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-119 Bevacizumab gamma

Stand: Juli 2024

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

Bevacizumab gamma
[neovaskuläre (feuchte) altersbedingte Makuladegeneration (nAMD)]

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.	• Photodynamische Therapie (PDT), Photokoagulation mittels Laser • Protonentherapie bei altersabhängiger Makuladegeneration • photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfovealer klassischer choriodaler Neovaskularisation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>Beschlüsse über die Nutzenbewertung nach § 35a SGB V:</u> • Aflibercept (Beschluss vom 6. Juni 2013) • Brolucizumab (Beschluss vom 2. Mai 2024) • Faricimab (Beschluss vom 6. April 2023) <u>sonstige Beschlüsse:</u> • Protonentherapie bei altersabhängiger Makuladegeneration (Beschluss vom 17. September 2009) • photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfovealer klassischer choriodaler Neovaskularisation (Beschluss vom 16. Oktober 2000)
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:	
Bevacizumab gamma Lytenava™	Anwendungsgebiet laut Zulassung vom 27.05.2024: Lytenava wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersbedingten Makuladegeneration (*neovascular age-related macular degeneration*, nAMD).
Ranibizumab S01LA04 Lucentis®	Lucentis wird angewendet bei Erwachsenen zur: […] – Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD)
Aflibercept S01LA05 Eylea®	Eylea wird angewendet bei Erwachsenen zur Behandlung – der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) (siehe Abschnitt 5.1)
Brolucizumab S01LA06 Beovu®	Beovu wird angewendet bei Erwachsenen zur: – Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD) (siehe Abschnitt 5.1)
Faricimab S01LA09 Vabysmo®	Vabysmo wird angewendet zur Behandlung von erwachsenen Patienten mit: – neovaskulärer (feuchter) altersabhängiger Makuladegeneration (nAMD)
Verteporfin S01LA01 Visudyne®	Visudyne wird angewendet für die Behandlung von […] – Erwachsenen mit exsudativer (feuchter) altersbezogener Makuladegeneration (AMD) mit vorwiegend klassischen subfovealen chorioidalen Neovaskularisationen (CNV) *Der erste Schritt besteht in einer 10-minutigen intravenösen Infusion von Visudyne. Der zweite Schritt besteht in der Lichtaktivierung von Visudyne 15 Minuten nach Beginn der Infusion.*

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-119 (Bevacizumab gamma)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. Juni 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AMD	Altersabhängigen Makuladegeneration
AM-RL	Arzneimittel-Richtlinie
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCVA	Best-Corrected Visual Acuity
CNV	Choroidal Neovascularization
CRT	Central Retinal Thickness
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IVI	Intravitreal injections
KI	Konfidenzintervall
LoE	Level of Evidence
MD	Mean Difference
nAMD	Neovaskuläre Altersabhängige Makuladegeneration
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
OCT	Optical Coherence Tomography
OR	Odds Ratio
PCV	Polypoidal Choroidal Vasculopathy
PDT	Photodynamische Therapie
PRN	Pro Re Nata
RCT	Randomized Controlled Trial
RF	Reduced-Fluence
RR	Relatives Risiko
SF	Standard-Fluence
T&E	treat-and-extend
TRIP	Turn Research into Practice Database
VA	visual acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WMD	Weighted Mean Difference

1 Indikation

Behandlung erwachsener Personen mit neovaskulärer (feuchter) altersabhängiger Makuladegeneration (nAMD).

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 Makuladegeneration 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 15.05.2023 durchgeführt, die folgende am 23.05.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die detaillierte Darstellung der letzten 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 641 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 5 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es liegen keine Cochrane Reviews im vorliegenden Anwendungsgebiet vor.

3.2 Systematische Reviews

Tricco AC et al., 2021 [4].

Anti-vascular endothelial growth factor therapy for age-related macular degeneration: a systematic review and network meta-analysis

Fragestellung

The comparative safety and efficacy between anti-vascular endothelial growth factor agents (anti-VEGFs) and between combined therapies for patients with neovascular age-related macular degeneration (nAMD) is unclear. We conducted a systematic review to examine the comparative safety and efficacy anti-VEGFs for adults with nAMD.

Methodik

Population:

- Patients aged 50 years or older with neovascular AMD

Intervention:

- Intravitreal injection of anti-VEGF agents (aflibercept, bevacizumab, ranibizumab, brolucizumab, or conbercept), alone or in any combination.

Komparator:

- Anti-VEGF agents compared to each other, photodynamic therapy with verteporfin (PDT), corticosteroids (intravitreal injection or implant: triamcinolone acetonide (IVTA), dexamethasone implant (DXM), fluocinolone acetonide implant), and laser photocoagulation

Endpunkte:

- Primary: proportion of patients experiencing vision gain of ≥ 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and vision loss of ≥ 15 ETDRS letters
- Secondary: difference in mean change in best-corrected visual acuity (BCVA) from baseline in ETDRS letters, legal blindness, vision-related function, all-cause mortality, arterial and/or venous thromboembolic events (ATE or VTE), bacterial endophthalmitis (BE), increased intraocular pressure, retinal detachment, adverse events (AE), serious AE, and withdrawals due to AE

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials until June 3, 2019

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

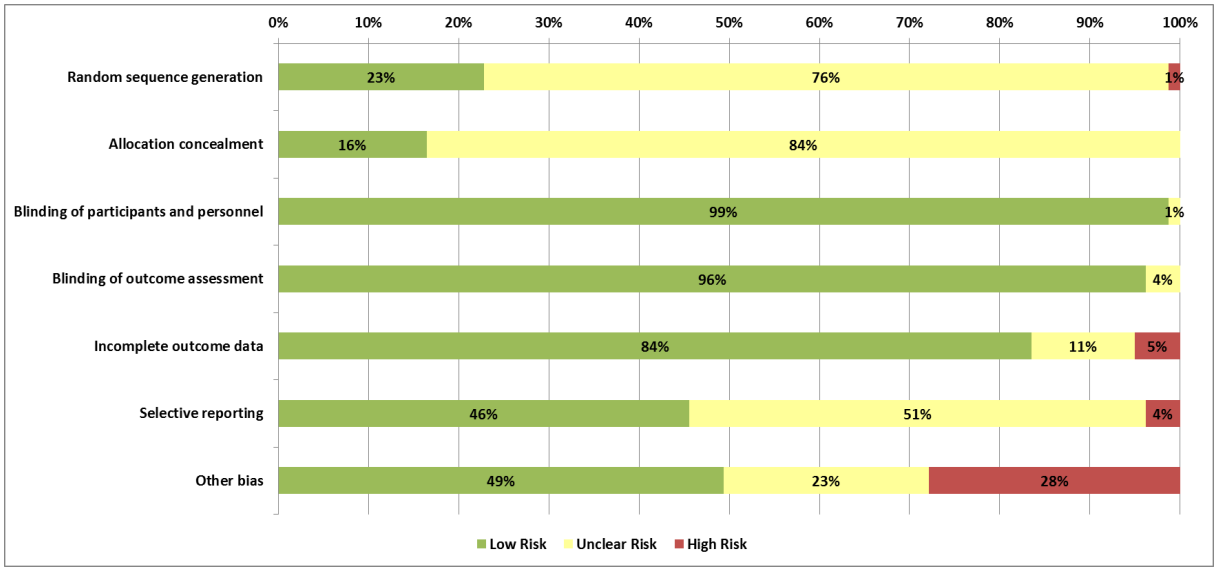
Anzahl eingeschlossener Studien:

- 92 RCTs plus 8 companion reports
- Most studies conducted in Europe (36%) and North America (32%).
- Most common intervention was ranibizumab (53.2%)

Charakteristika der Population:

- Average age of patients with neovascular AMD was between 60 and 83 years
- Proportion of women: 56%

Qualität der Studien:



Studienergebnisse:

Der Fokus der Ergebnisdarstellung liegt auf Vergleichen zu den im AWG zugelassenen Wirkstoffen.

Primary outcome: Vision gain

- All […] agent-to-agent comparisons received moderate to low confidence ratings

Rank-heat plot

- The SUCRA curve demonstrated that the anti-VEGF agents were superior to all other comparators, yet none of the anti-VEGF agents were consistently superior to each other across all outcomes

Table 2 Network meta-analyses results comparing anti-VEGF agents

Treatment comparison	NMA estimate (95% CrI) (95% Pr
Proportion of patients experiencing vision gain (≥ 15 ETDRS letters) 34 RCTs, 8809 patients, 12 treatments + placebo No inconsistency was observed in the overall NMA (chi-square = 1.79, $p = 0.41$) Between-study variance: 0.02 (0.00–0.14)	
Bevacizumab vs aflibercept	0.96 [(0.64–1.39) (0.54–1.62)]
Ranibizumab vs aflibercept	1.09 [(0.78–1.47) (0.65–1.76)]
Ranibizumab vs bevacizumab	1.14 [(0.9–1.43) (0.73–1.8)]
Brolucizumab vs aflibercept	1.2 [(0.85–1.71) (0.71–2.03)]
Brolucizumab vs bevacizumab	1.26 [(0.76–2.14) (0.67–2.44)]
Brolucizumab vs ranibizumab	1.11 [(0.71–1.8) (0.61–2.07)]
Conbercept vs aflibercept	0.19 [(0.06–0.65) (0.05–0.68)][a]
Conbercept vs bevacizumab	0.2 [(0.06–0.69) (0.06–0.73)][a]
Conbercept vs ranibizumab	0.17 [(0.05–0.59) (0.05–0.63)][a]
Conbercept vs brolucizumab	0.15 [(0.05–0.56) (0.04–0.59)][a]
Proportion of patients experiencing vision loss of ≥ 15 ETDRS letters 36 RCTs, 9081 patients, 13 treatments + placebo No inconsistency was observed in the overall NMA (chi-square = 0.25, $p = 0.88$) Between-study variance: 0.02 (0.00–0.13)	
Bevacizumab vs aflibercept	0.94 [(0.51–1.67) (0.47–1.81)]
Ranibizumab vs aflibercept	0.9 [(0.55–1.43) (0.5–1.59)]
Ranibizumab vs bevacizumab	0.96 [(0.69–1.35) (0.6–1.57)]
Brolucizumab vs aflibercept	0.96 [(0.57–1.63) (0.51–1.79)]
Brolucizumab vs bevacizumab	1.03 [(0.47–2.27) (0.44–2.43)]
Brolucizumab vs ranibizumab	1.08 [(0.53–2.19) (0.49–2.36)]
Conbercept vs aflibercept	0.24 [(0–4.29) (0–4.4)]
Conbercept vs bevacizumab	0.26 [(0–4.65) (0–4.67)]
Conbercept vs ranibizumab	0.27 [(0–4.67) (0–4.79)]
Conbercept vs brolucizumab	0.24 [(0–4.71) (0–4.85)]
Mortality 24 RCTs, 10 treatments + placebo, 8875 patients No inconsistency in the network (chi-squared = 0.69, p-value = 0.71) Between study variance: 0.01 (0.00-0.17)	
Bevacizumab vs aflibercept	0.58 [(0.15–1.98) (0.15–2.09)]
Ranibizumab vs aflibercept	0.59 [(0.17–1.8) (0.16–1.9)]
Ranibizumab vs bevacizumab	1.02 [(0.6–1.73) (0.54–1.94)]
Brolucizumab vs aflibercept	0.7 [(0.24–1.91) (0.23–2558)]
Brolucizumab vs bevacizumab	1.21 [(0.24–6.49) (0.23–2558)]
Brolucizumab vs ranibizumab	1.19 [(0.25–5.98) (0.24–2558)]
Difference in mean change in BCVA 26 RCTs, 10 treatments + placebo, 5916 patients No inconsistency in the network (chi-squared = 2.62, p-value = 0.27) Between-study variance: 6.29 (3.28–11.27)	
bevacizumab vs aflibercept	2.21 [(− 1.1 to 5.42) (− 3.96 to 8.22)]
ranibizumab vs aflibercept	1.09 [(− 1.53 to 3.7) (− 4.62 to 6.81)]
ranibizumab vs bevacizumab	− 1.11 [(− 3.07 to 0.92) (− 6.5 to 4.28)]
brolucizumab vs aflibercept	− 0.46 [(− 4.26 to 3.33) (− 6.84 to 5.81)]
brolucizumab vs bevacizumab	− 2.68 [(− 7.69 to 2.43) (− 9.72 to 4.54)]
brolucizumab vs ranibizumab	− 1.57 [(− 6.12 to 3.07) (− 8.34 to 5.32)]
conbercept vs aflibercept	− 15.17 [(− 23.8 to − 6.5) (− 25.35 to − 4.89)] [a]
conbercept vs bevacizumab	− 17.35 [(− 25.84 to − 8.57) (− 27.14 to − 7.16)] [a]
conbercept vs ranibizumab	− 16.23 [(− 24.57 to − 7.74) (− 25.97 to − 6.25)] [a]
conbercept vs brolucizumab	− 14.68 [(− 24.01 to − 5.17) (− 25.48 to − 3.94)] [a]

Treatment comparison	NMA estimate (95% CrI) (95% PrI)
Adverse events (AEs) 15 RCTs, 8 treatments + placebo, 5785 patients No inconsistency in the network (chi-squared = 0.01, *p*-value = 0.93) Between-study variance: 0.01 (0.00–0.15)	
Bevacizumab vs aflibercept	1.11 [(0.53–2.1) (0.49–2.25)]
Ranibizumab vs aflibercept	1.23 [(0.76–1.93) (0.67–2.16)]
Ranibizumab vs bevacizumab	1.11 [(0.71–1.87) (0.63–2.12)]
Brolucizumab vs aflibercept	1.07 [(0.77–1.46) (0.67–1.69)]
Brolucizumab vs bevacizumab	0.97 [(0.48–2.14) (0.45–2.34)]
Brolucizumab vs ranibizumab	0.87 [(0.5–1.55) (0.46–1.72)]
Conbercept vs aflibercept	0.74 [(0.28–2) (0.26–2.09)]
Conbercept vs bevacizumab	0.67 [(0.22–2.15) (0.21–2.3)]
Conbercept vs ranibizumab	0.61 [(0.22–1.68) (0.21–1.77)]
Conbercept vs brolucizumab	0.69 [(0.25–1.96) (0.23–2.08)]
Arterial thromboembolic events (ATE) 15 RCTs, 8 treatments + placebo, 6365 patients No source of inconsistency in the network (no closed loops) Between-study variance: 0.03 (0.00–0.48)	
Bevacizumab vs aflibercept	1.13 [(0.31–4.32) (0.29–4.78)]
Ranibizumab vs aflibercept	1.81 [(0.61–5.86) (0.54–6.68)]
Ranibizumab vs bevacizumab	1.6 [(0.85–3.15) (0.7–3.85)]
Brolucizumab vs aflibercept	0.66 [(0.28–1.52) (0.24–1.82)]
Brolucizumab vs bevacizumab	0.58 [(0.12–2.61) (0.11–2.93)]
Brolucizumab vs ranibizumab	0.36 [(0.09–1.42) (0.08–1.57)]
Conbercept vs aflibercept	0.73 [(0.01–38.5) (0.01–39.9)]
Conbercept vs bevacizumab	0.66 [(0.01–31.63) (0.01–32.15)]
Conbercept vs ranibizumab	0.41 [(0.01–19.15) (0.01–20.03)]
Conbercept vs brolucizumab	1.1 [(0.02–62.85) (0.02–64.99)]

Note: The NMA estimates are odds ratios for all outcomes except the mean change in BCVA, which is reported as mean differences

[a] Statistically significant difference

Fazit der Autorinnen und Autoren

Anti-VEGF agents are superior to other medications on the market, especially when administered alone. The anti-VEGF agents have similar effectiveness and safety profiles. The only observed differences were that ranibizumab, bevacizumab, aflibercept, and brolucizumab were statistically superior to conbercept in terms of the proportion of patients with nAMD who experienced moderate vision gain. However, this finding is based on indirect evidence through one small trial comparing conbercept with placebo. This does not account for drug-specific differences when assessing anatomic and functional treatment efficacy in variable dosing regimens.

Kommentare zum Review

Siehe auch:

- Matonti F et al., 2022 [3]: This new meta-analysis revealed superior efficacy, reflected by improvements in VA and CRT with both monthly PRN regimens, but this improved efficacy was achieved with a higher IVI number. On the other hand, the T&E regimens demonstrated similar efficacy to the monthly regimens, but with a reduced IVI number. When comparing the T&E regimens of aflibercept and ranibizumab, aflibercept was associated with a reduced IVI number compared with ranibizumab, but the recorded parameters showed similar efficacy.
- Li G et al., 2023 [2]: Comprehensive evidence confirms that Faricimab achieves non-inferior or even better CST improvement than other anti-VEGF therapies with extended

dosing intervals, but more long-term follow-up studies are needed to support our conclusions.

- Yen WT et al., 2024 [5]: The intravitreal bispecific anti-VEGF/angiopoietin 2 (Ang2) antibody faricimab with a extended injection interval was non-inferior to first-line anti-VEGF agents in BCVA. It was safe and had better anatomical recovery.

3.3 Leitlinien

American Academy of Ophthalmology, 2019 [1].

Age-Related Macular Degeneration

Leitlinienorganisation/Fragestellung

American Academy of Ophthalmology entwickelte eine “Preferred Practice Pattern Guideline”

Ziel der LL: to provide guidance for the pattern of practice, not for the case of a particular individual

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar, keine Patientenvertretung;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Keine Informationen zu formalen Konsensusprozesse;
- Externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Literature searches to update the PPP were undertaken in March 2018 and June 2019 in PubMed and the Cochrane Library

LoE/GoR

- Application of methods from SIGN and GRADE to grade strength of the total body of evidence and all studies used to form a recommendation are graded for strength of evidence individually

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good 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
Insufficient 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 Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

Hinweise

Die Leitlinie enthält Informationen zu Wirkstoffen, die nach 2019 von der FDA zugelassen wurden. Es sind keine systematischen Updates der Leitlinie zu diesen Wirkstoffen beschrieben. Die entsprechenden Änderungen wurden extrahiert.

Empfehlungen

Neovaskuläre AMD (nAMD)

Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD and a Cochrane systematic review demonstrates the effectiveness of these agents to maintain visual acuity.[167] *(I+, Good quality, Strong recommendation)*

Hintergrundinformation:

With the introduction of the VEGF inhibitors pegaptanib sodium (Macugen®, Eyetech, Inc., Cedar Knolls, NJ) in 2004, off-label bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) in 2005, ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA) in 2006, and aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) in 2011, more effective treatments for neovascular AMD exist. The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies.

Aflibercept is a pan–VEGF-A and placental growth factor (PGF) blocker approved by the US Food and Drug Administration (FDA) that has been documented to be of similar efficacy to ranibizumab in the head-to-head phase III VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials.[168] In these pivotal studies, the currently approved 2-mg dose of aflibercept was administered by intravitreal injection every 4 weeks and every 8 weeks after three monthly loading doses. In the first year, both study arms were similar to 0.5- mg ranibizumab dosed every 4 weeks.

Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF. It is FDA approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer. Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab.[169,170] Because preliminary reports appeared favorable, ophthalmologists began to use intravitreal bevacizumab off-label to treat CNV.

Comparative trials and uncontrolled case series reported improvements in VA and decreased retinal thickness by optical coherence tomography (OCT) following intravitreal bevacizumab treatment.[171-177] Informed consent information is available on the benefits and risks of intravitreal bevacizumab and its off-label status.[178]

Intravitreal **ranibizumab** (0.5 mg) is FDA approved for the treatment of all subtypes of neovascular AMD, based on results from three double-masked, randomized controlled trials.[179,180] (siehe Anhang Abbildung 10.) Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment developed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of all isoforms of human VEGF-A.

The Comparison of AMD Treatment Trials (CATT) was a multicenter clinical trial that compared the safety and effectiveness of bevacizumab with ranibizumab and an individualized dosing regimen (as needed, or PRN) with monthly injections. At 1 year, the CATT study found that ranibizumab and bevacizumab had comparable equivalence VA improvements for monthly dosing.[174] Ranibizumab PRN had similar VA improvements compared with a fixed schedule of monthly injections. Further follow-up at 2 years showed that the two drugs remained comparable in both efficacy and safety, but the PRN arms together did not perform as well in terms of maintaining the visual gains at the end of year 1 compared with the two monthly arms, especially in the bevacizumab PRN group.[183] The CATT 5-year follow-up study demonstrated vision gains during the first 2 years that were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti- VEGF therapy as a major long-term therapeutic advance for neovascular AMD.[184] Similar results were seen in the 2-year Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial conducted in the United Kingdom.[185,186] (See Glossary.)

Presently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab.[184] A meta-analysis by Nguyen in 2018 of over 8,000 eyes comparing all three drugs concluded that bevacizumab and ranibizumab had equivalent efficacy for bestcorrected visual acuity (BCVA), whereas ranibizumab had greater reduction in central macular thickness, and aflibercept and ranibizumab had comparable efficacy for BCVA and central macular thickness.[187] The review by Chen in 2015 also elicited similar results.[188] The systemic safety data in the CATT and IVAN studies are inconclusive and two Cochrane systematic reviews have also concluded that if a difference in safety between these anti-VEGF drugs exists, it is minimal.[189,190] (I+, Good quality, Strong recommendation) A real world analysis of 13,859 patients found that all three agents improved visual acuity similarly over 1 year.[191]

Pegaptanib sodium is a selective VEGF antagonist that binds to the 165 isoform of VEGF-A. It was the first anti-VEGF agent available for treating neovascular AMD. Pegaptanib sodium injection is FDA approved for the treatment of all subtypes of neovascular AMD, with a recommended dosage of 0.3 mg injected every 6 weeks into the vitreous. These recommendations were based on results from two double-masked, randomized controlled trials.[181] (See Table 3.) Unlike the other anti-VEGF agents that are currently available (ranibizumab, aflibercept, and bevacizumab), pegaptanib treatment does not improve VA on average in patients with new-onset neovascular AMD and is rarely used in current clinical practice.

Randomized clinical trials have been performed to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin PDT, following the publication of results from uncontrolled case series.[192-195] However, the data do not currently support the use of combination therapy with steroids, especially given the long-term side effects of glaucoma and cataract that are associated with corticosteroid use.

The DENALI and MONT BLANC studies (ranibizumab and verteporfin PDT compared with ranibizumab alone) did not show a significant benefit of adding PDT to anti-VEGF therapy in new-onset neovascular AMD.[196,197] (See Glossary.) However, the EVEREST study demonstrated that fewer anti-VEGF injections were needed in combination therapy compared with anti-VEGF monotherapy in eyes with the PCV variant of neovascular AMD.[198] A 2017 meta-analysis and systematic review also concluded that treatment of PCV by PDT combined with ranibizumab is valuable in improving VA and maintaining long-term effectiveness but recommended further study.[199,200] A randomized trial of 310 subjects has shown aflibercept to effectively treat PCV in 85% of patients; 15% required PDT for control.[200] A 2018 metaanalysis of 16 studies by Gao et al compared 587 patients in the monotherapy group with various anti-VEGF agents against 673 patients in the combination group and found no statistically significant difference between groups in mean BCVA, the proportion of patients who gained 15 or more letters, or central retinal thickness at the end of the study.[201] However, combination therapy did require fewer anti-VEGF injections, as noted in other studies with reduced-fluence PDT demonstrating this reduction in number of injections at a statistically significant level as opposed to the standard fluence group.[201]

Subfoveal Choroidal Neovascularization

In addition to intravitreal injections of VEGF inhibitors, verteporfin PDT and thermal laser photocoagulation surgery remain approved options for the treatment of subfoveal lesions. Current practice patterns support the use of anti-VEGF monotherapy for patients with newly diagnosed neovascular AMD and suggest that these other therapies are rarely needed. Photodynamic therapy with verteporfin has FDA approval for the treatment of AMD-related, predominantly classic, subfoveal CNV; treatment trial results are described in Table 3. The efficacy of thermal laser photocoagulation surgery for CNV was studied in the MPS (early 1990s) in a randomized, controlled, multicenter trial.[148-151] The MPS directly treated eyes that had subfoveal lesions using thermal laser surgery,[150] but the outcomes were poor and do not compare with the positive VA benefits found with current anti-VEGF therapy. Thus, thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment.

Table 3 (at the end of this section) summarizes the findings from randomized controlled trials of verteporfin PDT and VEGF inhibitors for the treatment of subfoveal CNV. The entry criteria varied among these studies and may have contributed to the differences among treatment cohorts.

Juxtafoveal Choroidal Neovascularization

Although randomized, controlled clinical trials have not routinely included patients with juxtafoveal CNV, many clinicians extrapolated the data from current trials to consider intravitreal injections of anti-VEGF agent as the primary therapy for juxtafoveal lesions. In the MPS, treatment of well-demarcated juxtafoveal CNV lesions resulted in a small overall treatment benefit.151 The rates of "persistence" (CNV leakage within 6 weeks of laser photocoagulation surgery) and "recurrence" (CNV leakage more than 6 weeks after laser photocoagulation surgery) were high (80%) at 5 years. After 5 years of follow-up, 52% of eyes treated for juxtafoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 61% of untreated eyes.[151]

Extrafoveal Choroidal Neovascularization

There still remains a possible role for thermal laser surgery treatment in eyes with extrafoveal and peripapillary CNV lesions as defined by the MPS.[148,202] Although photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a substantial reduction in the risk of severe visual loss for the first 2 years, recurrence or persistence occurs in approximately 50% of cases, thus reducing this benefit over the subsequent 3 years of follow-up.[148] After 5 years of follow-up, 48% of eyes treated for extrafoveal lesions progressed to VA loss of 30 or more letters when compared with 62% of untreated eyes.148 The historical data are important to recognize in current practice patterns, as none of the anti-VEGF or PDT trials included extrafoveal lesions. Practitioners have extrapolated and applied data from the dramatic improvements seen in the treatment of subfoveal lesions to extrafoveal lesions. The current trend is to use anti- VEGF agents in preference to laser photocoagulation surgery. Laser surgery for extrafoveal lesions remains a less commonly used, yet reasonable, therapy. Current therapies that have insufficient data to demonstrate clinical efficacy include radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal corticosteroids with verteporfin PDT. Therefore, at this time, these therapies are not recommended.

Indications for Treatment for Choroidal Neovascularization

Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4. The criteria for treatment of AMD and the techniques of therapy are described in the aflibercept, bevacizumab, ranibizumab, pegaptanib, MPS, and AREDS literature. Aflibercept, ranibizumab, and pegaptanib-injection product labeling and other literature discuss techniques of intravitreal injection.[181,207,239-241] Recently, conbercept has shown promising results in the management of wet AMD,[242] although it has yet to receive FDA approval for its use. Similarly, abicipar has completed phase II clinical trials and has shown an extended duration of effect with a good safety profile; however, it has not received FDA approval. [243,244] Recently reported results from the HAWK and HARRIER phase III clinical trials showed that **brolucizumab** achieved its primary endpoint of noninferiority of BCVA change compared with aflibercept at week 48. Patients treated with brolucizumab achieved superior reductions in central subfield thickness compared with aflibercept. Fewer patients treated with brolucizumab had sub-retinal fluid, inter-retinal fluid, and sub-RPE fluid. Brolucizumab received FDA approval in October 2019.[245] The Archway phase III study showed that patients receiving a ranibizumab implant had visual acuity gains equivalent to patients receiving monthly ranibizumab injections, and that approximately 98% could receive continuous treatment for six months before requiring a refill or supplemental ranibizumab. This ranibizumab implant received FDA approval in October 2021. A 3 times higher rate of endophthalmitis than monthly injections has been reported, with the majority of these associated with conjunctival erosions or retractions.*

*See: Holekamp NM, Campochiaro PA, Chang M, et al. Archway Randomized Phase 3 Trial of the Port Delivery System With Ranibizumab for Neovascular Age-Related Macular Degeneration, Ophthalmology (2021), doi: https://doi.org/10.106/j.ophtha.2021.09.016.

As is the case with most clinical trials, these treatments trials do not provide clear guidance for the management of all patients encountered in clinical practice. To date, the major prospective randomized anti-VEGF treatment trials (Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD [ANCHOR], Minimally Classic/Occult Trial of the Anti- VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA], VIEW, CATT, IVAN, HARBOR) used either a fixed continuous ~~treatment~~ regimen (approximately every 4 or 8 weeks) or an individualized discontinuous treatment regimen (PRN).[168,174,179,180,183,185,186,246]

The PRN regimens using ranibizumab appear to have efficacy and safety comparable to fixed monthly regimens over 1 year of treatment, but they do not maintain the initial visual gains with longer follow-up.[183,255] Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens and other PRN anti-VEGF regimens.[183] Vision gains during the first 2 years of the CATT clinical trials were not maintained at the 5-year follow-up visit, but 50% of the patients maintained a VA of 20/40.[184]

A continuous, variable dosing regimen that attempts to individualize therapy, commonly referred to as "treat and extend," is frequently used in clinical practice as an alternative to the two treatment approaches above.248-251 Prospective studies such as Lucentis Compared to Avastin Study (LUCAS) have shown similar efficacy between monthly and treat-and-extend for bevacizumab and ranibizumab.[256]

Subretinal hemorrhages are relatively common in neovascular AMD. Small subretinal hemorrhages are a sign of active CNV or PCV and may be managed with anti-VEGF therapy. For the management of larger submacular hemorrhages, the SST study was inconclusive. Pneumatic displacement procedures, the use of tPA, and/or pars plana vitrectomy have been proposed. The data on management of these larger hemorrhages are inadequate to make a recommendation at this time.[257]

The risks, benefits, and complications of the treatment and the alternatives to it should be discussed with the patient and informed should be consent obtained.[146,258]

TABLE 4 Treatment Recommendations and Follow-up for Age-Related Macular Degeneration

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations
Neovascular AMD		
Aflibercept intravitreal injection 2.0 mg as described in published reports[168]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist. A maintenance treatment regimen of every 8 weeks has been shown to have results comparable to every 4 weeks in the first year of therapy. • Monitoring of monocular near vision (reading/Amsler grid)
Bevacizumab intravitreal injection 1.25 mg as described in published reports[172-177,183,185,240,248] The ophthalmologist should provide appropriate informed consent with respect to the off-label status.[178]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters. • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)
Brolucizumab intravitreal injection 6.0 mg as described in FDA labeling[245]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)
Ranibizumab intravitreal injection 0.5 mg as recommended in literature[174,179,180,183,185,207,246,249-251]	Macular CNV	• Patients should be instructed to promptly report symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or an increased number of floaters.[207] • Return examination approximately 4 weeks after treatment initially; subsequent follow-up and treatment depends on the clinical findings and judgment of the treating ophthalmologist • Monitoring of monocular near vision (reading/Amsler grid)
Less Commonly Used Treatments for Neovascular AMD		
PDT with verteporfin as recommended in the TAP and VIP reports[182,252-254*]	• Macular CNV, new or recurrent, where the classic component is >50% of the lesion and the entire lesion is ≤5400 µm in greatest linear diameter • Occult CNV may be considered for PDT with vision <20/50 or if the CNV is <4 MPS disc areas in size when the vision is >20/50 • Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases	• Return examination approximately every 3 months until stable, with retreatments as indicated • Monitoring of monocular near vision (reading/Amsler grid)
Thermal laser photocoagulation surgery as recommended in the MPS reports is rarely used[148,151,247]	• May be considered for extrafoveal classic CNV, new or recurrent • May be considered for juxtapapillary CNV	• Return examination with fluorescein angiography approximately 2–4 weeks after treatment, and then at 4–6 weeks and thereafter depending on the clinical and angiographic findings • Retreatments as indicated • Monitoring of monocular near vision (reading/Amsler grid)

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy

* Contraindicated in patients with porphyria or known allergy.

Complications of Treatment

Possible complications of the four main modalities of treatment for AMD are listed below. Retinal pigment epithelium rips (tears) may occur with or without these treatment modalities, yet this is not a contraindication to continued anti-VEGF therapy.

Intravitreal Pharmacotherapy

All anti-VEGF treatments may carry theoretical risks for systemic arterial thromboembolic events and increased intraocular pressure, although the results of clinical trials studying these risks remain inconclusive.[259-262] A recent review of the literature concluded that anti- VEGF therapy is safe and effective for neovascular AMD.[263] The risks of intravitreal anti- VEGF agents in pregnant or lactating women have not been studied.[264,265] Intravitreal pharmacotherapy can result in endophthalmitis, noninfectious inflammation, retinal tear, or detachment.

Aflibercept injection

- Endophthalmitis (cumulative ≤1.0% over 1 year in VIEW studies)[168]

At 1 year, there were no statistically significant differences in rates of serious systemic adverse events such as death, arteriothrombotic events, or venous thrombotic events between ranibizumab and aflibercept.[168,266]

Bevacizumab injection

- Reported safety data are limited by relatively short and variable follow-up periods and by differences in reporting criteria.[267,268]
- Reported ocular adverse events include bacterial endophthalmitis per injection (0.16%), tractional retinal detachments (0.16%), uveitis (0.09%), rhegmatogenous retinal detachment (0.02%), and vitreous hemorrhage (0.16%).[240,269]

The CATT study had limited statistical power to identify any differences in treatmentrelated adverse events between bevacizumab and ranibizumab. At 1 year, there were no statistically significant differences in rates of death, arteriothrombotic events, or venous thrombotic events for the two drugs. There was a higher rate of serious systemic events (e.g., arteriothrombotic events, venous thrombosis, or gastrointestinal disorders such as hemorrhage) among patients treated with bevacizumab compared with ranibizumab (24% vs. 19%; P=0.04), and this statistically significant difference was persistent at 2 years of follow-up.[174,183] The IVAN trial showed greater serum VEGF suppression with bevacizumab but did not show any statistically significant difference in serious systemic adverse events.[185]

Ranibizumab injection

- Endophthalmitis (cumulative ≤1.0% over 2 years in MARINA study; <1.0% over 1 year in ANCHOR study)
- Retinal detachment or traumatic injury to the lens (<0.1% of treated cases during the first year of treatment)[179,180]

Pegaptanib sodium injection270

- Endophthalmitis (1.3% of treated cases during the first year of treatment)
- Traumatic injury to the lens (0.6% of treated cases during the first year of treatment)
- Retinal detachment (0.7% of treated cases during the first year of treatment)
- Anaphylaxis/anaphylactoid reactions including angioedema (rare; these were reported following FDA approval)

Verteporfin Photodynamic Therapy

A severe decrease in central vision occurred within 1 week following treatment in 1% to 4% of patients, and may be permanent[182,252,253]

- Infusion site extravasation
- Idiosyncratic back pain during infusion of the drug (1%–2% of patients)[182,252,25

- Photosensitivity reaction (<3% of patients).[182,252,253] The stated, current recommendations are to avoid direct sunlight for the first 5 days after a treatment.

Verteporfin is contraindicated in patients with porphyria or a known allergy or sensitivity to the drug. Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breastfeeding, or of pediatric age, because these patients were not studied in published reports

Thermal Laser Photocoagulation Surgery

- Severe vision loss following treatment, which may be permanent
- Rupture of Bruch's membrane with subretinal or vitreous hemorrhage
- Effects on the fovea in subfoveal or juxtafoveal CNV

Thermal laser is no longer recommended for subfoveal CNV. Introduction or enlargement of a pre-existing scotoma, with or without VA loss, is not a complication of thermal laser photocoagulation surgery; rather, it is an anticipated side effect of the treatment. Similarly, recurrence or persistence of CNV, or the development of new CNV and further visual deterioration after adequate thermal laser surgery, is usually a result of the disease process and is not a complication. These realities must be emphasized to the patient and family before treatment.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 05 of 12, May 2024) am 22.05.2024

#	Suchfrage
1	MeSH descriptor: [Macular Degeneration] this term only
2	MeSH descriptor: [Wet Macular Degeneration] explode all trees
3	(macular AND (degeneration* OR dystroph*)):ti,ab,kw
4	((age OR wet OR exudative OR neovascular) AND maculopath*):ti,ab,kw
5	((AMD OR wAMD OR nAMD OR ARMD OR wARMD OR nARMD) AND macular):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from May 2019 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 22.05.2024

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

#	Suchfrage
1	Macular Degeneration[mh:noexp]
2	Wet Macular Degeneration[mh]
3	macular[tiab] AND (degeneration*[tiab] OR dystroph*[tiab])
4	(age[tiab] OR wet[tiab] OR exudative[tiab] OR neovascular[tiab]) AND maculopath*[tiab]
5	(AMD[tiab] OR wAMD[tiab] OR nAMD[tiab] OR ARMD[tiab] OR wARMD[tiab] OR nARMD[tiab]) AND macular[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (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]

#	Suchfrage
	OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
8	(#7) AND ("2019/05/01"[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 22.05.2024

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

#	Suchfrage
1	Macular Degeneration[mh:noexp]
2	Wet Macular Degeneration[mh]
3	macular[tiab] AND (degeneration*[tiab] OR dystroph*[tiab])
4	(age[tiab] OR wet[tiab] OR exudative[tiab] OR neovascular[tiab]) AND maculopath*[tiab]
5	(AMD[tiab] OR wAMD[tiab] OR nAMD[tiab] OR ARMD[tiab] OR wARMD[tiab] OR nARMD[tiab]) AND macular[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2019/05/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 23.05.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)

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

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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

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Verfasser	
Name der Institution	Deutsche Ophthalmologische Gesellschaft (DOG) (Mitglied der AWMF), Retinologische Gesellschaft (RG), Berufsverband der Augenärzte Deutschlands e.V. (BVA)
Datum der Erstellung	1. Juni 2024

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
… wird angewendet zur Behandlung von erwachsenen Patienten mit einer neovaskulären (feuchten) altersbedingten Makuladegeneration (nAMD).
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.)*
Die Behandlung der neovaskulären altersabhängigen Makuladegeneration (nAMD) wurde 2020 und 2022 in Stellungnahmen der ophthalmologischen Fachgesellschaften ausführlich dargestellt [1,2]. Nach Sicherung der Diagnose hat bisher eine Therapie mit Hemmstoffen des *vascular endothelial growth factor* (VEGF) zu erfolgen. Ein zugelassener Wirkstoff hemmt zusätzlich den Wachstumsfaktor Angiopoietin 2. Für die intravitreale operative Medikamenten-applikation (IVOM) ist nach der initialen Therapie eine Festlegung der Wiederbehandlungs-strategie gemäß individueller Kriterien angeraten. Nachdem in den ersten Zulassungsstudien eine Wiederbehandlung mit festen Intervallen zur Kontrolle und Behandlung erfolgte, steht mittlerweile die Anpassung der Behandlungsintervalle in Abhängigkeit von der Aktivität der zugrundeliegenden Gefäßmembran im Vordergrund. Eine Unterbehandlung führt zu schlechteren funktionellen Ergebnissen. Allerdings gehen von jeder operativen Medikamentenapplikation neben dem Aufwand für Patient und Arzt auch Risiken aus, insbesondere die Gefahr einer infektiösen Entzündung potentiell mit irreversiblem Sehverlust. Daher ist der Grundsatz „so viel wie nötig, so wenig wie möglich“ zielführend. In früheren Verfahren der frühen Nutzenbewertung (Aflibercept: A12-19 / BAnz AT 27.06.2013 B3, Brolucizumab: A20-23 / BAnz AT 01.10.2020 B6, Faricimab: A22-110 / BAnz AT 27.04.2023 B3, Brolucizumab (G-BA-Beschluss 2.5.24 https://www.g-ba.de/downloads/39-261-6578/2024-05-02_AM-RL-XII_Brolucizumab_D-984.pdf) hatten pharmazeutische Unternehmer keine Studiendaten vorlegen können, in denen die zweck-mäßige Vergleichstherapie (Ranibizumab oder Aflibercept) gemäß deren Zulassung oder der jeweils aktuellen medizinischen Fachinformation eingesetzt worden war. Allerdings sehen die Fachinformationen unterschiedliche Wiederbehandlungsstrategien vor und lassen der ärztlichen Therapiefreiheit ausdrücklich Spielraum [1]. In die Beurteilung, ob eine

Wiederbehandlung erfolgen soll, gehen sinnvollerweise viele Parameter wie die Funktion des Partnerauges, der Allgemeinzustand, Begleiterkrankungen und die Prognose von Sehfunktion und Lebenserwartung ein.

Vergleichende Studien konnten bisher nur die Frage einer Nicht-Unterlegenheit („non-inferiority“) beantworten.

Statistisch signifikante Unterschiede in Parametern/Endpunkten müssen noch keinen klinisch relevanten Unterschied bedeuten [3]. Zudem müssen Verzerrungspotential und Sensitivität (Fallzahlplanung, Studiendesign) berücksichtigt werden. Die Reduktion notwendiger Wiederbehandlungen bei vergleichbarer Wirksamkeit würde im klinischen Alltag durchaus einen relevanten Vorteil bieten. Weil bisher bei allen intravitrealen VEGF-Inhibitoren eine Phase mit regelmäßigen Behandlungen für den Therapiestart vorgesehen ist, werden sich relevante Unterschiede in den Zahlen der notwendigen Behandlungen erst mit zunehmender Behandlungsdauer auswirken.
Sicherheitsrelevante Ereignisse sind möglicherweise nur mit sehr großen Fallzahlen zu beurteilen. Für die wirtschaftlichen Auswirkungen müssen neben der Prozedur und dem Medikament auch die Kosten der Kontrolluntersuchungen sowie z.B. Fahrtkosten zu den Kontrollen und Behandlungen berücksichtigt werden.

Es gibt Hinweise auf eine jährliche Zunahme der zu behandelnden Patienten mit nAMD [4]. Diese Zunahme wird mit einer früheren Diagnose und dem demographischen Wandel erklärt. In der deutschen Versorgungspraxis findet die IVOM-Therapie im Rahmen der gesetzlichen Krankenversorgung statt. Es gibt zudem Selektivverträge, die von Maßnahmen der Qualitätskontrolle und Anreizen zu einem wirtschaftlichen Medikamenteneinsatz getragen werden [5,6]. In Deutschland wurden Biosimilars und mit einem wesentlichen Anteil auch der bis 2024 nicht zugelassene Wirkstoff Bevacizumab eingesetzt [7,8], für den eine vergleichbare Wirksamkeit und Sicherheit in randomisierten kontrollierten Studien nachgewiesen wurde [9,10].

Der Charakter der chronischen Erkrankung bedeutet für die nAMD, dass der Adhärenz eine wesentliche Bedeutung zukommt [11,12]. Registerdaten und nicht-interventionelle Studien belegen, dass im klinischen Alltag eine Unterbehandlung mit schlechteren funktionellen Ergebnissen assoziiert ist [13,14].

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.)

Basis der Entscheidung über die Behandlungsindikation ist die klinische Untersuchung mit Erhebung der bestkorrigierten Sehschärfe, Untersuchung von vorderem und hinterem Augenabschnitt und die optische Kohärenztomographie (OCT) [1,2]. Für die Bestätigung einer behandlungsbedürftigen Läsion ist initial außerdem eine Fluoreszenz-Angiographie gefordert.
Insbesondere die Untersuchung mit Hilfe der OCT (Banz AT 22.03.2019 B2) liefert hochaufgelöste Bilder der zentralen Netzhaut, in denen nicht nur über die Detektion von Flüssigkeit in und unter der Netzhaut und Veränderungen der entsprechenden Netzhautschichten die Aktivität der nAMD-Läsionen beurteilt werden kann, sondern auch Hinweise auf eine limitierte Visusprognose und einen sinnvollen Therapie-Abbruch gefunden werden können. Neu aufgetretene Blutungen und eine Sehverschlechterung sind weitere Aktivitätskriterien, die auf eine notwendige Wiederbehandlung hinweisen können.
Bisher gibt es keine Belege dafür, dass unterschiedliche Strategien der Wiederbehandlung (PRN: Kontrolle und Wiederbehandlung bei Aktivität, Behandlungsserien, Treat & Extend: Verkürzung oder Verlängerung der Behandlungsintervalle je nach Aktivität) für individuelle

Entscheidungen oder Subgruppen der Erkrankung Vorteile bieten. Daher werden verschiedene Behandlungsstrategien als Option in den Fachinformationen ermöglicht.

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