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: 2023-B-128-z Lanadelumab

Stand: August 2023

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

Lanadelumab
routinemäßige Prophylaxe von Attacken des hereditären Angioödems (2 bis 11 Jahre)

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: - Berotralstat (Beschluss vom 02.12.2021) - Lanadelumab (Beschluss vom 04.11.2021; Neubewertung nach Überschreitung der 50 Mio. € Umsatzgrenze) - 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:	
Lanadelumab B06AC05 Takhzyro	Anwendungsgebiet laut Zulassungsantrag: „pädiatrische Patienten von 2 bis 11 Jahre zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE)“
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]*
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 13/2022]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-128z (Lanadelumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. Juni 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
C1-INH	C1-Esterase-Inhibitor
EAACI	European Academy of Allergy and Clinical Immunology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HAE	Hereditären Angioödem
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WAO	World Allergy Organization
WHO	World Health Organization

1 Indikation

Pädiatrische Patienten von 2 bis 11 Jahre zur routinemäßigen Prophylaxe von wiederkehrenden Attacken des hereditären Angioödems (HAE).

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

2 Systematische Recherche

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

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 17.05.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 62 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 3 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:

- intervention that had been tested for the prevention of HAE attacks:
  - including concentrated C1-INH (either derived from blood or produced as a recombinant protein), as well as the drugs danazol, tranexamic acid, berotralstat 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 RoB 1 tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 studies (912 participants)

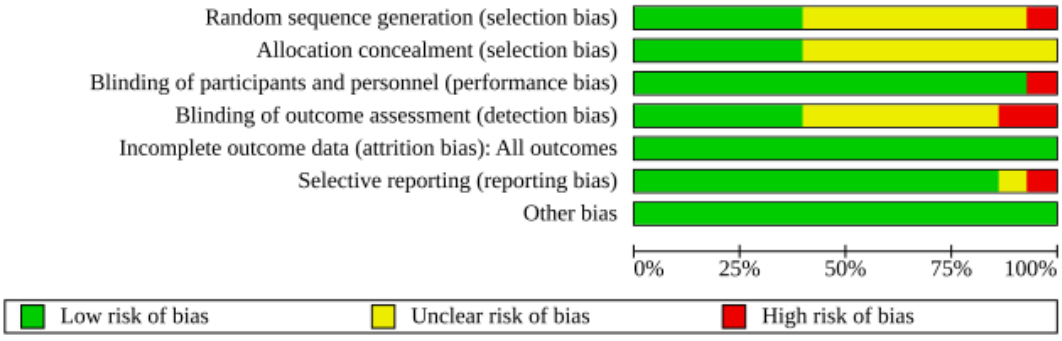
Charakteristika der Population/Studien:

- 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:

- We judged all included studies at low risk of other bias as we identified no other sources of bias.
- Our findings are limited by the small number of studies and the small number of participants in each study. Therefore, our confidence in these findings is low.

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



Studienergebnisse:

- 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 (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).

- Quality of life
  - For quality of life, avoralstat, berotralstat, C1-INH (all forms) and lanadelumab increased quality of life compared with placebo; there were no data for danazol. Four studies reported on changes in disability during treatment with C1-INH, berotralstat and lanadelumab; all three drugs decreased disability compared with placebo.
- Adverse events
  - 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.
- 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 (during follow-up)	**Study population**		N/A	N/A	N/A	Outcome not reported.
	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**[a]	—
	The number of HAE attacks in the control group was 1.8 per week	The number of HAE attacks per week in the intervention groups was **0.92 attacks lower** (1.31 lower to 0.53 lower)				
Mortality (during follow-up)	**Study population**		N/A	N/A	N/A	No deaths reported.
	N/A	N/A				
Serious adverse events (during follow-up)	**Study population**		**RR 1.50** (0.06 to 34.66)	29 (1)	⊕⊙⊙⊙ **Very low**[a]	No events reported in the placebo group, 1 event reported in the rhC1-INH group.
	0 per 1000	**0 per 1000** (0 to 0)				
Quality of life standardised mean difference (during follow-up)	**Study population**		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Disability (any validated scale) (during follow-up)	**Study population**		N/A	N/A	N/A	Outcome not reported.
	N/A	N/A				
Adverse events (during follow-up)	**Study population**		**RR 1.39** (0.71 to 2.70)	29 (1)	⊕⊕⊙⊙ **Low**[b]	—
	286 per 1000	**398 per 1000** (203 to 772)				

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

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

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

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

*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.

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

- Bitte Übersicht der zugelassenen AM beachten.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews im vorliegenden AWG identifiziert.

3.3 Leitlinien

Maurer M et al., 2022 [3].

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

Zielsetzung/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).

This is the second revision and update of the international guideline for the diagnosis and management of HAE,4,5 which was developed by the World Allergy Organization (WAO) in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium, trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz, unklar;
- Formale Konsensusprozesse (trifft zu) und externes Begutachtungsverfahren (unklar) dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt, trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert, trifft zu.

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.
- Each manuscript/trial included in the guideline was evaluated with regard to its methodological quality (Table 1), and the 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

- Consensus was established as described in the previous revision of the WAO/EAACI guideline for HAE, with the exception that an online DELPHI process was used rather than a consensus conference, due to the COVID- 19 pandemic. The DELPHI process was facilitated
- 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.

Empfehlungen

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]

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]

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]

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]

10 | MANAGEMENT OF HAE- 1/2 IN CHILDREN

10.3 | Therapy of HAE in children

RECOMMENDATION 21 (evidence level A; 94% agreement)

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

Hintergrundinfos:
Like adults, all pediatric HAE-1/ 2 patients need to have a treatment action plan (see below) and on-demand therapy (Recommendation 21).143,214,307‐309 C 1-INH and i catibant a re t he only approved on-demand treatments for children with HAE-1/ 2.116,117,119,120 Both are effective, well tolerated and show a good safety profile. For abdominal attacks, parenteral fluid replacement may be required as children are more susceptible to hypovolemia and dehydration, and extravasation into the peritoneal cavity and the intestinal lumen can be substantial. When C1-INH and icatibant are not available, SDP is preferred over FFP, but both are considered second-line treatment. Ecallantide is licensed for the use in adolescents in the United States.[118]
As in adults, preprocedural prophylaxis is recommended for medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract.165,166 Plasma- derived C1INH is the first- line preprocedural prophylactic option, and short courses of attenuated androgens should only be used second line, when C1- INH concentrate is not available. With either option, ondemand therapy should be available because short- term prophylaxis is not 100% effective.168 The indications for long-term prophylaxis in adolescents are the same as in adults (see above). The preferred therapy in children

younger than 12 years of age for long- term prophylaxis is pdC1- INH. The dosing interval and dose may need to be adjusted according to the individual response. When C1- INH concentrate is not available for long- term prophylaxis, antifibrinolytics (ie, tranexamic acid 20– 50 mg/kg) are preferred to androgens because of their better safety profile; however, efficacy is questioned by many, and data in support of its use are not available. Epsilon aminocaproic acid is less well tolerated than tranexamic acid. Androgens are not recommended for long- term prophylaxis in children and adolescents prior to Tanner Stage V. The administration of androgens requires careful safety monitoring. The continued need for regular prophylaxis with androgens and the dosing should be reviewed on a regular basis. Initial danazol dose for children is 2.5 mg/kg per day with subsequent adjustment, until symptom suppression or the maximum tolerated, or maximum recommended dose is reached, with a maximum single dose of 200 mg per day. Androgens result in masculinization and hypogonadism in boys and menstruation irregularities in girls. Unfavorable effects on behavior are possible. Reduction in ultimate body height may occur owing to the premature closure of epiphyseal growth plates.6,7,297– 299,310,311

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

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

As in adults, most attacks in children with HAE- 1/2 occur without an obvious trigger.312 Infections seem to be more common triggers of attacks in childhood. Compulsory and recommended vaccinations for children are safe, and the prevention of infections (eg, throat infections) may reduce the frequency of attacks. Medicinal products that can cause edema as an adverse effect are less frequently used in children. Treatment with an ACE inhibitor is less often necessary during childhood. However, early initiation of oral estrogen- containing contraceptives is increasingly common, may trigger attacks and should be avoided. Hormonal contraception with progesterone- only pills may benefit many young women with HAE- 1/2275,313,314 or at least should not increase attack frequency. Other triggers like strenuous physical activities involving mechanical trauma and emotional challenges (stress) are essential elements of childhood and adolescence.315 Restrictions of suspected triggers should be individualized and sensibly applied, along with the use of prophylaxis where necessary, with the aim of avoiding any limitations in activities and lifestyle. The aim of HAE- 1/2 management at all ages is to normalize the lives of patients.297,316 Providing pediatric patients and their families with appropriate information is indispensable to support them to adopt a suitable lifestyle and to avoid complications. Educators, teachers, and health care personnel responsible for the child at day care or school should receive written information on the disease, with advice on the management of HAE attacks, including the urgency of treatment for airway attacks. C1- INH or icatibant for emergency use should be available at home, school, and travel including school field trips. An action plan is necessary, and the family and local hospital should have therapies available for emergency treatment, and this should be included in the treatment plan. All HAE patients have a potential for receiving human blood products. Vaccinations for hepatitis A and B are recommended by many experts.295,297 All patients should be considered to receive influenza vaccine and other routine vaccinations.

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

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Betschel S et al., 2019 [2].

The International/Canadian Hereditary Angioedema Guideline

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium, trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz, trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt, trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt, trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert, unklar.

Recherche/Suchzeitraum:

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

LoE/GoR

- Criteria for determining Levels of Evidence and Strength of Recommendation were adapted from the GRADE system [20–22], and the process was based primarily on the Journal of Clinical Epidemiology's 2011–2013 series of articles describing the GRADE methodology.

Empfehlungen zur Langzeitprophylaxe für HAE-1 und HAE-2

Recommendation 26 (Empfehlungsgrad: siehe Kasten)

Recommendation 26

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

Level of Evidence: High (100% Agree)
Strength of Recommendation: Strong (100% Agree)

Clinical considerations

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

Recommendation 27 (Empfehlungsgrad: siehe Kasten)

Recommendation 27

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

Level of Evidence: High (95% Agree, 5% Disagree)
Strength of Recommendation: Strong (92.5% Agree, 5% Disagree, 2.5% Abstain)

Clinical considerations

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

Recommendation 28 (Empfehlungsgrad: siehe Kasten)

Recommendation 28

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

Level of Evidence: Consensus (90% Agree, 10% Disagree)
Strength of Recommendation: Strong (97.37% Agree, 2.63% Disagree)

Clinical considerations

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

Recommendation 29 und 30 (Empfehlungsgrad: siehe Kasten)

Recommendation 29

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

Level of Evidence: Consensus (89.47% Agree, 7.89% Disagree, 2.63% Abstain)
Strength of Recommendation: Strong (88.89% Agree, 5.56% Disagree, 5.56% Abstain)

Recommendation 30

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

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

Clinical considerations

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

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

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

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

There is a moderate level of evidence showing the benefit of the anti-fibrinolytic agent tranexamic acid as an LTP agent. This benefit was demonstrated in a randomized placebo-controlled trial with 18 subjects ≥ 12 years taking 1 g of tranexamic acid three times a day

[125], and a double-blind crossover study of ε-aminocaproic acid in 9 patients aged 7 to 40 years [126]. These data suggested that anti-fibrinolytic agents could be useful for LTP for HAE-1/2. However, their role in current LTP was felt to be justified only in certain patient groups due to the lack of efficacy and the potential side effects at the dosage studied. The recommended dosage for tranexamic acid is 30–50 mg/kg daily divided in 2 or 3 doses to a maximum of 6 g per day.

Langzeitprophylaxe in pädiatrischen Patienten

Recommendation 34 (Empfehlungsgrad: siehe Kasten)

Recommendation 34

When long-term prophylaxis is indicated in paediatric patients, pdC1-INH is the treatment of choice.

Level of Evidence: Consensus (100% Agree)
Strength of Recommendation: Strong (97.5% Agree, 2.5% Disagree)

Clinical considerations

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

Recommendation 35 (Empfehlungsgrad: siehe Kasten)

Recommendation 35

Androgens should not be used for long-term prophylaxis in paediatric patients.

Level of Evidence: Moderate (87.18% Agree, 7.69% Disagree, 5.13% Abstain)
Strength of Recommendation: Strong (84.62% Agree, 12.82% Disagree, 2.56% Abstain)

Clinical considerations

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

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

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2023) am 17.05.2023

#	Suchfrage
1	[mh "Hereditary Angioedemas"]
2	(c1 AND inhibitor* AND deficienc*):ti,ab,kw
3	hereditary: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"):ti,ab,kw OR (quincke* NEXT edema* OR quincke* NEXT oedema):ti,ab,kw
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from May 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 17.05.2023

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

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

#	Suchfrage
	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])
8	(#7) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 17.05.2023

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

#	Suchfrage
1	angioedema, hereditary[mh]
2	((C1[tiab] AND inhibitor*[tiab]) AND deficienc*[tiab])
3	hereditary[tiab]
4	(((angioedema*[tiab] OR "angio edema*"[tiab] OR angiooedema*[tiab] OR "angio oedema*"[tiab] OR "angioneurotic edema*"[tiab] OR "angioneurotic oedema*"[tiab] OR "giant urticaria*"[tiab] OR "HAE"[tiab])) OR (quincke*[tiab] AND edema*[tiab])) OR (quincke*[tiab] AND oedema*[tiab])
5	#3 AND #4
6	#1 OR #2 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.05.2023

- 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)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO