Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-223 Ravulizumab

Stand: Januar 2019

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

Ravulizumab
Paroxysmale nächtliche Hämoglobinurie (PNH)

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 Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*keine*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
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:	
Ravulizumab	*Geplantes Anwendungsgebiet laut Beratungsanforderung:* Ravulizumab wird angewendet zur Behandlung von Erwachsenen mit paroxysmaler nächtlicher Hämoglobinurie (PNH).
Eculizumab L04AA25 Soliris® i.v. Lösung	Soliris® wird angewendet zur Behandlung von Erwachsenen, Kindern und Jugendlichen mit – Paroxysmaler Nächtlicher Hämoglobinurie (PNH) Der klinische Nutzen ist bei Patienten mit Hämolyse, zusammen mit einem oder mehreren klinischen Symptomen als Hinweis auf eine hohe Krankheitsaktivität, nachgewiesen, unabhängig von der Transfusionshistorie (siehe Abschnitt 5.1). […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-223 (Ravulizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. November 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
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
PNH	Paroxysmale nächtliche Hämoglobinurie
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erwachsene mit paroxysmaler nächtlicher Hämoglobinurie (PNH).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation: *paroxysmale nächtliche Hämoglobinurie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 14.11.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 38 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 2 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten Dokumente identifiziert.

3.2 Cochrane Reviews

Martí-Carvajal AJ et al., 2014 [2].

Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria (Review)

Fragestellung

To assess the clinical benefits and harms of eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria (PNH).

Methodik

Population:

- Any patient with a confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) according to the International PNH interest group criteria

Intervention:

- Eculizumab

Komparator:

- Placebo, best available therapy, or any other comparison.

Endpunkte:

- Primary: Overall survival.
- *Anmerkung: Secondary Outcomes im Ergebnisteil dargestellt.*

Recherche/Suchzeitraum:

- The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2014, Issue 05).
- MEDLINE (Ovid) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (from 1946 to 15 May 2014).
- PubMed (up to May 2014).
- EMBASE (OVID) (from 1980 to 25 June 2014).
- LILACS (from 1982 to 25 June 2014).
- Handrecherche in Referenzlisten, Studienregister

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

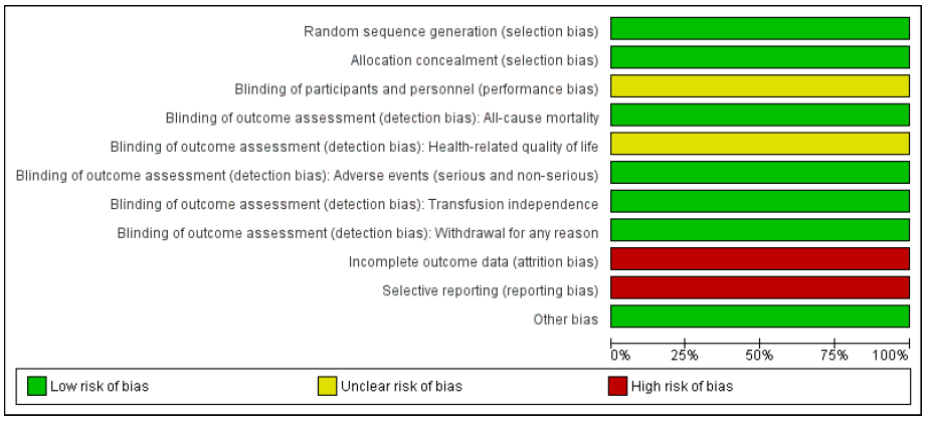
Ergebnisse

Anzahl eingeschlossener Studien:

- 1 (n=87)

Charakteristika der Studie/ Population:

- 1 sponsored drug company trial with 26 weeks of follow-up
- 87 participants (median age 41 years; range: 20 to 85)
- 52/87 of participants female
- Trial conducted in 34 sites in Europe, Australia, Canada and the US from October 2004 to June 2005
- 14% of participants dropped out and imbalance between groups of 18%
- Clinically relevant and reasonably expected outcomes not reported



Studienergebnisse:

- Overall survival: not assessed in study but the main publication reported that no patients died during the study
- Health-related quality of life:
  - Based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
  - Statistically and clinically significant increase in the global health status scale in the eculizumab group compared with the placebo group (mean difference (MD) 19.4, 95% CI 8.25 to 30.55; P = 0.0007)
- Fatigue:
  - Based on the Functional Assessment of Chronic Illness Therapy Fatigue instrument
  - Statistical and clinical significant reduction in fatigue compared with placebo group (MD 10.4, 95%CI 9.97 to 10.83; P = 0.00001)
- Any fatal or nonfatal thrombotic event: 1 episode of thrombosis occurred in placebo group
- Adverse events:
  - Non-significant statistical difference between the eculizumab group: 9.3% vs the placebo group: 20.4% (RR 0.45, 95% CI 0.15 to 1.37; P = 0.16)
  - Non-significant statistical difference according to the most frequent adverse events (Headache, nasopharyngitis, upper respiratory tract infection, back pain, and nausea)

- Transfusion independence: (51% in the eculizumab group and none in the placebo group (RR 46.02, 95% CI 2.88 to 735.53; P = 0.007)

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Eculizumab compared with placebo for paroxysmal nocturnal hemoglobinuria

Patient or population: patients with paroxysmal nocturnal hemoglobinuria
Intervention: eculizumab
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Placebo	Eculizumab				
Overall survival - not measured	See comment	See comment	Not estimable	87 (1 study)	See comment	This outcome was not measured in the included study
All-cause mortality Follow-up: at 26 weeks of treatment[2]	See comment	See comment	Not estimable	87 (1 study)	See comment	No patients died during the execution of the included study. The small sample size of the included trial does not allow to make judgments about the quality of evidence
Health-related quality of life European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Scale from: 0 to 100 (a higher score means a better outcome) Follow-up: at 26 weeks of treatment[2]	The mean change from baseline in the health-related quality of life score in the control group was **-8.5**	The mean change from baseline in the health-related quality of life score in the intervention group was **19.4 higher** (8.25 to 30.55)		87 (1 study)	⊕⊕◯◯ **low**[3,4]	
Fatigue Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). Scale from: 0 to 52 (a higher score means a better outcome) Follow-up: data at 26 weeks of treatment[2]	The mean change from baseline in the fatigue score in the control group was **-4.0 points**	The mean change from baseline in the fatigue score in the intervention group was **10.4 higher** (9.97 to 10.83 more)		87 (1 study)	⊕⊕⊕◯ **moderate**[3]	
Adverse events (serious and nonserious) Medical Dictionary for Regulatory Activities (MedDRA) Follow-up: data at 26 weeks of treatment[2,9]	**205 per 1000**	**92 per 1000** (31 to 280)	**RR 0.45** (0.15 to 1.37)	87 (1 study)	⊕⊕◯◯ **low**[5]	
Transfusion independence Follow-up: data at 26 weeks of treatment[2]	**20 per 1000**[6]	**920 per 1000** (58 to 1000)	**RR 46.02** (2.88 to 735.53)	87 (1 study)	⊕⊕⊕◯ **moderate**[7]	
Withdrawal for any reason Follow-up: data at 26 weeks of treatment[2]	**227 per 1000**	**45 per 1000** (11 to 200)	**RR 0.20** (0.05 to 0.88)	87 (1 study)	⊕⊕⊕◯ **moderate**[8]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Anmerkung/Fazit der Autoren

Implications for practice

Regarding clinical effectiveness and harms, there is limited evidence of eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria (PNH). The results are based on one small sponsored drug company RCT with a high risk of bias. Even though this trial reports no mortality; information is absent for the main clinical outcomes such as nonfatal thrombotic events, transformation to myelodysplastic syndrome and acute myelogenous leukemia, and development and recurrence of aplastic anemia. In addition, safety data remain unclear. Therefore, prescription of eculizumab for treating patients with PNH can neither be supported nor rejected, unless new evidence from a large high quality trial alters this conclusion.

3.3 Systematische Reviews

Es wurden keine relevanten Quellen identifiziert.

3.4 Leitlinien

Devos T et al., 2018 [1].

Diagnosis and management of PNH: review and recommendations from a Belgian expert panel

Leitlinienorganisation/Fragestellung

[…] the management of PNH patients is discussed from Belgian experience and recommendations are provided in order to advise on treatment possibilities in PNH under the current Belgian reimbursement criteria.

Methodik

Grundlage der Leitlinie

- An 8-member independent panel consisting of haematologists and clinical biologists
- Panel members thoroughly reviewed and discussed the diagnosis and management of PNH patients during three meetings (between June and December 2015) and came to a consensus on the identification and treatment of PNH.

Recherche/Suchzeitraum:

- Nicht berichtet.

Loe/ GoR

- The Strength of Recommendations Taxonomy (SORT):

Strength of Recommendation Taxonomy (SORT)

In general, only key recommendations for readers require a grade of the "Strength of Recommendation." Recommendations should be based on the highest quality evidence available. For example, vitamin E was found in some cohort studies (level 2 study quality) to have a benefit for cardiovascular protection, but good-quality randomized trials (level 1) have not confirmed this effect. Therefore, it is preferable to base clinical recommendations in a manuscript on the level 1 studies.

Strength of recommendation	*Definition*
A	Recommendation based on consistent and good-quality patient-oriented evidence.*
B	Recommendation based on inconsistent or limited-quality patient-oriented evidence.*
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,* or case series for studies of diagnosis, treatment, prevention, or screening.

Use the following table to determine whether a study measuring patient-oriented outcomes is of good or limited quality, and whether the results are consistent or inconsistent between studies.

Study quality	*Diagnosis*	*Treatment/prevention/screening*	*Prognosis*
Level 1—good-quality patient-oriented evidence	Validated clinical decision rule SR/meta-analysis of high-quality studies High-quality diagnostic cohort study†	SR/meta-analysis of RCTs with consistent findings High-quality individual RCT‡ All-or-none study§	SR/meta-analysis of good-quality cohort studies Prospective cohort study with good follow-up
Level 2—limited-quality patient-oriented evidence	Unvalidated clinical decision rule SR/meta-analysis of lower-quality studies or studies with inconsistent findings Lower-quality diagnostic cohort study or diagnostic case-control study§	SR/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings Lower-quality clinical trial‡ Cohort study Case-control study	SR/meta-analysis of lower-quality cohort studies or with inconsistent results Retrospective cohort study or prospective cohort study with poor follow-up Case-control study Case series
Level 3—other evidence	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening		

Consistency across studies	
Consistent	Most studies found similar or at least coherent conclusions (coherence means that differences are explainable) *or* If high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation
Inconsistent	Considerable variation among study findings and lack of coherence *or* If high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

Sonstige methodische Hinweise

„Alexion Pharma provided logistical support.“

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen, da die Auswahl der Evidenzgrundlage nicht beschrieben ist. Empfehlungen sind zudem nicht leicht zu identifizieren, sondern im Fließtext eingebettet. Aufgrund fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Empfehlungen

PNH Treatment: Subclinical PNH

- In subclinical PNH, patients are asymptomatic and do not need any treatment
- Necessary to closely monitor these patients

PNH Treatment: Haematopoietic stem cell transplantation

- Allogeneic HSCT is the only treatment available that could potentially cure PNH
  - o associated with acceptable survival in PNH,
  - o may cause morbidity and mortality due to graft-versus-host disease, infection and organ dysfunction.[2,39,56,57]
  - o may cause infertility and decreased quality of life (QoL)
- **This treatment should not be offered as initial therapy.[2,39,58] (recommendation level C).**
- Possible exceptions:
  - o Eculizumab failure, in which allotransplant can be offered as an option alongside interventions like splenectomy, steroids or dose/interval adaptations of eculizumab.[2,39,58]

  - PNH with concomitant AA, if HSCT is indicated for AA. SAA guidelines for transplantation are applicable [2,39,56] (recommendation level B).
- Prospective evidence to guide our choice of conditioning and stem cell source is lacking.[56]

PNH Treatment: Eculizumab

- **Starting treatment with eculizumab in patients with major PNH symptoms may be considered even in the absence of transfusion-dependent anaemia (recommendation level B).**
- Under Belgian reimbursement restrictions, the need for four erythrocyte transfusions over the last 2 years is mandatory, despite the recent EMA-label that recommends treatment in case of clinical symptoms indicative of high disease activity
- Efficacy and safety of eculizumab demonstrated in 2 phase III trials and in an extension study:
  - TRIUMPH study: eculizumab reduced haemolysis and transfusion requirements in transfusion-dependent PNH patients.[60]
  - 89/97 patients demonstrated fast response and maintained a complete inhibition of haemolysis.[61]
  - Long-term safety and efficacy shown over 66 months of treatment.[47]

2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-2811.
39. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal haemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.
47. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2013;162(1):62-73.
56. Marotta S, Pagliuca S, Risitano AM. Hematopoietic stem cell transplantation for aplastic anaemia and paroxysmal nocturnal hemoglobinuria: current evidence and recommendations. Expert Rev Hematol. 2014;7(6):775-789.
58. Villegas A, Arrizabalaga B, Bonanad S, et al. Spanisch consensus statement for diagnosis and treatment of paroxysmal nocturnal hemoglobinuria. Med Clin (Barc). 2016;146(6): 278 e1-278 e7.
60. Hillmen P, Young NS, Shubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355(12):1233-1243.
61. Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111:1840-1847.

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Es wurden keine relevanten Quellen identifiziert.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 12.11.2018

#	Suchfrage
1	MeSH descriptor: [Hemoglobinuria, Paroxysmal] explode all trees
2	(paroxysmal or nocturnal):ti,ab,kw and (haemoglobinuria or hemoglobinuria):ti,ab,kw
3	(PNH):ti,ab,kw
4	(marchiafava next micheli):ti,ab,kw or (struebing or strubing) ti,ab,kw
5	{OR #1-#4}
6	#5 with Cochrane Library publication date from Nov 2013 to Nov 2018

Systematic Reviews in Medline (PubMed) am 12.11.2018

#	Suchfrage
1	Hemoglobinuria, Paroxysmal[mh]
2	(paroxysmal[tiab] OR nocturnal[tiab]) AND (haemoglobinuria[tiab] OR hemoglobinuria[tiab])
3	PNH[tiab]
4	(marchiafava[tiab] AND micheli[tiab]) OR (struebing[tiab] OR strubing[tiab])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
7	((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 12.11.2018

#	Suchfrage
1	Hemoglobinuria, Paroxysmal[mh]
2	(paroxysmal[tiab] OR nocturnal[tiab]) AND (haemoglobinuria[tiab] OR hemoglobinuria[tiab])
3	PNH[tiab]
4	(marchiafava[tiab] AND micheli[tiab]) OR (struebing[tiab] OR strubing[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 ("2013/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp])
	(#7) NOT retracted publication[ptyp]

Referenzen

1. **Devos T, Meers S, Boeckx N, Gothot A, Deeren D, Chatelain B, et al.** Diagnosis and management of PNH: review and recommendations from a Belgian expert panel. Eur J Haematol 2018;101(6):737-749.
2. **Martí-Carvajal A, Anand V, Cardona A, Solà I.** Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria. Cochrane Database of Systematic Reviews [online]. 2014(10):Cd010340. URL: http://dx.doi.org/10.1002/14651858.CD010340.pub2.