



**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: Erwachsene mit neovaskulärer (feuchter)
altersabhängiger Makuladegeneration (AMD)**

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

Brolucizumab

[neovaskuläre (feuchte) altersabhängige 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 subfoveolärer klassischer choriodaler Neovaskularisation

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

Beschlüsse über die Nutzenbewertung nach § 35a SGB V:

- Aflibercept (Beschluss vom 6. Juni 2013)
- Brolucizumab (Beschluss vom 3. September 2020)
- Faricimab (Beschluss vom 06. April 2023)

sonstige Beschlüsse:

- Protonentherapie bei altersabhängiger Makuladegeneration (Beschluss vom 17. September 2009)
- photodynamische Therapie (PDT) mit Verteporfin bei altersabhängiger feuchter Makuladegeneration mit subfoveolärer 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:	
Brolucizumab S01LA06 Beovu	<u>Anwendungsgebiet laut Fachinformation:</u> Beovu wird angewendet bei Erwachsenen zur Behandlung der neovaskulären (feuchten) altersabhängigen Makuladegeneration (AMD).
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)
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) <i>Der erste Schritt besteht in einer 10-minütigen intravenösen Infusion von Visudyne. Der zweite Schritt besteht in der Lichtaktivierung von Visudyne 15 Minuten nach Beginn der Infusion.</i>

Quellen: AMIce-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

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

Vorgang: neovaskuläre (feuchte) altersabhängige Makuladegeneration (AMD)

Auftrag von: Abt. AM

Bearbeitet von: Abt. FB Med

Datum: Juni 2023

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Abkürzungsverzeichnis

AMD	Altersabhängigen Makuladegeneration
AM-RL	Arzneimittel-Richtlinie
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCVA	Best-Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusion
CNV	Choroidal Neovascularization
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
DME	Diabetic Macular Edema
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
KI	Konfidenzintervall
LoE	Level of Evidence
MD	Mean Difference
nAMD	Neovaskuläre Altersabhängige Makuladegeneration
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NVAMD	Neovascular Age-related Macular Degeneration
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
RVO	Retinal Vein Occlusion
SF	Standard-Fluence
TRIP	Turn Research into Practice Database
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WMD	Weighted Mean Difference

1 Indikation

Behandlung erwachsener Patienten mit neovaskulärer (feuchter) altersabhängiger Makuladegeneration (AMD).

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.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 15.05.2023 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 531 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 7 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Solomon SD et al., 2019 [4].

Update von Solomon SD et al., 2014 ¹

Anti-vascular endothelial growth factor for neovascular age-related macular degeneration (Review)

Fragestellung

To investigate ocular and systemic effects of, and quality of life associated with, intravitreal injection of three anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) versus no anti-VEGF treatment for patients with neovascular AMD.

To compare the relative effects of one of these anti-VEGF agents versus another when administered in comparable dosages and regimens.

Methodik

We included only randomized controlled trials (RCTs) in this review. We included only trials in which participants were followed for at least one year. We also included outcomes at two-year follow-up when these data were available.

Population:

- We included trials in which participants had neovascular AMD as defined by study investigators.

Intervention/Komparator:

- We included studies that compared anti-VEGF treatment versus another treatment, sham treatment, or no treatment. We did not include studies that compared different doses of one anti-VEGF treatment against another, studies that included no control or comparator group, or studies that used anti-VEGF agents in combination with other treatments. We did not include studies of aflibercept (VEGF Trap-Eye/EYLEA solution) or studies that compared different treatment schedules (e.g. monthly vs as needed dosing), because other Cochrane reviews have evaluated these interventions.

Endpunkte:

Primary outcomes

- best-corrected visual acuity (BCVA) at one-year follow-up. All included RCTs randomized only one eye per participant (i.e. the study eye); therefore we defined the primary outcome for the comparison of treatments as the proportion of participants who gained 15 or more letters (three lines) of BCVA in the study eye when BCVA was measured on a visual acuity chart with a LogMAR scale.

Secondary outcomes

- Visual acuity outcomes
- Proportion of participants who gained 15 or more letters of BCVA in the study eye as measured at two-year follow-up

¹ Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014(8):CD005139.

- Proportion of participants who lost fewer than 15 letters of visual acuity at one year and at two years
- Proportion of participants who lost fewer than 30 letters of visual acuity at one year and at two years
- Proportion of participants for whom blindness was avoided in the study eye, defined as eyes with visual acuity better than
- 20/200 at one year and at two years
- Proportion of participants maintaining visual acuity, defined as a gain of zero or more letters (i.e. no loss of BCVA from baseline) at one year and at two years
- Mean change in visual acuity from baseline to one year and to two years
- Other secondary outcomes
- Contrast sensitivity, reading speed, or any other validated measure of visual function as measured in the included studies
- Assessment of morphologic characteristics by fluorescein angiography or optical coherence tomography (OCT), including mean change in size of CNV, mean change in size of total lesion, and mean change in central retinal
- Central retinal thickness (CRT)
- Quality of life measures, as assessed with any validated measurement scale
- Economic data, such as comparative cost analyses
- Ocular or systemic adverse outcomes

Recherche/Suchzeitraum:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Eyes and Vision Trials Register (searched January 31, 2018); MEDLINE Ovid (1946 to January 31, 2018); Embase Ovid (1947 to January 31, 2018); the Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to January 31, 2018); the International Standard Randomized Controlled Trials Number (ISRCTN) Registry (2018); ClinicalTrials.gov (searched November 28, 2018); and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched January 31, 2018). We did not impose any date or language restrictions in electronic searches for trials.

Qualitätsbewertung der Studien:

- risk of bias was assessed using the Cochrane Risk of Bias tool
- GRADE Working Group grades of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- We had classified one newly included study as ongoing in the 2014 version of this review. Overall, we identified and included 16 RCTs (n=6.347).
- Of six studies that compared anti-VEGF monotherapy versus control, one study evaluated three doses of pegaptanib versus sham injection (VISION 2004), three studies compared two doses of ranibizumab versus sham injections or PDT (ANCHOR 2006; MARINA 2006; PIER 2008), and two studies compared bevacizumab with other treatments for AMD (ABC 2010; Sacu 2009). The remaining ten studies were head-to-head trials of bevacizumab versus ranibizumab (Biswas 2011; BRAMD 2016; CATT 2011; GEFAL 2013; IVAN 2013; LUCAS 2015; MANTA 2013; SAVE-AMD 2017; Scholler 2014; Subramanian 2010).

Charakteristika der Population:

- The 16 trials were similar in that all enrolled both men and women 50 years of age or older who had subfoveal CNV secondary to AMD; one study also enrolled participants with juxtafoveal or extrafoveal CNV (BRAMD 2016).
- A majority of participants in most trials were women, but one trial enrolled a greater number of men than women (Subramanian 2010).

Qualität der Studien:

- Overall, we found the included studies to be at low risk for most categories of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Masking of participants (performance bias)	Masking of study personnel (performance bias)	Masking of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ABC 2010	+	+	+	+	+	+	?	+
ANCHOR 2006	+	+	+	+	+	+	+	?
Biswas 2011	+	?	?	+	+	?	?	+
BRAMD 2016	+	+	+	+	+	+	?	+
CATT 2011	+	+	?	+	+	?	+	+
GEFAL 2013	+	+	+	+	+	+	?	+
IVAN 2013	+	+	+	+	+	+	?	+
LUCAS 2015	+	+	+	+	+	+	?	+
MANTA 2013	+	+	+	+	+	+	?	+
MARINA 2006	+	+	+	+	+	+	+	?
PIER 2008	+	?	+	+	+	+	+	?
Sacu 2009	+	+	+	+	+	+	+	+
SAVE-AMD 2017	?	?	?	?	?	?	+	?
Scholler 2014	+	?	?	?	+	?	?	?
Subramanian 2010	?	+	+	+	+	+	?	+
VISION 2004	+	+	+	+	+	+	+	?

Other potential sources of bias:

We considered various other aspects of trial design and reporting, trial sponsorship, and financial interests of investigators as other potential sources of bias. Pharmaceutical companies marketing the study drugs under investigation sponsored ANCHOR 2006, MARINA 2006, PIER 2008, and VISION 2004, and submitted data from these trials to the FDA to obtain approval for ranibizumab and pegaptanib. In addition, pharmaceutical company sponsors had important roles in trial design, analysis, and reporting. Some investigators from other trials reported that they received trial agents or financial support from pharmaceutical companies; however, because the companies did not directly sponsor these trials, we did not judge them to be at risk of bias for this domain (CATT 2011; GEFAL 2013; IVAN 2013; Scholler 2014). We observed no other potential sources of bias for the remaining eight studies.

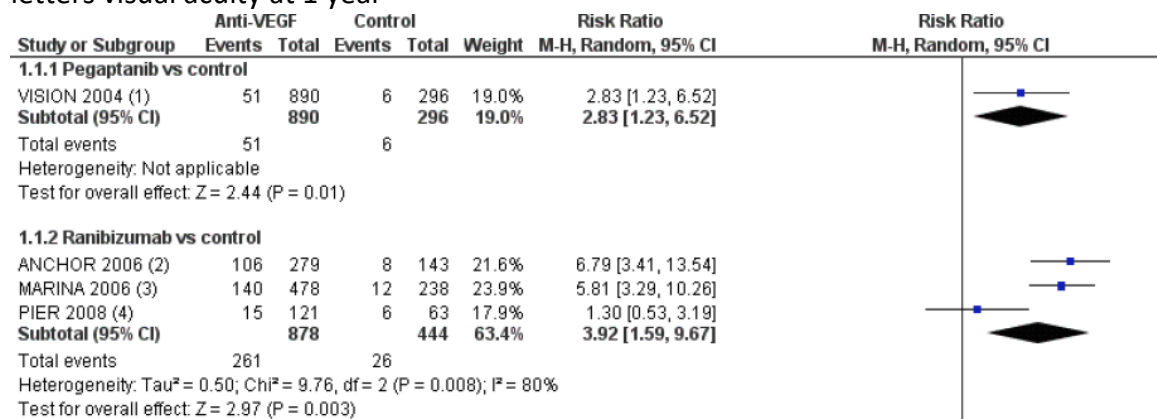
Studienergebnisse:

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

Primary Outcome:

Gain of 15 or more letters visual acuity

Abb.1: Comparison Anti-VEGF treatment versus control, Outcome: Gain of 15 or more letters visual acuity at 1 year



Footnotes

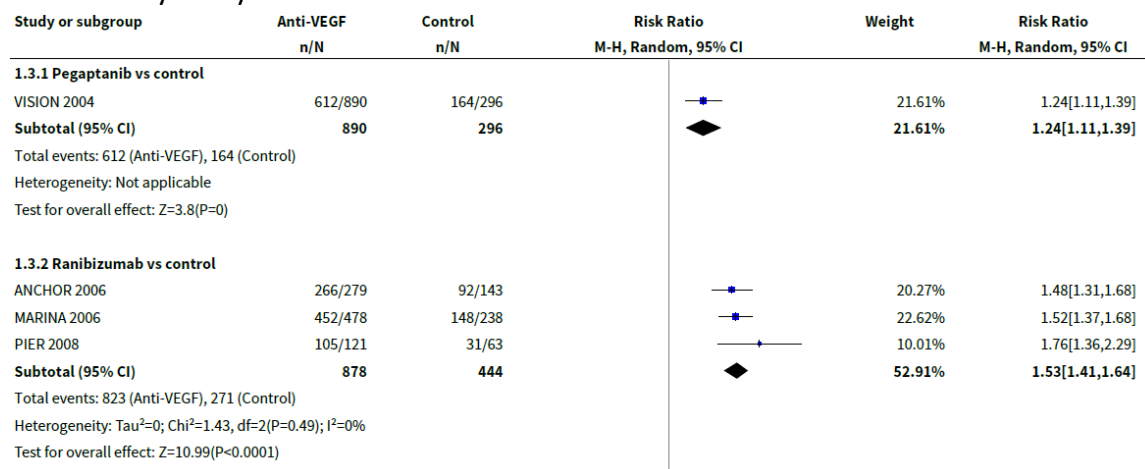
- (1) Control group in the VISION study received sham injections
- (2) Control group in the ANCHOR study received sham injections plus active verteporfin photodynamic therapy
- (3) Control group in the MARINA study received sham injections
- (4) Control group in the PIER study received sham injections

- At two years, data were available from only the three ranibizumab trials. The proportion of participants who were treated with ranibizumab and had gained 15 or more letters at two years was nearly six times the proportion of those treated with control who gained 15 or more letters (RR 5.77, 95% CI 3.38 to 9.84). We graded the certainty of evidence for the two-year outcome also as moderate, again downgrading for imprecision (-1).

Secondary Outcomes:

Loss of fewer than 15 letters of visual acuity

Abb.: Comparison Anti-VEGF treatment versus control, Loss of fewer than 15 letters visual acuity at 1 year








- At two years, the beneficial effect of ranibizumab for this outcome persisted at a similar magnitude when compared with control therapy (three ranibizumab trials). Sixty percent more participants treated with ranibizumab lost fewer than 15 letters of visual

acuity at two-year follow-up as participants in control groups (RR 1.62, 95% CI 1.32 to 1.98), high certainty of evidence

Loss of fewer than 30 letters of visual acuity

Abb.: Comparison Anti-VEGF treatment versus control, Loss of fewer than 30 letters visual acuity at 1 year.

Study or subgroup	Anti-VEGF n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Pegaptanib vs control					
VISION 2004	798/890	231/296		24.17%	1.15[1.08,1.23]
Subtotal (95% CI)	890	296		24.17%	1.15[1.08,1.23]
Total events: 798 (Anti-VEGF), 231 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.22(P<0.0001)					
1.5.2 Ranibizumab vs control					
ANCHOR 2006	279/279	124/143		24.08%	1.15[1.08,1.23]
MARINA 2006	473/478	204/238		26.77%	1.15[1.11,1.22]
Subtotal (95% CI)	757	381		50.85%	1.15[1.11,1.22]
Total events: 752 (Anti-VEGF), 328 (Control)					
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P=1); I ² =0%					
Test for overall effect: Z=6.89(P<0.0001)					

- When comparing ranibizumab groups versus controls, we estimated a 22% benefit of ranibizumab with respect to loss of fewer than 30 letters of visual acuity after two years (RR 1.22, 95% CI 1.15 to 1.29), (high certainty of evidence)

Prevention of blindness in the study eye (visual acuity better than 20/200)

- Treatment with pegaptanib or ranibizumab resulted in fewer blind study eyes at one year follow-up; the summary effect estimate (risk ratio) for visual acuity better than 20/200 was 1.58 (95% CI 1.34 to 1.86) for the two anti-VEGF agents compared with control (high certainty of evidence both at one year and at two years)

Mean change in visual acuity

- Participants treated with pegaptanib were able to read 7 more letters at one-year follow-up (mean difference [MD] 6.7 (95% CI 4.4 to 9.0) and participants treated with ranibizumab were able to read 18 more (MD= 17.8, 95% CI 16.0 to 19.6) compared with participants given control treatment (moderate certainty of evidence, after downgrading for inconsistency).
- participants treated with ranibizumab were able to read 20 more letters (MD 20.1, 95% CI 18.1 to 22.2) at two years compared to control group (high certainty of evidence).

Reduction in size lesion at one year (Mean number of disc areas)

- Pegaptanib treatment resulted in smaller mean lesion size at one-year follow-up compared with sham treatment (MD 0.86 DAs, 95% CI 0.35 to 1.37), (moderate certainty of evidence, after downgrading for imprecision).
- The mean reduction in the size of the lesion was greater by 2.34 disc areas (95% CI 1.88 to 2.81) among participants treated with ranibizumab compared with participants treated with control interventions (ANCHOR and PIER study) after one year. At two years, this effect persisted in ANCHOR (MD 2.44, 95% CI 1.87 to 3.00) but not in PIER (MD 0.59, 95% CI -0.55 to 1.73), (moderate certainty of evidence, after downgrading for inconsistency).

Quality of life outcomes

- At one year, overall vision-related quality of life improved more often among participants in ranibizumab groups than among those in control groups (MD 6.7, 95% CI 3.4 to 10.0). The mean difference was greater in MARINA 2006 (MD 8.2, 95% CI 6.0 to 10.4) than in ANCHOR 2006 (MD 4.8, 95% CI 1.7 to 7.9). This difference between the two

trials may have occurred because participants in the control group in ANCHOR 2006 received an active treatment (verteporfin PDT therapy).

Adverse events

- Ocular inflammation and increased intraocular pressure (IOP) after intravitreal injection were the most frequently reported serious ocular adverse events. Researchers reported endophthalmitis in less than 1% of anti-VEGF-treated participants and in no cases among control groups. The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups; however, the numbers of events and trial participants may have been insufficient to show a meaningful difference between groups (evidence of low to moderate-certainty). Investigators rarely measured and reported data on visual function, quality of life, or economic outcomes.

Fazit der Autorinnen und Autoren

Results of this review show the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; studies show that ranibizumab and bevacizumab improved visual acuity in some eyes that received these agents and were equally effective. Available information on the adverse effects of each medication does not suggest a higher incidence of potentially vision-threatening complications with intravitreal injection of anti-VEGF agents compared with control interventions; however, clinical trial sample sizes were not sufficient to estimate differences in rare safety outcomes. Future Cochrane Reviews should incorporate research evaluating variable dosing regimens of anti-VEGF agents, effects of long-term use, use of combination therapies (e.g. anti-VEGF treatment plus photodynamic therapy), and other methods of delivering these agents.

Kommentare zum Review

- In zwei der drei Studien zu Ranibizumab wurde gegen Scheinmedikation verglichen. Einzig die Anchor-Studie verglich Ranibizumab gegen PDT mit Verteporfin.

3.2 Systematische Reviews

Tricco AC et al., 2021 [5].

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

Siehe auch: Ye L et al., 2020 [7], Matonti F et al., 2022 [2], Wang X et al., 2022 [6]

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:

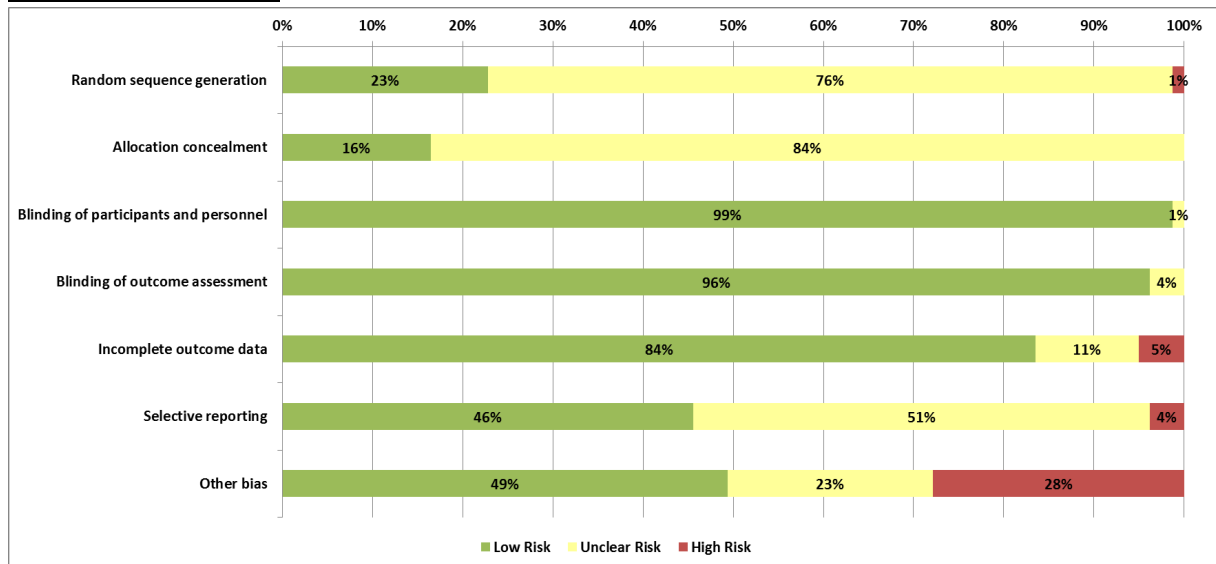
- 92 RCTs plus 8 companion reports
- Most studies conducted in Europe (36%) and North America (32%).

- 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) (0.23–2.558)]
Brolucizumab vs bevacizumab	1.21 [(0.24–6.49) (0.23–2.558)]
Brolucizumab vs ranibizumab	1.19 [(0.25–5.98) (0.24–2.558)]
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

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.

3.3 Leitlinien

National Institute for Health and Care Excellence, 2018 [3].

NICE Guideline NG82

Methods, evidence and recommendations

January 2018

Age-related macular degeneration: diagnosis and management

Leitlinienorganisation/Fragestellung

- 1) What is the effectiveness of different antiangiogenic therapies (including photodynamic therapy) for the treatment of late AMD (wet active)?
- 2) What is the effectiveness of adjunctive therapies for the treatment of late AMD (wet active)?

Methodik

Grundlage der Leitlinie

This guideline covers diagnosing and managing age-related macular degeneration (AMD) in adults. It aims to improve the speed at which people are diagnosed and treated to prevent loss of sight. This guidance replaces NICE technology appraisal guidance on the use of photodynamic therapy for age-related macular degeneration (TA68).

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz dargelegt;
- Formale Konsensusprozesse und 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:

- The search undertaken by the Cochrane group on photodynamic therapy (PDT) for AMD up to 2005. We also conducted an additional update search on PDT. The search undertaken by the Cochrane group on anti-vascular endothelial growth factor (anti-VEGF) treatment for neovascular AMD up to 2015. An update search carried out near the end of guideline development identified 2 further studies including.

LoE/GoR

- The risk of bias of included RCTs was assessed using the **Cochrane risk of bias tool**.
- **GRADE** was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines' (2014). A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken.

Table 2: Rationale for downgrading evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about factors including the design or execution of the study, including concealment of allocation, blinding and loss to follow up. This was based on intervention checklists in the NICE guidelines manual (2012).
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using visual inspection and the statistic, I^2 where; $I^2 < 50\%$ was categorised as no inconsistency, $I^2 \geq 50\%$ was categorised as serious inconsistency, and $I^2 \geq 50\%$ plus obvious additional heterogeneity on visual inspection categorised as very serious inconsistency.
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention, comparator and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	If MIDs (one corresponding to meaningful benefit; one corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one MID, and twice if it crosses both MIDs. If an MID was not defined for the outcomes, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant).

Strength of recommendation

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer...') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Zu Fragestellung 1:

Four studies on photodynamic therapy (PDT) for AMD, one study comparing PDT and anti-vascular endothelial growth factor, twelve studies on bevacizumab and/or ranibizumab and two studies for aflibercept met the study inclusion criteria and were included in the review. The update search identified two further studies: one RCT compared the effectiveness of bevacizumab and ranibizumab treatment and one study compared vision-related function between people who received aflibercept and ranibizumab injection.

Siehe Anhang: Abbildung 1 (Anhang)

Zu Fragestellung 2:

A total of 17 RCTs were included in the review – twelve with ranibizumab as the anti-VEGF used and five with bevacizumab. Fourteen studies compared anti-VEGF monotherapy with anti-VEGF + PDT, two compared anti-VEGF monotherapy with anti-VEGF + steroids and one

compared anti-VEGF + PDT with anti-VEGF + PDT + steroids. An update search carried out near the end of guideline development identified further one study.

Siehe Anhang: Abbildung 2 (Anhang)

Zu Fragestellung 1:

Empfehlungen Antiangiogenic therapies

Empfehlung 21:

Offer intravitreal anti-vascular endothelial growth factor (VEGF) treatment² for late AMD (wet active) for eyes with visual acuity within the range specified in recommendation 26.

Empfehlung 22:

Be aware that no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments³ have been seen in the trials considered by the guideline committee.

Empfehlung 23:

In eyes with visual acuity of 6/96 or worse, consider anti-VEGF treatment for late AMD (wet active) only if a benefit in the person's overall visual function is expected (for example, if the affected eye is the person's better-seeing eye).

Empfehlung 24:

Be aware that anti-VEGF treatment for eyes with late AMD (wet active) and visual acuity better than 6/12 is clinically effective and may be cost effective depending on the regimen used.^{4,5}

Empfehlung 25:

Do not offer photodynamic therapy alone for late AMD (wet active). Recommendations from NICE technology appraisals

Empfehlung 26:

Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:

- all of the following circumstances apply in the eye to be treated:
 - the best-corrected visual acuity is between 6/12 and 6/96

² At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines, and the MHRA's guidance on the supply of unlicensed medicinal products ("specials"), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

³ Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

⁴ At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#), and the MHRA's guidance on the [supply of unlicensed medicinal products \("specials"\)](#), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.

⁵ Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs.

- there is no permanent structural damage to the central fovea
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension
- there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

and

- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). [This recommendation is from Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155).]

Empfehlung 29.:

Aflibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:

- it is used in accordance with the recommendations for ranibizumab NICE technology appraisal guidance 155 (re-issued in May 2012 [see recommendation 26]) and
- the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme. [This recommendation is from Aflibercept solution for injection for treating wet age-related macular degeneration (NICE technology appraisal guidance 294).]

Empfehlung 30:

People currently receiving aflibercept solution for injection whose disease does not meet the criteria in recommendation 29 should be able to continue treatment until they and their clinician consider it appropriate to stop. [This recommendation is from Aflibercept solution for injection for treating wet age-related macular degeneration (NICE technology appraisal guidance 294).]

Hintergrundinfos:

Siehe Anhang: Abbildung 3, Abbildung 4, Abbildung 5, Abbildung 6

Zu Fragestellung 2:

Empfehlungen Adjunctive therapies

Empfehlung 31:

Do not offer photodynamic therapy as an adjunct to anti-VEGF as first-line treatment for late AMD (wet active).

Empfehlung 32:

Only offer photodynamic therapy as an adjunct to anti-VEGF as second-line treatment for late AMD (wet active) in the context of a randomised controlled trial.

Empfehlung 33:

Do not offer intravitreal corticosteroids as an adjunct to anti-VEGF for late AMD (wet active).

Hintergrundinfos:

siehe Anhang: Abbildung 7, Abbildung 8, Abbildung 9

Anmerkung:

There are currently licensed treatments for wet AMD and a treatment (**bevacizumab**) which has been used to treat AMD despite not having a marketing authorisation for such use. It is clear that, without authorisation in the product's SPC, **the use of bevacizumab in AMD is off-label**. NICE has previously performed technology appraisals, which are incorporated in this guideline, on the licensed anti-VEGF agents. These recommend **afibercept and ranibizumab** for late AMD (wet active), and commissioners in England and Wales are bound to fund them as a result. **For this guideline**, the committee has considered the published evidence on clinical effectiveness and cost effectiveness of **all treatments for late AMD (wet active), regardless of license status**.

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 SIGN¹ 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 GRADE² 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 GRADE² 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 **brolocizumab** achieved its primary endpoint of noninferiority of BCVA change compared with aflibercept at week 48. Patients treated with brolocizumab achieved superior reductions in central subfield thickness compared with aflibercept. Fewer patients treated with brolocizumab had sub-retinal fluid, inter-retinal fluid, and sub-RPE fluid. Brolocizumab 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.opht.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.^{182,255} 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.¹⁸² 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 consent should be 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 ¹⁶⁹	Macular CNV	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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)

Ranibizumab intravitreal injection 0.5 mg as recommended in literature ^{17,47,9,18,19,3,18,5,20,7,2,46,249-251}	Macular CNV	<ul style="list-style-type: none"> 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 ^{17,47,9,18,19,3,18,5,20,7,2,46,249-251}	Macular CNV	<ul style="list-style-type: none"> 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.¹⁰⁷ 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 ^{82,252-254*}	<ul style="list-style-type: none"> Macular CNV, new or recurrent, where the classic component is >50% of the lesion and the entire lesion is $\leq 5400 \mu\text{m}$ 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 	<ul style="list-style-type: none"> 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 ^{181,12,47}	<ul style="list-style-type: none"> May be considered for extrafoveal classic CNV, new or recurrent May be considered for juxtapapillary CNV 	<ul style="list-style-type: none"> 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 $\leq 1.0\%$ 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 treatment-related 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 $\leq 1.0\%$ 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 2023)
am 11.05.2023

#	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 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 11.05.2023

verwendete Suchfilter:

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

#	Suchfrage
1	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

#	Suchfrage
	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 11.05.2023

verwendete Suchfilter:

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

#	Suchfrage
1	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 ("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 15.05.2023

- 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

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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

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 2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
... wird angewendet zur Behandlung erwachsener Patienten mit neovaskulärer (feuchter) altersabhängiger Makuladegeneration (AMD).
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? <i>(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)</i>
<p>Die Behandlung der neovaskulären altersabhängigen Makuladegeneration (nAMD) wurde zuletzt in einer ergänzenden Stellungnahme der ophthalmologischen Fachgesellschaften ausführlich dargestellt [1,2].</p> <p>Nach Sicherung der Diagnose hat bisher eine Therapie mit Hemmstoffen des <i>vascular endothelial growth factor</i> (VEGF) zu erfolgen. Ein zugelassener Wirkstoff hemmt zusätzlich den Wachstumsfaktor Angiopoietin 2. Für die intravitreale operative Medikamentenapplikation (IVOM) ist nach der initialen Therapie eine Festlegung der Wiederbehandlungsstrategie 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 mit dem potenziellen irreversiblen Sehverlust. Daher ist der Grundsatz „so viel wie nötig, so wenig wie möglich“ zielführend.</p> <p>In früheren Verfahren der frühen Nutzenbewertung (Aflibercept: A12-19 / BAnz AT 27.06.2013 B3, Brolicizumab: A20-23 / BAnz AT 01.10.2020 B6, Faricimab: A22-110 / BAnz AT 27.04.2023 B3) hatten pharmazeutische Unternehmer keine Studiendaten vorlegen können, in denen die zweckmäßige 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 ausdrücklichen Spielraum [1]. In die Beurteilung, ob eine Wiederbehandlung erfolgen soll, gehen sinnvollerweise viele Parameter wie die Funktion des Partnerauges, der</p>

Allgemeinzustand, Begleiterkrankungen und die Prognose von Sehfunktion und Lebenserwartung ein.

Zu berücksichtigen ist, dass vergleichende Studien bisher zumeist die Frage einer Nicht-Unterlegenheit („non-inferiority“) bewerten sollten. Statistische Signifikanz ist nicht gleichbedeutend mit einem klinisch relevanten Unterschied [3]. Zudem müssen Verzerrungspotential und Sensitivität (Fallzahlplanung, Studiendesign) berücksichtigt werden.

Eine Reduktion notwendiger Wiederbehandlungen um mindestens 20 oder 30% 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, ist damit zu rechnen, dass sich relevante Unterschiede an notwendigen IVOM erst mit zunehmender Behandlungsdauer auswirken.

Unterschiede auf seltene sicherheitsrelevante Ereignisse durch Wirkstoffe oder unterschiedlichen Behandlungshäufigkeiten sind nur mit sehr großen Fallzahlen zu belegen. Für die wirtschaftlichen Auswirkungen müssen neben der Prozedur und dem Medikament auch die Kosten der Kontrolluntersuchungen sowie z.B. Fahrtkosten zu den wohnortnahen Kontrollen (führten alle Augenärzte durch) und den teilweise weiter entfernten IVOM (bietet nur ein Teil der Augenärzte an) 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 Krankenversicherung statt. Es gibt zudem Selektivverträge, die von Maßnahmen der Qualitätskontrolle und Anreizen zu einem wirtschaftlichen Medikamenteneinsatz getragen werden [5,6]. In Deutschland wird mit einem wesentlichen Anteil auch der nicht zugelassene Wirkstoff Bevacizumab eingesetzt [7,8], für den eine vergleichbare Wirksamkeit und Sicherheit in randomisierten kontrollierten Studien nachgewiesen wurde [9,10]. Seit 2023 werden zudem die ersten Biosimilar von Ranibizumab eingesetzt [1].

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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