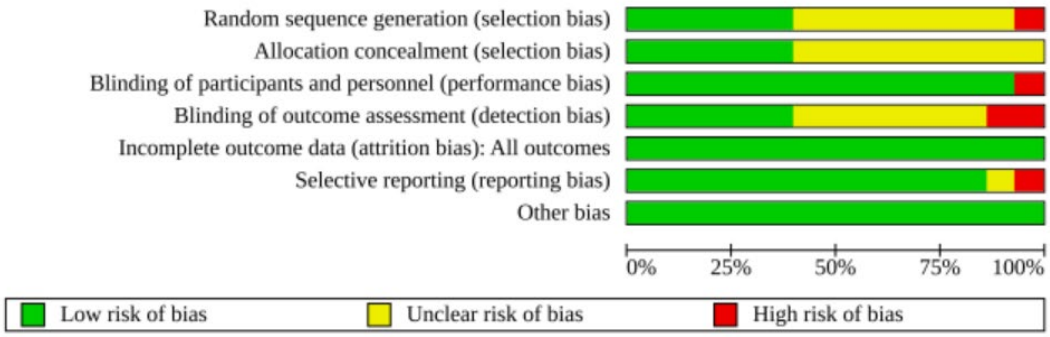
- 15 studies (912 participants)

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

Longhurst HJ et al., 2024 [2].

Hereditary Angioedema Attacks in Patients Receiving Long-Term Prophylaxis: A Systematic Review

Fragestellung

The objective of this systematic review was to evaluate the proportion of type I/II hereditary angioedema (HAE-C1INH) patients who experience attacks while receiving Long-term prophylaxis (LTP), the characteristics of these attacks, and associated on-demand therapy use.

Methodik

Population:

- Patients with type I/II hereditary angioedema

Intervention:

- LTP use with one of the following drugs: intravenous (IV) C1 inhibitor (C1INH), subcutaneous (SC) C1INH, lanadelumab, berotralstat, androgens (including danazol, stanozolol, oxandrolone, or methyltestosterone), antifibrinolytics (including aminocaproic acid or tranexamic acid [TA]), or any investigational LTP agent with published phase 2 or 3 clinical data (including garadacimab and donidalorsen).

Komparator:

- placebo, patients receiving on-demand therapy only, or patient baseline measurements (i.e., before initiation of LTP)

Endpunkte:

- primary outcome: proportion of patients receiving LTP who achieved attack-free status
- attack severity

Recherche/Suchzeitraum:

- A systematic search was conducted in PubMed to identify peer-reviewed publications in English since January 1, 2002
- The initial search was conducted on May 17, 2022, and was updated on May 15, 2023

Qualitätsbewertung der Studien:

- Assessments for risk of bias were performed for included studies using the Risk of Bias 2 tool for RCTs (rated as high, moderate, or low risk of bias)
- Newcastle-Ottawa Scale for observational studies (rated on a star system on the selection of study groups, the comparability of the groups, and the ascertainment of the outcome of interest)

Ergebnisse

Anzahl eingeschlossener Studien:

- 45 primary studies:
  - 13 were RCTs (8 were phase 3 RCTs, 4 were phase 2 RCTs, and 1 was a phase 1b RCT),
  - 7 were open-label studies

- 25 were observational studies (12 retrospective case series or chart reviews, 10 prospective cohort or registry studies, and 3 patient surveys).

Charakteristika und Qualität der Studien:

- *Methodikeranmerkung: Es werden lediglich die beschriebenen RCT und Open-Label-Extension-Studien abgebildet. Die entsprechenden Studienergebnisse der im AWG zugelassenen Wirkstoffe sind in den nachfolgenden Ergebnistabellen durch eine Markierung hervorgehoben.*

Study identifier	First author, year	Study design	LTP agent	Dose	Comparator	No. of patients	Study population	Duration of treatment	Primary outcome	Risk of bias/quality
RCTs and open-label extension studies										
pdC1INH replacement										
NCT02052141	Aygören-Pürsün, 2019 [23]	Phase 3 Crossover Single-blind Multicenter	Cinryze (IV)	500 U 1000 U	NA	12	Children aged ≥6 to <12 years	2 × 12-week crossover periods	Monthly normalized number of attacks in each 12-week treatment period	High risk
NCT01005888 (LEVP2005-1 Part B)	Lumry, 2013 [21] Zuraw, 2010 [42]	Phase 3 Crossover Double-blind Multicenter	Cinryze (IV)	1000 U	Placebo	24	Children aged ≥6 years and adults	2 × 12-week crossover periods	Normalized number of attacks in each 12-week treatment period	Low risk
NCT00462709 (LEVP2006-4 CHANGE-3)	Zuraw, 2012 [14] Lumry, 2013 [21] Zuraw, 2010 [42] Baker, 2013 [22]	Phase 3 Open-label extension Multicenter	Cinryze (IV)	1000 U	NA	146	Children aged ≥1 year and adults	Median: 248 days (up to 2.6 years)	Number of attacks during the treatment period	NA
NCT01576523	Zuraw, 2015 [15]	Phase 2 Open-label Crossover Multicenter	Berinert (SC)	1500 IU 3000 IU 6000 IU	NA	18	Adults aged ≥18 years	2 × 4-week treatment periods	Mean trough C1INH activity at week 4[a]	NA
NCT01912456 (COMPACT)	Longhurst, 2017 [9] Craig, 2019 [44] Li, 2019 [41]	Phase 3 Crossover Double-blind Multicenter	Berinert (SC)	40 IU/kg 60 IU/kg	Placebo	90	Adolescents aged ≥12 years and adults	2 × 16-week crossover periods	Time-normalized number of attacks in each 16-week treatment period	Moderate risk
NCT02316353 (COMPACT-OLE)	Craig, 2019 [43] Craig, 2022 [13] Bernstein, 2020 [19] Levy, 2020 [18] Levy, 2020 [56]	Phase 3 Open-label extension Parallel Multicenter	Berinert (SC)	40 IU/kg[b] 60 IU/kg[b]	NA	126	Children aged ≥6 years and adults	≥52 weeks to 140 weeks[c]	Long-term safety[d]	NA
Japanese study	Fukuda, 2023 [20]	Phase 3 Open-label Single-arm Multicenter	Berinert (SC)	60 IU/kg	Baseline (3-month period before screening) or run-in (up to 8 weeks)	9	Adolescents aged ≥12 years and adults	16 weeks	Time-normalized number of attacks/month during the treatment period; C1INH activity at week 16[e]	NA
Lanadelumab										
NCT02093923	Banerji, 2017 [50]	Phase 1b Parallel Double-blind Multicenter	Lanadelumab	30 mg 100 mg 300 mg 400 mg	Placebo	37	Adults aged ≥18 years	6 weeks[f]	Number of attacks per week from day 8 to day 50	Moderate risk
NCT02586805 (HELP)	Banerji, 2018 [8] Johnston, 2021 [57] Riedl, 2020 [16] Craig, 2022 [58]	Phase 3 Parallel Double-blind Multicenter	Lanadelumab	150 mg 300 mg (Q2W) 300 mg (Q4W)	Placebo	125	Adolescents aged ≥12 years and adults	26 weeks	Number of attacks in the 26-week treatment period	Low risk
NCT02741596 (HELP-OLE)	Banerji, 2022 [24] Craig, 2022 [58]	Phase 3 Open-label extension Multicenter	Lanadelumab	300 mg[g]	NA	212	Adolescents aged ≥12 years and adults	Mean (SD): 29.6 (8.2) months	Long-term safety; number of investigator-confirmed HAE attacks per month during the treatment period[h]	NA
Berotralstat										
NCT02870972 (ApeX-1)	Aygören-Pürsün, 2018 [33]	Phase 2 Parallel Double-blind Multicenter	Berotralstat	62.5 mg 125 mg 250 mg 350 mg	Placebo	77[i]	Adults aged 18 to 70 years	28 days	Number of confirmed attacks from day 8 to day 28 (the effective dosing period)	Low risk
NCT03485911 (ApeX-2)	Zuraw, 2021 [10] Wedner, 2021 [35]	Phase 3 Parallel Double-blind Multicenter	Berotralstat	110 mg 150 mg	Placebo[j]	121[k]	Adolescents aged ≥12 years and adults[l]	48 weeks	Rate of confirmed attacks during the 24-week treatment period (part 1); long-term safety (part 2)[m]	Low risk
NCT03873116 (ApeX-J)	Ohsawa, 2021 [59]	Phase 3 Parallel Double-blind Multicenter	Berotralstat	110 mg 150 mg	Placebo[j]	19	Adolescents aged ≥12 years and adults	52 weeks	Rate of confirmed attacks during the 24-week placebo-controlled treatment period	Low risk
NCT03472040 (ApeX-S)	Farkas, 2021 [34]	Phase 3 Open-label extension Parallel Multicenter	Berotralstat	150 mg 110 mg[n]	NA	227	Adolescents aged ≥12 years and adults[o]	48 weeks	Long-term safety and tolerability[p]	NA

Studienergebnisse:

Table 1 Proportion of patients who received long-term prophylaxis who were attack free in phase 3 randomized placebo-controlled trials

Study identifier	Duration of treatment	Study population	No. of patients	LTP agent and comparator	Proportion of attack-free patients, %
NCT01912456 (COMPACT) [9]	2×16-weeks	Adolescents aged ≥ 12 years and adults	90	SC pdC1INH 40 IU/kg twice weekly	38
				SC pdC1INH 60 IU/kg twice weekly	40
				Placebo (Group 1)	9
				Placebo (Group 2)	0
NCT02586805 (HELP) [8, 16]	26 weeks	Adolescents aged ≥ 12 years and adults	125	Lanadelumab 150 mg Q4W	39
				Lanadelumab 300 mg Q4W	31
				Lanadelumab 300 mg Q2W	44
				Placebo	2
		Adolescents aged ≥ 12 years and adults (post hoc analysis of steady state [days 70–182])	120	Lanadelumab 150 mg Q4W	54
				Lanadelumab 300 mg Q4W	45
				Lanadelumab 300 mg Q2W	77
				Placebo	3
NCT04656418 (VANGUARD) [17]	6 months	Adolescents aged ≥ 12 years and adults	64	Garadacimab 200 mg QM[a]	62
				Placebo	0

LTP, long-term prophylaxis; *pdC1INH*, plasma-derived C1 inhibitor; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *QM*, once monthly; *SC*, subcutaneous. [a]Patients received a 400-mg SC loading dose on day 1

Table 2 Proportion of patients who received long-term prophylaxis who were attack free in phase 3 non-placebo-controlled trials and real-world observational studies

Study identifier/design	Duration of treatment	Study population	No. of patients	LTP agent and comparator	Proportion of attack-free patients, %
NCT02316353 (COMPACT OLE) [13, 18, 19]	52–140 weeks	Children aged ≥ 6 years and adults[b]	63	SC pdC1INH 60 IU/kg twice weekly	44
		Subgroup: adults aged ≥ 65 years	10	SC pdC1INH 40 or 60 IU/kg twice weekly	30
		Subgroup: children aged ≥ 6 to < 18 years	10	SC pdC1INH 40 or 60 IU/kg twice weekly	10
Japanese open-label study [20]	16 weeks	Adolescents aged ≥ 12 years and adults	9	SC pdC1INH 60 IU/kg twice weekly	67
NCT00462709 (CHANGE-3 OLE) [14, 21, 22]	248 days (median)	Children aged ≥ 1 year and adults	146	IV pdC1INH 1000 U every 3–7 days	35
		Subgroup: children aged ≥ 2 to < 18 years	23	IV pdC1INH 1000 U every 3–7 days	22
		Subgroup: pregnant women	11	IV pdC1INH 1000 U every 3–7 days	55
NCT02052141 (Pediatric crossover trial) [23]	2 × 12-weeks	Children aged ≥ 6 to < 12 years	12	IV pdC1INH 500 U every 3–4 days	25
				IV pdC1INH 1000 U every 3–4 days[a]	33
NCT02741596 (HELP OLE) [24]	33 months (median)	Adolescents aged ≥ 12 years and adults	209	Lanadelumab 300 mg Q2W[c]	37
Canadian retrospective chart review [25]	12 months	Patients aged 24–74 years commencing lanadelumab	12	Lanadelumab 300 mg Q2W[d]	25
Single-center retrospective chart review [26]	36 weeks (median)	Patients aged 21–55 years commencing lanadelumab	9	Lanadelumab 300 mg Q2W or Q4W	56
US-HAEA patient survey [27]	NR	Patients from the US-HAEA registry	344[e]	Attenuated androgens[f]	26[e]
Chinese retrospective cohort [28]	1 year	Patients aged ≥ 11 years of age from China	74	Danazol[f]	34[g]
German retrospective chart review [29]	11 years (mean)	Patients aged 15–74 years from Germany/Denmark	118	Danazol[f]	24
Swiss retrospective cohort [30]	1 year	Patients aged ≥ 5 years from Switzerland	26	Danazol[f]	38
			10	Tranexamic acid[f]	20
CREAK retrospective chart review [31]	6 months	Patients aged ≥ 16 years from France	12	Tranexamic acid[f]	8

CREAK, National Reference Centre for Angioedema (France); *IV*, intravenous; *LTP*, long-term prophylaxis; *NR*, not reported; *OLE*, open-label extension; *pdC1INH*, plasma-derived C1 inhibitor; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *SC*, subcutaneous; *US-HAEA*, United States Hereditary Angioedema Association

[a]IV pdC1INH 1000 U every 3 or 4 days exceeds the recommended dose for children < 12 years of age [32]. [b]Post hoc analysis in patients randomly assigned to the SC pdC1INH 60 IU/kg treatment arm. [c]In rollover patients, a single dose of lanadelumab 300 mg was received at study entry and until the patient experienced their first attack, following which the patient received lanadelumab 300 mg Q2W. Non-rollover patients received lanadelumab 300 mg Q2W from study entry onward. [d]One patient switched from lanadelumab 300 mg Q2W to Q4W. [e]Percentage of attack-free patients among 344 patients who received attenuated androgens at the time of the survey. [f]The dosage and dosing frequency of each LTP were variable or were not reported. [g]The study results showed the outcome as the proportion of patients who had ≤ 1 attack per year rather than the proportion of patients who were attack free

Table 3 Attack severity in patients who received long-term prophylaxis in phase 3 randomized placebo-controlled trials

First author, year of publication	Duration of treatment	No. of patients	Assessment of attack severity	LTP agent and dose	Attack severity, mean (SD) or n (%)		
					LTP	Placebo	*P* value
Longhurst, 2017 [9]; Li, 2019 [41]	2× 16-weeks	90	Attack severity score, mean (SD)[a]	SC pdC1INH 40 IU/kg twice weekly	1.8 (0.6)	2.0 (0.5)	NR
				SC pdC1INH 60 IU/kg twice weekly	1.6 (0.6)	1.9 (0.5)	NR
Zuraw, 2010 [42]	2× 12-weeks	24	Attack severity score, mean (SD)[a]	IV pdC1INH 1000 U every 3–4 days	1.3 (0.9)	1.9 (0.4)	< 0.001
Banerji, 2018 [8]	26 weeks	125	Patients with a maximum attack severity of 'severe', n (%)[b]	Lanadelumab 150 mg Q4W	5 (18)	14 (34)	0.18
				Lanadelumab 300 mg Q4W	4 (14)	14 (34)	0.02
				Lanadelumab 300 mg Q2W	2 (7)	14 (34)	0.02
Craig, 2023 [17]	6 months	64	Patients with a maximum attack severity of 'severe', n (%)[c]	Garadacimab 200 mg QM[d]	5 (13)	10 (42)	NR

IV, intravenous; *LTP*, long-term prophylaxis; *NR*, not reported; *pdC1INH*, plasma-derived C1 inhibitor; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *QM*, once monthly; *SC*, subcutaneous; *SD*, standard deviation.

[a]Attack severity score was based on a 3-point scale, with 1 indicating mild, 2 indicating moderate, and 3 indicating severe. [b]The difference from placebo was analyzed using Fisher exact test. [c]Proportions were calculated with the number of patients in the treatment period for ≥ 30 days as the denominator ($n = 39$ for garadacimab; $n = 24$ for placebo). [d]Participants received a 400-mg SC loading dose of garadacimab or placebo on day 1

Table 4 Proportion of attacks treated with on-demand therapy in patients who received long-term prophylaxis in phase 3 randomized placebo-controlled trials, open-label extensions studies, and real-world observational studies

First author, date of publication	Study details	No. of patients	LTP agent and comparator	Attacks treated with on-demand therapy, n/N (%)	Treated attacks requiring 2 doses of on-demand therapy, n/N (%)	Treated attacks requiring ≥ 3 doses of on-demand therapy, n/N (%)
Li, 2019 [41]	Phase 3 COMPACT RCT	90	SC pdC1INH 40 IU/kg twice weekly	99/145 (68)	7/99 (7)	0/99 (0)
			SC pdC1INH 60 IU/kg twice weekly	35/71 (49)	0/35 (0)	0/35 (0)
			Placebo[a]	779/975 (80)	60/779 (8)	29/779 (4)
Craig, 2022 [13]; Levy, 2020 [18]	Phase 3 COMPACT OLE	63	SC pdC1INH 60 IU/kg twice weekly	229/371 (62)	25/229 (11)	12/229 (5)
		10[b]	SC pdC1INH 40/60 IU/kg twice weekly	16/38 (42)	NR	NR
Rasmussen, 2016 [37]	Prospective cohort	6	IV pdC1INH 1000 U twice weekly	63/67 (94)	NR	NR
Banerji, 2018 [8]	Phase 3 HELP RCT	125	Lanadelumab 150 mg Q4W	55/84 (65)	NR	NR
			Lanadelumab 300 mg Q4W	87/105 (83)	NR	NR
			Lanadelumab 300 mg Q2W	38/46 (83)	NR	NR
			Placebo	506/572 (88)	NR	NR
Farkas, 2021 [34]	Phase 3 APeX-S OLE	227	Berotralstat 150 mg QD[c]	82%[d]	NR	NR
Aberer, 2017 [36]	Prospective registry	448	LTP (IV pdC1INH, androgens, TA)[e]	≥ 90% of 973 attacks[f]	9% of 973 attacks[f]	1% of 973 attacks[f]
			On-demand therapy only	≥ 92% of 2255 attacks[f]	8% of 2255 attacks[f]	1% of 2255 attacks[f]

IV, intravenous; *LTP*, long-term prophylaxis; *NR*, not reported; *OLE*, open-label extension; *pdC1INH*, plasma-derived C1 inhibitor; *Q2W*; every 2 weeks; *Q4W*; every 4 weeks; *QD*, once daily; *QM*, once monthly; *RCT*, randomized controlled trial; *SC*, subcutaneous; *TA*, tranexamic acid.

[a]Placebo calculated by combining two placebo groups. [b]Pediatric subgroup analysis of children aged ≥ 6 to < 18 years. [c]The study was initially designed to evaluate berotralstat 150 mg QD, but the protocol was amended to include a berotralstat 110 mg QD in selected patients. [d]The absolute number of attacks and treated attacks were not reported. [e]The dosage and dosing frequency of LTP were not reported. [f]The study reported the proportion of patients who treated attacks with 1, 2, and ≥ 3 doses of on-demand therapy. The absolute number of treated attacks was not reported

Fazit der Autoren

This systematic review confirmed that achieving an attack free status in many patients with HAE-C1INH remains a challenging goal. Although the use of LTP reduces attack frequency, patients continue to experience attacks in all anatomic locations, including potentially life-

threatening laryngeal attacks. Most attacks that occurred in patients who received LTP were treated with ≥ 1 dose of an on-demand therapy, and unrestricted access to effective on-demand therapy remains essential for all people with HAE-C1INH, including patients receiving LTP.

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

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, Kőhalmi 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 o ther 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]

Referenzen

126. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513-522.
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.
205. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. N Engl J Med.2017;376(12):1131-1140.
213. Aygoren-Pursun E, Soteres DF, Nieto-Martinez SA, et al. A randomized trial of human C1 inhibitor prophylaxis in children with hereditary angioedema. Pediatr Allergy Immunol. 2019;30(5):553-561.
214. Lumry W, Manning ME, Hurewitz DS, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. J Pediatr. 2013;162(5):1017–1022.e1011-1012.
215. Lumry WR, Martinez-Saguerl, Yang WH, et al. Fixed-dose subcutaneous C1-inhibitor liquid for prophylactic treatment of C1-INH-HAE: SAHARA randomized study. J Allergy Clin Immunol Pract. 2019;7(5):1610-1618.e1614.
216. Zuraw BL, Cicardi M, Longhurst HJ, et al. Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate. Allergy. 2015;70(10):1319-1328.
217. Bernstein JA, Manning ME, Li H, et al. Escalating doses of C1 esterase inhibitor (CINRYZE) for prophylaxis in patients with hereditary angioedema. J Allergy Clin Immunol Pract. 2014;2(1):77-84.
218. Giardino F, Cicardi M, Neri S. Use of subcutaneous-C1 INH for acute therapy and prophylaxis of a child with HAE. Pediatr Allergy Immunol. 2015;26(3):296-297.
219. Kruger R, Dahlinger N, Magerl M, von Bernuth H, Wahn V. Daily subcutaneous administration of human C1 inhibitor in a child with hereditary angioedema type 1. Pediatr Allergy Immunol. 2016;27(2):223-224.
220. Weller K, Kruger R, Maurer M, Magerl M. Subcutaneous self-injections of C1 inhibitor: an effective and safe treatment in a patient with hereditary angio-oedema. Clin Exp Dermatol. 2016;41(1):91-93.
221. Lumry WR, Craig T, Zuraw B, et al. Health-related quality of life with subcutaneous C1-inhibitor

for prevention of attacks of hereditaryangioedema. J Allergy Clin Immunol Pract. 2018;6(5):1733-1741. e1733.
222. Andarawewa S, Aygoren-Pursun E. Subcutaneous C1-Inhibitor Concentrate for prophylaxis during pregnancy and lactation in a patient with C1-INH-HAE.Clin Case Rep. 2021;9(3):1273-1275.
223. Weller K, Maurer M, Fridman M, Supina D, Schranz J, Magerl M. Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase. Allergy Asthma Proc. 2017;38(2):143-151.
224. Bernstein JA, Li HH, Craig TJ, et al. Indirect comparison of intravenous vs. subcutaneous C1-inhibitor placebo-controlled trials for routine prevention of hereditary angioedema attacks. Allergy Asthma Clin Immunol. 2019;15:13.
225. Hahn J, Nordmann-Kleiner M, Trainotti S, Hoffmann TK, Greve J. Successful long-term prophylactic treatment with subcutaneous C1 esterase inhibitor in a patient with hereditary angioedema. J Pharm Pract. 2020;33(6):907-911.
226. Craig T, Busse P, Gower RG, et al. Long-term prophylaxis therapy in patients with hereditary angioedema with C1 inhibitor deficiency.Ann Allergy Asthma Immunol. 2018;121(6):673-679.
227. Rasmussen ER, Aagaard L, Bygum A. Real-life experience with long-term prophylactic C1 inhibitor concentrate treatment of patients with hereditary angioedema: effectiveness and cost. Ann Allergy Asthma Immunol. 2016;116(5):476-477.

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]

Referenzen

195. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compare with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA. 2018;320(20):2108-2121.
196. Buttgereit T, Vera C, Weller K, et al. Lanadelumab efficacy, safety, and injection interval extension in HAE: a real-life study. J Allergy Clin Immunol Pract. 2021;9(10):3744-3751.
204. Banerji A, Bernstein JA, Johnston DT, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: the HELP OLE study. Allergy. 2022;77(3):979-990.
235. Banerji A, Busse P, Shennak M, et al. Inhibiting plasma kallikrein for hereditary angioedema prophylaxis. N Engl J Med. 2017;376(8):717-728.
236. Chyung Y, Vince B, Iarrobino R, et al. A phase 1 study investigating DX-2930 in healthy subjects. Ann Allergy Asthma Immunol. 2014;113(4):460-466. e462.
237. Riedl MA, Maurer M, Bernstein JA, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks. Allergy. 2020;75(11):2879-2887.
238. Takeda. Prescribing Information Lanadelumab 2021. https://www.ema.europa.eu/en/medicines/human/ EPAR/takhzyro. Accessed August 21, 2021.

Berotralstat

RECOMMENDATION 17
We **recommend** the use of berotralstat as first-line long-term prophylaxis
81% agreement, evidence level A

Berotralstat 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] Berotralstat 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 Berotralstat, became less frequent with time and typically self-resolved. [242,243]

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

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 berotralstat, 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]

Referenzen

126. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med.2010;363(6):513-522. 196. Buttgereit T, Vera C, Weller K, et al. Lanadelumab efficacy, safety, and injection interval extension in HAE: a real-life study. J Allergy Clin Immunol Pract. 2021;9(10):3744-3751
198. Hahn J, Trainotti S, Wigand MC, Schuler PJ, Hoffmann TK, Greve J. Prospective analysis in patients with HAE under prophylaxis with lanadelumab: a real-life experience. J Drugs Dermatol. 2020;19(10):978-983.
201. Zarnowski J, Rabe M, Kage P, Simon JC, Treudler R. Prophylactic treatment in hereditary angioedema is associated with reduced anxiety in patients in Leipzig, Germany. Int Arch Allergy Immunol. 2021;182:18.
205. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. N Engl J Med.2017;376(12):1131-1140.
206. Wedner HJ, Aygoren-Pursun E, Bernstein J, et al. Randomized trial of the efficacy and safety of berotralstat (BCX7353) as an oral prophylactic therapy for hereditary angioedema: results of APeX-2 through 48 weeks (Part 2). J Allergy Clin Immunol Pract. 2021;9(6):2305-2314. e2304.
219. Kruger R, Dahlinger N, Magerl M, von Bernuth H, Wahn V. Daily subcutaneous administration of human C1 inhibitor in a child with hereditary angioedema type 1. Pediatr Allergy Immunol. 2016;27(2):223-224.
220. Weller K, Kruger R, Maurer M, Magerl M. Subcutaneous self-injections of C1 inhibitor: an effective and safe treatment in a patient with hereditary angio-oedema. Clin Exp Dermatol. 2016;41(1):91-93.
235. Banerji A, Busse P, Shennak M, et al. Inhibiting plasma kallikrein for hereditary angioedema prophylaxis. N Engl J Med.2017;376(8):717-728.
239. Ohsawa I, Honda D, Suzuki Y, et al. Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: a phase 3 randomized trial. Allergy. 2021;76(6):1789-1799.

240. Aygoren-Pursun E, Bygum A, Grivcheva-Panovska V, et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. N Engl J Med. 2018;379(4):352-362.
241. BioCryst. Prescribing information Orladeyo. 2021. https://www.ema.europa.eu/en/medicines/human/ EPAR/orladeyo. Accessed August 21, 2021
245. Valerieva A, Caccia S, Cicardi M. Recombinant human C1 esterase inhibitor (Conestat alfa) for prophylaxis to prevent attacks in adult and adolescent patients with hereditary angioedema. Expert Rev Clin Immunol. 2018;14(9):707-718.
246. Castaldo AJ, Jervelund C, Corcoran D, Boysen HB, Christiansen SC, Zuraw BL. Assessing the cost and quality-of-life impact of on-demand-only medications for adults with hereditary angioedema. Allergy Asthma Proc. 2021;42(2):108-117.
247. Mendivil J, Murphy R, de la Cruz M, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. Orphanet J Rare Dis. 2021;16(1):94.

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 pulmonarye 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]

Referenzen

6. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. J Allergy Clin Immunol. 2004;114(3):629-637.
7. Bowen T, Cicardi M, Bork K, et al. Hereditary angiodema: a current state-of- the- art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol. 2008;100(1 Suppl 2):S30-S40
248. Agostoni A, Cicardi M, Martignoni GC, Bergamaschini L, Marasini B. Danazol and stanozolol in long-term prophylactic treatment of hereditary angioedema. J Allergy Clin Immunol. 1980;65(1):75-79.
249. Blackmore WP. Danazol in the treatment of hereditary angio-neurotic oedema. J Int Med Res. 1977;5(Suppl 3):38-43.

250. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol. 2008;100(2):153-161.
251. Farkas H, Czaller I, Csuka D, et al. The effect of long-term danazol prophylaxis on liver function in hereditary angioedema-a longitudinal study. Eur J Clin Pharmacol. 2010;66(4):419-426.
252. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. N Engl J Med. 1976;295(26):1444-1448.
254. Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Heller C, Klingebiel T. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. Transfusion. 2009;49(9):1987-1995.
255. Sheffer AL, Fearon DT, Austen KF. Clinical and biochemical effects of stanozolol therapy for hereditary angioedema. J Allergy Clin Immunol. 1981;68(3):181-187.
256. Zotter Z, Veszeli N, Csuka D, Varga L, Farkas H. Frequency of the virilising effects of attenuated androgens reported by women with hereditary angioedema. Orphanet J Rare Dis. 2014;9:205.
257. Bouillet L, Gompel A. Hereditary angioedema in women: specific challenges. Immunol Allergy Clin North Am. 2013;33(4):505-511.
258. Brunskill PJ. The effects of fetal exposure to danazol. Br J Obstet Gynaecol. 1992;99(3):212-215.
259. Wentz AC. Adverse effects of danazol in pregnancy. Ann Intern Med. 1982;96(5):672-673.
260. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. Ann Allergy Asthma Immunol. 2015;114(4):281-288. e287.
261. Stankovic I, Vlahovic-Stipac A, Putnikovic B, Cvetkovic Z, Neskovic AN. Concomitant administration of simvastatin and danazol associated with fatal rhabdomyolysis. Clin Ther. 2010;32(5):909-914.
262. Johnston DT, Henry Li H, Craig TJ, et al. Androgen use in hereditary angioedema: a critical appraisal and approaches to transitioning from androgens to other therapies. Allergy Asthma Proc. 2021;42(1):22-29.
263. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema.
Allergy Asthma Proc. 2008;29(3):225-231 264. Sheffer AL, Fearon DT, Austen KF. Methyltestosterone therapy in hereditary angioedema. Ann Intern Med. 1977;86(3):306-308.
270. Lundh B, Laurell AB, Wetterqvist H, White T, Granerus G. A case of hereditary angioneurotic oedema, successfully treated with epsilon-aminocaproic acid. Studies on C'1 esterase inhibitor, C'1 activation, plasminogen level and histamine metabolism. Clin Exp Immunol. 1968;3(7):733-745.
271. Gwynn CM. Therapy in hereditary angioneurotic oedema. Arch Dis Child. 1974;49(8):636-640.
272. Blohme G. Treatment of hereditary angioneurotic oedema with tranexamic acid. A random double-blind cross-over study. Acta Med Scand. 1972;192(4):293-298.
273. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med. 1972;287(9):452-454.
274. Lundh B. Tranexamic acid in hereditary angioneurotic edema–a progress report. N Engl J Med. 1973;288(1):53.
275. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. J Allergy Clin Immunol. 2012;129(2):308-320.
276. Farkas H, Harmat G, Fust G, Varga L, Visy B. Clinical management of hereditary angio-oedema in children. Pediatr Allergy Immunol. 2002;13(3):153-161.

MANAGEMENT OF HAE- 1/2 IN CHILDREN

Therapy of HAE in children

RECOMMENDATION 21

- 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 icatibant are the 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, on demand 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]

Primary prevention and other management considerations in children with HAE

Hinweis: 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):

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.

214. Lumry W, Manning ME, Hurewitz DS, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. J Pediatr. 2013;162(5):1017–1022. e1011-1012.
307. Farkas H, Reshef A, Aberer W, et al. Treatment effect and safety of icatibant in pediatric patients with hereditary angioedema. J Allergy Clin Immunol Pract. 2017;5(6):1671-1678. e1672.
308. Lumry W, Soteres D, Gower R, et al. Safety and efficacy of C1 esterase inhibitor for acute attacks in children with hereditary angioedema. Pediatr Allergy Immunol. 2015;26(7):674-680.
309. Farkas H, Csuka D, Zotter Z, et al. Treatment of attacks with plasma-derived C1-inhibitor concentrate in pediatric hereditary angioedema patients. J Allergy Clin Immunol. 2013;131(3):909-911.
116. Shire. Cinryze prescribing information. 2021. http://pi.shire conte nt.com/PI/PDFs/Cinryze_USA_ENG.pdf. Accessed August 16, 2021.
117. CSL Behring. Berinert 500 prescribing information. 2021. http:// cslbe hring.vo.llnwd.net/o33/u/central/PI/US/Berin ert/EN/Berin ert-Presc ribin g-Information.pdf. Accessed August 16, 2021.
118. Takeda. Kalbitor prescribing information. 2020. https://www.shire conte nt.com/PI/PDFs/Kalbitor_USA_ENG.pdf. Accessed August 16, 2021.
119. PharmingGroup. Ruconest prescribing information. 2020. https:// www.rucon est.com/wp-conte nt/uploa ds/Rucon est_PI_Apr20 20.pdf. Accessed August 16, 2021.
120. Takeda. Prescribing information icatibant. 2021. https://www. shire conte nt.com/PI/PDFs/Firazyr_USA_ENG.pdf. Accessed August 16, 2021
297. Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300-313.
298. Frank MM, Zuraw B, Banerji A, et al. Management of children with hereditary angioedema due to C1 inhibitor deficiency. Pediatrics. 2016;138(5):e20160575.
299. Wahn V, Aberer W, Aygoren-Pursun E, et al. Hereditary angioedema in children and adolescents -A consensus update on therapeutic strategies for German-speaking countries. Pediatr Allergy Immunol. 2020;31(8):974-989.
310. Farkas H, Csuka D, Zotter Z, Varga L, Fust G. Prophylactic therapy in children with hereditary angioedema. J Allergy Clin Immunol. 2013;131(2):579-582. e571-572.
311. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents-a consensus on therapeutic strategies. Eur J Pediatr. 2012;171:1339-1348.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2025) am 02.01.2025

#	Suchschritt
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 Jan 2020 to present, in Cochrane Reviews

Leitlinien und Systematische Reviews in PubMed am 02.01.2025

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

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

#	Suchschritt
	Leitlinien
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 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])
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 ("2020/01/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

#	Suchschritt
	systematische Reviews
9	angioedema, hereditary[mh]
10	hereditary[tiab] OR congenital*[tiab] OR inborn[tiab] OR inherited[tiab] OR familial[tiab]
11	#9 OR #2 OR (#10 AND #3) OR #4
12	(#11) 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 (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 synthes*[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 synthes*[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])
13	(#12) AND ("2020/01/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT "The Cochrane database of systematic reviews"[Journal]
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	systematische Reviews ohne Leitlinien
16	(#15) NOT (#8)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 06.01.2025

- 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

1. **Beard N, Frese M, Smertina E, Mere P, Katelaris C, Mills K.** Interventions for the long-term prevention of hereditary angioedema attacks. Cochrane Database of Systematic Reviews [online]. 2022(11):Cd013403. URL: http://dx.doi.org/10.1002/14651858.CD013403.pub2.
2. **Longhurst HJ, Cancian M, Grivcheva-Panovska V, Koleilat M, Magerl M, Savic S, et al.** Hereditary angioedema attacks in patients receiving long-term prophylaxis: a systematic review. Clin Rev Allergy Immunol 2024;67(1-3):83-95.
3. **Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al.** The international WAO/EAACI guideline for the management of hereditary angioedema - the 2021 revision and update. Allergy 2022;77(7):1961-1990.
4. **Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al.** The international WAO/EAACI guideline for the management of hereditary angioedema - the 2021 revision and update. World Allergy Organ J 2022;15(3):100627.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

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)				

***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.

[a]Downgraded two levels for imprecision.
[b]Downgraded 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 (1)	⊕⊕◯◯ **Low**[a]	—
	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)				
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 (1)	⊕⊕⊕◯ **Moderate**[c]	—
	663 per 1000	**683 per 1000** (557 to 842)				

*__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(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.

[a]Downgraded two levels for imprecision.
[b]Downgraded three levels for imprecision.
[c]Downgraded 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.

[a]Downgraded two levels for imprecision.
[b]Downgraded 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**[a]	—
	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 standardised mean difference (lower is better) (during follow-up)	**Study population**		—	16 (1)	⊕⊖⊖⊖ **Very low**[a]	—
	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)				
Disability standardised mean difference (lower is better) (during follow-up)	**Study population**		—	16 (1)	⊕⊖⊖⊖ **Very low**[a]	—
	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)				
Adverse events (during follow-up)	**Study population**		N/A	N/A	N/A	Outcome not reported.
	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.

[a]Downgraded 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**[c]	—
	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**[c]	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.

[a]Downgraded three levels for imprecision.
[b]Downgraded 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.

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-312

Verfasser	
Name der Institution	**Deutsche Gesellschaft für Allergologie und Klinische Immunologie (DGAKI), federführend** Deutsche Dermatologische Gesellschaft (DDG) Gesellschaft für Pädiatrische Allergologie (GPA)
Datum der Erstellung	10. Februar 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Routinemäßige Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE) bei Erwachsenen und Jugendlichen ab 12 Jahren.
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 Plazebo zweimal pro Woche. Die Resultate zeigten eine hohe Attackenreduktion bei CSL830 gegenüber Plazebo. 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, Plazebo-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 Antikonzeption 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. Stanozolol ist nicht mehr verfügbar. Die Wirksamkeit der Androgene ist hoch. In einer doppelblinden, randomisierten Cross-over-Studie mit Danazol (600 mg pro Tag) versus Plazebo 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 zunahmen 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 Stanozolol 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, Epsilonaminocapronsäure (EACA) und Tranexamsäure. In einer doppelblinden Plazebo-kontrollierten Cross-over-Studie mit 16 g EACA täglich versus Plazebo zeigte sich bei 4 Patienten eine signifikante Wirksamkeit der EACA (Frank, Sergent et al. 1972). In einer weiteren Plazebo-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.

Die internationalen Leitlinien empfehlen grundsätzlich (Recommendation 14), dass bei allen Pat. mit HAE bei jedem Arztbesuch die Indikation für eine Langzeitprophylaxe abhängig von der Krankheitsaktivität, Krankheitslast und Krankheitskontrolle sowie den Patientenpräferenzen erwogen werden soll (Maurer M et al. 2022). Als First-Line Langzeitprophylaxe werden (Recommendation 15-17) aus Plasma gewonnenes C1-Inhibitor-Konzentrat, Lanadelumab und Berotralstat empfohlen. Nur als Second-Line werden Androgene empfohlen (Recommendation 18). Nicht empfohlen werden Antifibrinolytika wie Tranexamsäure (Maurer M et al. 2022).

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.

Eine kürzlicher Bericht aus acht deutschen Angioödem-Zentren über ihre Erfahrungen mit der Umsetzung der internationalen Leitlinie fasst zusammen, dass die Therapieauswahl für die Langzeitprophylaxe beim HAE individuell ist und regelmäßig angepasst werden muss, da auch der Verlauf der Erkrankung beim einzelnen Patienten unterschiedlich ist (Greve J et al. 2024). Ein Übersichtsartikel zu Therapieoptionen bei Kindern und Jugendlichen steht ebenfalls zur Verfügung (Fasshauer et Wedi 2024) und fasst die aktuell zugelassenen Therapien zur Langzeitprophylaxe ≥12 Jahre (pdC1-INH 2000/3000, pdC1-INH 500, Lanadelumab und Berotralstat) zusammen.

Referenzliste:

Ahuja, M., Dorr, A., Bode, E., Boulton, A. P. R., Buckland, M., Chee, S., Dalley, C., Denman, S., Ekbote, A., Elkhalifa, S., El-Shanawany, T., Eren, E., Herwadkar, A., Garcez, T., Ghanta, H., Grammatikos, A., Grigoriadou, S., Jain, R., Lorenzo, L., Manson, A., … Kiani-Alikhan, S. (2023). Berotralstat for the prophylaxis of hereditary angioedema-Real-world evidence data from the United Kingdom. Allergy 78(5): 1380–1383.

Banerji, A., J. A. Bernstein, D. T. Johnston, W. R. Lumry, M. Magerl, M. Maurer, I. Martinez-Saguer, A. Zanichelli, J. Hao, N. Inhaber, M. Yu, M. A. Riedl and H. O. Investigators (2022). "Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study." Allergy 77(3): 979-990.

Banerji, A., M. A. Riedl, J. A. Bernstein, M. Cicardi, H. J. Longhurst, B. L. Zuraw, P. J. Busse, J. Anderson, M. Magerl, I. Martinez-Saguer, M. Davis-Lorton, A. Zanichelli, H. H. Li, T. Craig, J. Jacobs, D. T. Johnston, R. Shapiro, W. H. Yang, W. R. Lumry, M. E. Manning, L. B. Schwartz, M. Shennak, D. Soteres, R. H. Zaragoza-Urdaz, S. Gierer, A. M. Smith, R. Tachdjian, H. J. Wedner, J. Hebert, S. M. Rehman, P. Staubach, J. Schranz, J. Baptista, W. Nothaft, M. Maurer and H. Investigators (2018). "Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial." JAMA 320(20): 2108-2121.

Beard, N., Frese, M., Smertina, E., Mere, P., Katelaris, C., & Mills, K. (2022). Interventions for the long-term prevention of hereditary angioedema attacks. Cochrane Database Syst Rev 11(11), CD013403.

Blohme, G. (1972). "Treatment of hereditary angioneurotic oedema with tranexamic acid. A random double-blind cross-over study." Acta Med Scand 192(4): 293-298.

Bork, K., Aygören-Pürsün, E., Bas, M. Biedermann T, Greve J, Hartmann K, Magerl M, Martinez-Saguer I, Maurer M, Ott H, Schauf L, Staubach P, Wedi B. Guideline: Hereditary angioedema due to C1 inhibitor deficiency. Allergo J Int 28: 16–29 (2019).

Bork, K., A. Bygum and J. Hardt (2008). "Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients." Ann Allergy Asthma Immunol 100(2): 153-161.

Bouillet, L., H. Longhurst, I. Boccon-Gibod, K. Bork, C. Bucher, A. Bygum, T. Caballero, C. Drouet, H. Farkas, C. Massot, E. W. Nielsen, D. Ponard and M. Cicardi (2008). "Disease expression in women with hereditary angioedema." Am J Obstet Gynecol 199(5), 484-e1.

Cicardi M, Castelli R, Zingale LC, Agostoni A (1997). Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. J Allergy Clin Immunol 2:194-6

Craig, T., Feuersenger, H., Pragst, I., & Dang, J. (2022). Prophylactic therapy with subcutaneous C1-inhibitor is associated with sustained symptom control in patients with hereditary angioedema. Allergy Asthma Proc 43(3): 202–208.

Farkas, H., Stobiecki, M., Peter, J., Kinaciyan, T., Maurer, M., Aygören-Pürsün, E., Kiani-Alikhan, S., Wu, A., Reshef, A., Bygum, A., Fain, O., Hagin, D., Huissoon, A., Jeseňák, M., Lindsay, K., Panovska, V. G., Steiner, U. C., Zubrinich, C., Best, J. M., Cornpropst, M., … Sheridan, W. P. (2021). Long-term safety and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. Clin Trans Allergy, 11(4), e12035.

Fasshauer M, Wedi B. Hereditary angioedema (HAE) in children and adolescents: New treatment options. Allergol Select. 2024;8:336-345.

Frank, M. M., J. S. Sergent, M. A. Kane and D. W. Alling (1972). "Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study." N Engl J Med 286(15): 808-812.
Fust, G., H. Farkas, D. Csuka, L. Varga and K. Bork (2011). "Long-term efficacy of danazol treatment in hereditary angioedema." Eur J Clin Invest.

Gelfand, J. A., R. J. Sherins, D. W. Alling and M. M. Frank (1976). "Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities." N Engl J Med 295(26): 1444-1448.

Greve J, Lochbaum R, Trainotti S, et al. The international HAE guideline under real-life conditions: From possibilities to limits in daily life - current real-world data of 8 German angioedema centers. Allergol Select. 2024;8:346-357.

Kiani-Alikhan, S., Gower, R., Craig, T., Wedner, H. J., Kinaciyan, T., Aygören-Pürsün, E., Banerji, A., Bernstein, J. A., Anderson, J., Collis, P., Johnston, D. T., Desai, B., Tomita, D., Gagnon, R., Tachdjian, R., Soteres, D. F., Farkas, H., Caballero, T., McNeil, D., Jacobs, J., … APeX-2 investigators (2024). Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial. J Allergy Clin Immunol Pract 12(3), 733–743.e10.

Longhurst, H., M. Cicardi, T. Craig, K. Bork, C. Grattan, J. Baker, H. H. Li, A. Reshef, J. Bonner, J. A. Bernstein, J. Anderson, W. R. Lumry, H. Farkas, C. H. Katelaris, G. L. Sussman, J. Jacobs, M. Riedl, M. E. Manning, J. Hebert, P. K. Keith, S. Kivity, S. Neri, D. S. Levy, M. L. Baeza, R. Nathan, L. B. Schwartz, T. Caballero, W. Yang, I. Crisan, M. D. Hernandez, I. Hussain, M. Tarzi, B. Ritchie, P. Kralickova, M. Guilarte, S. M. Rehman, A. Banerji, R. G. Gower, D. Bensen-Kennedy, J. Edelman, H. Feuersenger, J. P. Lawo, T. Machnig, D. Pawaskar, I. Pragst, B. L. Zuraw and C. Investigators (2017). "Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor." N Engl J Med 376(12): 1131-1140.

Longhurst, H. J. (2013). "Hereditary and other orphan angioedemas: a new prophylactic option at last?" Clin Exp Allergy 43(4): 380-382.

Lumry, W. R., Maurer, M., Weller, K., Riedl, M. A., Watt, M., Yu, M., Devercelli, G., Meunier, J., Banerji, A., & HELP OLE Study Group (2023). Long-term lanadelumab treatment improves health-related quality of life in patients with hereditary angioedema. Ann Allergy Asthma Immunol 131(1): 101–108.e3.

Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-1990.

Riedl, M. A., M. Maurer, J. A. Bernstein, A. Banerji, H. J. Longhurst, H. H. Li, P. Lu, J. Hao, S. Juethner, W. R. Lumry and H. Investigators (2020). "Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks." Allergy 75(11): 2879-2887.

Saule, C., I. Boccon-Gibod, O. Fain, G. Kanny, G. Plu-Bureau, L. Martin, D. Launay, L. Bouillet and A. Gompel (2013). "Benefits of progestin contraception in non-allergic angioedema." Clin Exp Allergy 43(4): 475-482.

Sheffer, A. L., K. F. Austen and F. S. Rosen (1972). "Tranexamic acid therapy in hereditary angioneurotic edema." N Engl J Med 287(9): 452-454.

Zuraw, B., W. R. Lumry, D. T. Johnston, E. Aygoren-Pursun, A. Banerji, J. A. Bernstein, S. C. Christiansen, J. S. Jacobs, K. V. Sitz, R. G. Gower, R. Gagnon, H. J. Wedner, T. Kinaciyan, R. Hakl, J. Hanzlikova, J. T. Anderson, D. L. McNeil, S. B. Fritz, W. H. Yang, R. Tachdjian, P. J. Busse, T. J. Craig, H. H. Li, H. Farkas, J. M. Best, D. Clemons, M. Cornpropst, S. M. Dobo, H. A. Iocca, D. Kargl, E. Nagy, S. C. Murray, P. Collis, W. P. Sheridan, M. Maurer and M. A. Riedl (2020). "Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial." J Allergy Clin Immunol.

Zuraw, B. L., P. J. Busse, M. White, J. Jacobs, W. Lumry, J. Baker, T. Craig, J. A. Grant, D. Hurewitz, L. Bielory, W. E. Cartwright, M. Koleilat, W. Ryan, O. Schaefer, M. Manning, P. Patel, J. A. Bernstein, R. A. Friedman, R. Wilkinson, D. Tanner, G. Kohler, G. Gunther, R. Levy, J. McClellan, J. Redhead, D. Guss, E. Heyman, B. A. Blumenstein, I. Kalfus and M. M. Frank (2010). "Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema." N Engl J Med 363(6): 513-522.