Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2023-B-107 Faricimab

Stand: Juni 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Faricimab **[Makulaödem infolge eines retinalen Venenverschlusses (RVV) (Venenastverschluss [VAV] oder Zentralvenenverschluss [ZVV])]** **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.	zentrale Laserkoagulation (fokaler oder GRID-Laser): nur beim VAV periphere Laserkoagulation (sektorförmige oder panretinale Lasertherapie): alle Verschlusstypen
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse zur frühen Nutzenbewertung nach § 35a SGB V: • Aflibercept: Beschluss vom 20. März 2014 (Makulaödem infolge eines retinalen Zentralvenenverschlusses) • Aflibercept: Beschluss vom 03. September 2015 (Makulaödem infolge eines retinalen Venenastverschlusses)
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:	
Faricimab S01LA09 Vabysmo®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Vabysmo wird angewendet zur Behandlung von erwachsenen Patienten mit: Einer Visusbeeinträchtigung aufgrund eines Makulaödems infolge eines retinalen Venenverschlusses (RVV) (Venenastverschluss [VAV] oder Zentralvenenverschluss [ZVV]).
VEGF-Inhibitoren	
Aflibercept S01LA05 Eylea®	Eylea wird angewendet bei Erwachsenen zur Behandlung: • einer Visusbeeinträchtigung aufgrund eines Makulaödems infolge eines retinalen Venenverschlusses (RVV) (Venenastverschluss [VAV] oder Zentralvenenverschluss [ZVV]) (siehe Abschnitt 5.1), • […]
Ranibizumab S01LA04 Lucentis®	Lucentis wird angewendet bei Erwachsenen zur: • Behandlung einer Visusbeeinträchtigung infolge eines Makulaödems aufgrund eines retinalen Venenverschlusses (RVV) (Venenastverschluss oder Zentralvenenverschluss) • […]
Glucocorticoide	
Dexamethason S01BA01 Ozurdex®	OZURDEX wird angewendet zur Behandlung von Erwachsenen mit: • Makulaödem als Folge eines retinalen Venenastverschlusses (VAV) oder retinalen Zentralvenenverschlusses (ZVV) (siehe Abschnitt 5.1)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-107 (Faricimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	23. Mai 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
CMT	Central macular thickness
CRVO	Central retinal vein occlusion
DME	Diabetic macular edema
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IVI	Intravitreal injections
KI	Konfidenzintervall
LoE	Level of Evidence
LPC	Laser photocoagulation
ME	Macular edema
MO	Macular oedema
NICE	National Institute for Health and Care Excellence
OCT	Optical coherence tomography
OR	Odds Ratio
RR	Relatives Risiko
RVO	Retinal vein occlusion
RVV	Retinaler Venenverschluss
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
VAV	Venenastverschluss
WHO	World Health Organization
ZVV	Zentralvenenverschluss

1 Indikation

Zur Behandlung von erwachsenen Patientinnen und Patienten mit einer Visusbeeinträchtigung aufgrund eines Makulaödems infolge eines retinalen Venenverschlusses (RVV) (Venenastverschluss [VAV] oder Zentralvenenverschluss [ZVV]).

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 Makulaödem 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 27.04.2023 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 357 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 13 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Rittiphairoj T et al., 2020 [9].

Intravitreal steroids for macular edema in diabetes

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Gao L et al., 2021 [3].

Fragestellung

To assess the effectiveness and safety of intravitreal steroid therapy compared with other treatments for DME.

Methodik

Population:

- participants with any type of DME (focal, diffuse, CME)

Intervention:

- intravitreal steroid therapy (intravitreal injection or surgical implantation) of any dosage and duration with other treatments for DME (e.g. observation, laser photocoagulation, anti VEGF agents).

Komparator:

- sham

Endpunkte:

- The primary outcome was visual acuity (VA), assessed as: (1) the change from baseline of best-corrected visual acuity (BCVA) as continuous data (converted into logMAR); and (2) three or more lines improvement from baseline (ETDRS, Snellen, or logMAR equivalent; one line improvement analyzed if three lines not available)
- The secondary outcome was mean change in retinal thickness from baseline as measured by optical coherence tomography (OCT).
- Adverse effects: Ocular adverse effects of interest were those related to steroids use (EURETINA 2017), at the longest available follow-up:
  1. cataract formation or progression (as defined by the trialists) or cataract surgery;
  2. ocular hypertension, as defined by the trialists;
  3. use of IOP-lowering medications;
  4. glaucoma surgery

Recherche/Suchzeitraum:

- search on 21 October, 2020.

Qualitätsbewertung der Studien:

- risk of bias of the included trials according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019b).

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 studies on 4348 people with diabetic macular edema 10 trials (4505 eyes).

Charakteristika der Population/Studien:

- participants of any age and sex with any type of DME (focal, diffuse, CME) as diagnosed in the trial.
- Trials in which participants were non-responsive to previous therapy (i.e. laser photocoagulation) or had no prior treatment were eligible for inclusion.

Qualität der Studien:

- Most trials had an overall unclear or high risk of bias.

Studienergebnisse:

- Visual acuity
  - Time frame was at 12 months, when intravitreal dexamethasone led to a better improvement of VA than sham (mean difference (MD) −0.08 logMAR, 95% confidence interval (CI) −0.12 to −0.05 logMAR; trials = 1; participants = 701; moderatecertainty evidence, downgraded for risk of bias).
  - No evidence of a difference at 24 months (MD 0.00 logMAR, 95% CI −0.04 to 0.05 logMAR; trial = 1; participants = 701; moderatecertainty evidence, downgraded for risk of bias), and evidence of a small difference at 36 months (MD −0.05, 95% CI −0.09 to 0.00; trials = 1; participants = 701; low-certainty evidence, downgraded for risk of bias and imprecision).
- Central retinal thickness
  - No data were available at 12 and 24 months.
  - There was a greater and clinically important reduction of retinal thickness with intravitreal dexamethasone at 36 months compared to sham 20 1 1.5 2 Favors dexamethasone (−81.00 µm, 95% CI −98.64 to −63.36 µm; moderate-certainty evidence, downgraded for risk of bias).
- Adverse events
  - Compared to sham, at 36 months intravitreal dexamethasone increased the risk of cataract progression by about 4 times (RR 3.89, 95% CI 2.75 to 5.50; moderate-certainty evidence, downgraded for risk of bias).
  - Dexamethasone also increased all IOPrelated events: IOP increase (RR 8.99, 95% CI 5.05 to 16.03) and use of IOP-lowering medications (RR 4.54, 95% CI 3.19 to 6.46; moderate-certainty evidence for both outcomes, downgraded for risk of bias; Analysis 1.5); about 4 in 10 participants treated with dexamethasone needed IOP-lowering medications.
  - The need for glaucoma surgery was increased but imprecisely estimated since only 1 to 2 out of 100 participants needed surgery for glaucoma (RR 5.04, 95% CI 0.59 to 42.95; low-certainty evidence, downgraded for risk of bias and imprecision.

SUMMARY OF FINDINGS

Summary of findings 1. Intravitreal dexamethasone implant 0.7 mg compared to sham for macular edema in diabetes

Intravitreal dexamethasone implant 0.7 mg compared to sham for macular edema in diabetes

Patient or population: macular edema in diabetes
Setting: retina clinics
Intervention: intravitreal dexamethasone implant 0.7 mg
Comparison: sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)
	Risk with sham	Risk with intravitreal dexamethasone			
Change in visual acuity (logMAR) - 12 months (negative is better)	The mean change in visual acuity - 12 months was 0.	MD −0.08 better (−0.12 better to −0.05 better)	-	701 (1 RCT)	⊕⊕⊕⊖ MODERATE 1
Gain of three or more lines visual acuity - 12 months	94 per 1000	131 per 1000 (86 to 200)	RR 1.39 (0.91 to 2.12)	701 (1 RCT)	⊕⊕⊕⊖ MODERATE 1
Change of retinal thickness - 36 months (negative is better)	The mean change in retinal thickness (micron) - 36 months was −51.	MD −81 micron (−100 to −63 micron)	-	701 (1 RCT)	⊕⊕⊕⊕ MODERATE 2
Cataract progression - 36 months	97 per 1000	378 per 1000 (267 to 534)	RR 3.89 (2.75 to 5.50)	697 (1 RCT)	⊕⊕⊕⊖ MODERATE2
Use of IOP-lowering medications - 36 months	91 per 1000	415 per 1000 (292 to 591)	RR 4.54 (3.19 to 6.46)	697 (1 RCT)	⊕⊕⊕⊖ MODERATE2
Surgery for glaucoma - 36 months	3 per 1000	14 per 1000 (1 to 43)	RR 5.04 (0.59 to 42.95)	697 (1 RCT)	⊕⊕⊖⊖ LOW 1 2

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

CI: confidence interval; **IOP:** intraocular pressure; **MD**: mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded −1 for imprecision: wide confidence intervals.
[2]Downgraded −1 for risk of bias: large loss to follow-up.

Summary of findings 2. Intravitreal dexamethasone implant 0.7 mg compared to intravitreal antiVEGF for macular edema in diabetes

Intravitreal dexamethasone implant 0.7 mg compared to intravitreal antiVEGF for macular edema in diabetes

Patient or population: macular edema in diabetes
Setting: retina clinics
Intervention: intravitreal dexamethasone implant 0.7 mg
Comparison: intravitreal antiVEGF

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of eyes (trials)	Certainty of the evidence (GRADE)
	Risk with intravitreal antiVEGF	Risk with intravitreal dexamethasone			
Change in visual acuity (logMAR) - 12 months (negative is better)	The mean change in visual acuity - 12 months was −0.16.	MD 0.07 worse (0.04 worse to 0.09 worse)	-	451 (2 RCTs)	⊕⊕⊕⊖ MODERATE 1
Gain of three or more lines visual acuity - 12 months	Inconsistent findings: one trial finding no evidence of a difference between dexamethasone and bevacizumab at 12 months (RR 0.99, 95% CI 0.70 to 1.40; 1 trial; 88 eyes), and the other found the chances of vision gain were half with dexamethasone compared with ranibizumab (RR 0.50, 95% CI 0.32 to 0.79; 1 trial; 432 eyes).			451 (2 RCTs)	⊕⊕⊖⊖ LOW 1 3
Change in retinal thickness (micron) - 12 months (negative is better)	The mean change in retinal thickness - 12 months was −140.	MD −21.09 thinner (−41.9 thinner to −0.28 thinner)	-	451 (2 RCTs)	⊕⊕⊖⊖ LOW 1 2
Cataract progression - 12 to 24 months	45 per 1000	129 per 1000 (68 to 246)	RR 4.23 (2.36 to 7.59)	335 (2 RCTs)	⊕⊕⊕⊖ MODERATE 1

Use of IOP-lowering medications - 24 months	82 per 1000	392 per 1000 (234 to 659)	RR 4.76 (2.84 to 7.99)	363 (1 RCT)	⊕⊕⊕⊖ MODERATE[1]
Surgery for glaucoma - 24 months	5 per 1000	16 per 1000 (26 to 44)	RR 3.02 (0.12 to 73.56)	363 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 4]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

antiVEGF: anti-vascular endothelial growth factor agent; **CI:** confidence interval; **IOP:** intraocular pressure; **MD**: mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded −1 for risk of bias: high or unclear risk of bias for at least one domain.
[2]Downgraded −1 for imprecision: wide confidence intervals.
[3]Downgraded −1 for inconsistency: heterogeneous results of two trials.
[4]Downgraded −2 for imprecision: very wide confidence intervals.

Summary of findings 3. Intravitreal fluocinolone acetonide implant 0.19 mg compared to sham for macular edema in diabetes

Intravitreal fluocinolone implant 0.19 mg compared to sham for macular edema in diabetes

Patient or population: macular edema in diabetes
Setting: retina clinics
Intervention: intravitreal fluocinolone acetonide implant 0.19 mg
Comparison: sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)
	Risk with sham	Risk with intravitreal fluocinolone implant			
Change in visual acuity (logMAR) - 12 months (negative is better)	The mean change in visual acuity was −0.04.	MD −0.04 better (−0.06 better to −0.01 better)	-	560 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]
Gain of three or more lines visual acuity - 12 months	119 per 1000	213 per 1000 (138 to 331)	RR 1.79 (1.16 to 2.78)	560 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]
Change in retinal thickness (micron) - 12 months (negative is better)	The mean change in retinal thickness was −67.	MD −76.00 thinner (−94.31 thinner to −57.69 thinner)	-	560 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]
Cataract progression - 24 months	500 per 1000	815 per 1000 (675 to 985)	RR 1.63 (1.35 to 1.97)	355 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]
Use of IOP-lowering medications - 24 months	141 per 1000	264 per 1000 (384 to 562)	RR 2.72 (1.87 to 3.98)	558 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]
Surgery for glaucoma - 24 months	5 per 1000	52 per 1000 (7 to 385)	RR 9.54 (1.28 to 70.93)	558 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **IOP:** intraocular pressure; **MD**: mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded −1 for risk of bias: unclear risk of bias for most domains.
[2]Downgraded −1 for imprecision: wide confidence intervals.

Summary of findings 4. Intravitreal triamcinolone acetonide injection 4 mg compared to sham for macular edema in diabetes

Intravitreal triamcinolone acetonide injection 4 mg compared to sham for macular edema in diabetes

Patient or population: macular edema in diabetes
Setting: retina clinics
Intervention: intravitreal triamcinolone acetonide injection 4 mg

Comparison: sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of eyes (trials)	Certainty of the evidence (GRADE)
	Risk with sham	Risk with intravitreal triamcinolone injection			
Change in visual acuity (logMAR) - 24 months** (negative is better)	The mean change in visual acuity was −0.02.	MD −0.11 better (−0.20 better to −0.03 better)	-	69 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Gain of three or more lines visual acuity - 24 months**	29 per 1000	118 per 1000 (14 to 1000)	RR 4.12 (0.48 to 34.99)	69 (1 RCT)	⊕◯◯◯ VERY LOW [1,3]
Change in retinal thickness (micron) - 24 months** (negative is better)	The mean change in retinal thickness was −71.	MD −59 thinner (−103.5 thinner to −14.5 thinner)	-	69 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Cataract progression - 24 months	143 per 1000	429 per 1000 (139 to 1000)	RR 3.00 (0.97 to 9.30)	49 (1 RCT)	⊕⊕◯◯ LOW [1,2]
Use of IOP-lowering medications - 24 months	14 per 1000	309 per 1000 (384 to 562)	RR 21.60 (1.32 to 354.7)	69 (1 RCT)	⊕◯◯◯ VERY LOW [1,3]
Surgery for glaucoma - 24 months	No surgeries were recorded in the study.				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**No data available at 12 months.

CI: confidence interval; **IOP:** intraocular pressure; **MD**: mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded −1 for risk of bias: high risk of bias for at least one domain.
[2]Downgraded −1 for imprecision: wide confidence intervals.
[3]Downgraded −2 for imprecision: very wide confidence intervals.

Summary of findings 5. Intravitreal triamcinolone acetonide injection 4 mg compared to macular laser for macular edema in diabetes

Intravitreal triamcinolone acetonide injection 4 mg compared to macular laser for macular edema in diabetes

Patient or population: macular edema in diabetes
Setting: retina clinics
Intervention: intravitreal triamcinolone acetonide injection 4 mg
Comparison: macular laser

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of eyes (trials)	Certainty of the evidence (GRADE)
	Risk with macular laser	Risk with intravitreal triamcinolone			
Change in visual acuity (logMAR) - 12 months (negative is better)	1 small study (31 participants) reported data favoring triamcinolone at 9 months (MD −0.18, 95% CI −0.29 to −0.07), and data from a large, multicenter study (584 eyes) favored macular laser at 12 months (MD 0.02, 95% CI −0.03 to 0.07).				⊕◯◯◯ VERY LOW [1,2]
Gain of three or more lines visual acuity - 12 months	140 per 1000	119 per 1000 (77 to 182)	RR 0.85 (0.55 to 1.30)	584 (1 RCT)	⊕⊕◯◯ LOW [1,3]
Change in retinal thickness (micron) (negative is better)	1 small study (31 participants) reported data favoring triamcinolone at 9 months (MD −83.00, 95% CI −171.60 to −5.60), and data from a large, multicenter study (454 participants) found no difference between groups at 12 months (MD 5.00, 95% CI −18.76 to 28.76).				⊕◯◯◯ VERY LOW [1,2]
Cataract progression - 9 to 24 months	286 per 1000	767 per 1000 (633 to 927)	RR 2.68 (2.21 to 3.24)	502 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]
Use of IOP-lowering medications - 9 to 24 months	71 per 1000	279 per 1000 (184 to 425)	RR 3.92 (2.59 to 5.96)	627 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]
Surgery for glaucoma - 9 to 24 months	1 per 1000	12 per 1000 (1 to 216)	RR 11.68 (0.63 to 216)	627 (2 RCTs)	⊕⊕◯◯ LOW [1,3]

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

CI: confidence interval; **IOP:** intraocular pressure; **MD**: mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded −1 for risk of bias: high risk of bias for at least one domain.
[2]Downgraded −2 for inconsistency: significant heterogeneity between studies.
[3]Downgraded −1 for imprecision: large confidence intervals.

Summary of findings 6. Intravitreal triamcinolone acetonide injection 4 mg compared to antiVEGF for macular edema in diabetes

Intravitreal triamcinolone acetonide injection 4 mg compared to antiVEGF for macular edema in diabetes

Patient or population: macular edema in diabetes
Setting: retina clinics
Intervention: intravitreal triamcinolone acetonide injection 4 mg
Comparison: antiVEGF

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)
	Risk with antiVEGF	Risk with intravitreal triamcinolone			
Change in visual acuity (logMAR) - 12 months (negative is better)	The mean change in visual acuity - 12 months was −0.12 logMAR.	MD 0.18 worse (0.10 worse to 0.26 worse)	-	30 (1 RCT)	⊕⊖⊖⊖ LOW [1,2]
Gain of three or more lines visual acuity	No data reported.				
Change in central retinal thickness (micron) - 12 months (negative is better)	Inconsistent, non-significant effects were found for triamcinolone versus bevacizumab or ranibizumab.			30 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1,3]
Cataract progression	No data reported.				
Use of IOP-lowering medications	No data reported on IOP-lowering medications, but the authors state that there was no difference in IOP change in the triamcinolone and bevacizumab groups.				
Surgery for glaucoma	No surgery for glaucoma reported.				

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

antiVEGF: anti-vascular endothelial growth factor agent; **CI:** confidence interval; **IOP:** intraocular pressure; **MD**: mean difference; **RCT:** randomized controlled trial

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

[1]Downgraded −1 for risk of bias: high risk of bias for at least one domain.
[2]Downgraded −1 for imprecision: wide confidence intervals.
[3]Downgraded −2 for inconsistency: heterogeneous results of two antiVEGF study arms.

Anmerkung/Fazit der Autoren

Intravitreal steroids may improve vision in people with DME compared to sham or control. Effects were small, about one line of vision or less in most comparisons. More evidence is available for dexamethasone or fluocinolone implants when compared to sham, and the evidence is limited and inconsistent for the comparison of dexamethasone with antiVEGF treatment. Any benefits should be weighed against IOP elevation, the use of IOP-lowering medication and, in phakic patients, the progression of cataract. The need for glaucoma surgery is also increased, but remains rare.

Shalchi Z et al., 2020 [11].

Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion

Es liegen weitere SRs mit derselben Schlussfolgerung zu dieser Fragestellung vor:

- Gao S et al., 2021 [4].
- Pranata R et al., 2021 [7].
- Veritti D et al., 2021 [12].
- Qiu XY et al., 2022 [8].

Fragestellung

To investigate the efficacy and gather evidence from randomised controlled trials (RCTs) on the potential harms of anti-vascular endothelial growth factor (VEGF) agents for the treatment of macular oedema (MO) secondary to branch retinal vein occlusion (BRVO).

Methodik

Population:

- participants with a diagnosis of unilateral or bilateral macular oedema

Intervention:

- anti-VEGF treatment

Komparator:

- another treatment (laser or steroid injection), no treatment, or placebo

Endpunkte:

- The primary outcome for this review was the proportion of participants with an improvement from baseline in best-corrected visual acuity (BCVA) of greater than or equal to 15 letters (three lines) on the Early Treatment in Diabetic Retinopathy Study (ETDRS) chart at six months and at 12 months of follow-up.
- Secondary outcomes:

  1. Mean visual acuity (VA) change at six and 12 months.

  2. The proportion of participants with a loss of 15 or more letters (ETDRS) compared with baseline at six and 12 months.

  3. Change in central retinal thickness (CRT) on optical coherence tomography (OCT) from baseline at 12 months.
- Quality of life
- Adverse outcomes We sought to report any ocular or systemic adverse outcomes reported in the trials.

Recherche/Suchzeitraum:

- The date of the last search was 12 June 2019.

Qualitätsbewertung der Studien:

- the methodological quality of the selected trials according to Chapter 8 of the Cochrane handbook for Systematic Reviews of Interventions (Higgins 2019)

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs of 1631 participants

Charakteristika der Population/Studien:

- participants of all ages and both genders who have had a diagnosis of unilateral or bilateral macular oedema secondary to branch retinal vein occlusion or hemi-retinal vein occlusion. All countries and ethnic groups were eligible for inclusion. We included treatment-naive and previously-treated eyes.

Qualität der Studien:

- Overall, we judged the studies to be at moderate or unclear risk of bias.
- Four of the eight studies did not mask participants or outcome assessors, or both.

Studienergebnisse:

Anti-VEGF treatment versus sham

- Improvement of 15 or more letters (primary outcome)
  - People receiving anti-VEGF showed better outcome than those treated with sham injections at six months (RR 1.72, 95% CI 1.19 to 2.49; 1 study, 283 participants; moderate-certainty evidence).
  - Unfortunately, this outcome was limited to only one trial and for only six months, as rescue treatment was available after this time (BLOSSOM)
- Mean change in best-corrected visual acuity (BCVA)
  - People receiving anti-VEGF showed better improvement in mean visual acuity than those receiving sham at six months (MD 7.50 letters, 95% CI 5.29 to 9.71; 1 study, 282 participants; moderate-certainty evidence)
- Loss of 15 or more letters
  - People receiving anti-VEGF showed better outcome than those treated with sham injections at six months (RR 0.24). However, the 95% CI (0.05 to 1.31) included 1.00
- Central retinal thickness (CRT)
  - No data was available for 12 months but results at six months showed participants receiving anti-VEGF had a greater reduction in central retinal thickness than those receiving sham (MD −57.50 microns, 95% CI −108.63 to −6.37; 1 study, 281 participants; moderate-certainty evidence
- Adverse events (AEs)
  - The anti-VEGF and sham cohorts reported similar levels of ocular and systemic adverse events. Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events were equally common in both groups. Endophthalmitis was rare.
- Quality of life
  - The mean improvement in quality of life (QoL) at 12 months on the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) (scored 0 to 100; higher score is better quality of life) was 7.60 higher (4.30 to 10.90) (1 study, 281 participants; moderatecertainty evidence

Anti-VEGF treatment versus laser photocoagulation

- Improvement of 15 or more letters (primary outcome)

  - Eyes receiving anti-VEGF showed better outcome than the laser arm at six months (RR 2.09, 95% CI 1.44 to 3.05; 2 studies, 201 participants; I2 = 0%; moderate-certainty evidence; Analysis 2.1). There were no results available for 12 months.
- Mean change in best-corrected visual acuity (BCVA)
  - People receiving anti-VEGF showed greater gains than those receiving laser at six months (MD 9.63 letters, 95% CI 7.23 to 12.03; 3 studies, 473 participants; I2 = 0%; moderate-certainty evidence; Analysis 2.2).
  - There were no results available for 12 months
- Central retinal thickness (CRT)
  - Mean change in CRT was greater in the anti-VEGF than the laser group at six months (MD −147.47 microns, 95% CI −200.19 to −94.75; 2 studies, 201 participants; I2 = 0%; moderate-certainty evidence) although no data was available for 12 months of treatment.
- Adverse events
  - Systemic adverse events were well-matched between the antiVEGF and laser cohorts. There was no sign that thromboembolic events were more common in either group (Figure 4). There were no episodes of endophthalmitis after any intravitreal anti-VEGF injection.
  - Central retinal thickness (CRT) Mean change in CRT was greater in the anti-VEGF than the laser
  - group at six months (MD −147.47 microns, 95% CI −200.19 to −94.75; 2 studies, 201 participants; I2 = 0%; moderate-certainty evidence; Analysis 2.3) although no data was available for 12 months of treatment.
- Quality of life
  - This data was not reported.

Anti-VEGF treatment versus steroid

- Improvement of 15 or more letters (primary outcome)
  - Participants receiving anti-VEGF showed better outcomes than steroid at six months (RR 1.67, 95% CI 1.33 to 2.10; 2 studies, 330 participants; I2 = 0%; high-certainty evidence; Analysis 3.1; Figure 5); and 12 months (RR 1.76, 95% CI 1.36 to 2.28; 1 study, 307 participants; high-certainty evidence)
- Mean change in best-corrected visual acuity (BCVA)
  - Eyes receiving anti-VEGF showed a great improvement in visual acuity than those in the steroid arm both at six months (MD 8.22 letters, 95% CI 5.69 to 10.76; 2 studies, 330 participants; I2 = 0%; high-certainty evidence; Analysis 3.3); and 12 months (MD 9.15 letters, 95% CI 6.32 to 11.97; 2 studies, 343 participants; I2 = 0%; high-certainty evidence).
- Central retinal thickness (CRT)
  - Central macular thickness showed a greater reduction at 12 months in eyes receiving anti-VEGF than those receiving steroid (MD −26.92 microns, 95% CI −65.88 to 12.04; 3 studies, 343 participants; I2 = 0%; moderate-certainty grade).
- Adverse events
  - Systemic adverse events were similar in the anti-VEGF and steroid cohorts. However, ocular adverse events were more common in the steroid cohort, who had greater rates of cataract formation (moderate-certainty evidence) and raised intraocular pressure (moderate-certainty evidence)

- Quality of life
  - Participants receiving anti-VEGF showed a greater improvement in quality of life at 12 months compared to those receiving steroid (MD 3.10, 95% CI 0.22 to 5.98; 1 study, 307 participants; moderatecertainty evidence)

Summary of findings 1. Anti-VEGF compared to sham for macular oedema secondary to branch retinal vein occlusion

Anti-VEGF v sham for macular oedema secondary to branch retinal vein occlusion

Patient or population: macular oedema secondary to branch retinal vein occlusion
Setting: eye hospital
Intervention: anti-VEGF
Comparison: sham injection

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with sham	Risk with anti-VEGF				
Gain of 15 letters or more of visual acuity at 6 months	6 months	269 per 1000	462 per 1000 (320 to 669)	RR 1.72 (1.19 to 2.49)	283 (1 RCT)	⊕⊕⊖ MODERATE[1]	
	12 months	Data not available because participants in sham group received anti-VEGF after 6 months					
Mean change in visual acuity letters at 6 months measured with a logMAR chart (higher letter score is better visual acuity)	6 months	The mean VA change with sham was 5 letters	The mean number of letters read with anti-VEGF was 7.50 letters more (5.29 more to 9.71 more)	-	282 (1 RCT)	⊕⊕⊖ MODERATE[1]	
	12 months	Data not available because participants in sham group received anti-VEGF after 6 months					
Mean central retinal thickness (CRT) change at 6 months in microns (lower value is better)		The mean CRT change with sham was −207 microns	The mean CRT with anti-VEGF was 57.5 microns less (108.63 less to 6.37 less)	-	281 (1 RCT)	⊕⊕⊖ MODERATE[1]	
Adverse outcomes at any time point	Cataract	11 per 1000	11 per 1000 (1 to 106)	RR 0.98 (0.09 to 10.66)	283 (1 RCT)	⊕ VERY LOW[2]	12 month results. Patients in the sham arm were able to receive rescue anti-VEGF after 6 months.
	Raised IOP*	1 per 1000	6 per 1000 (0 to 101)	RR 5.41 (0.30 to 96.88)	283 (1 RCT)	⊕ VERY LOW[2]	
	APTC events	22 per 1000	32 per 1000 (6 to 142)	RR 1.47 (0.30 to 7.14)	283 (1 RCT)	⊕ VERY LOW[2]	

	Endophthalmitis	No endophthalmitis was reported in either anti-VEGF (n = 190) or sham (n = 91) arms				
Mean change in quality of life (QoL) at 12 months on the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) (scored 0 to 100) (higher score is better quality of life)	The mean QoL change with sham was 0	The mean QoL score with anti-VEGF was 7.60 higher (4.30 to 10.90)	-	281 (1 RCT)	⊕⊕⊕ MODERATE[1]	Data collected at 6 months because participants in sham group received anti-VEGF after 6 months

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). Where no events observed in control group, we have used an estimate of 1 per 1000 for illustrative purposes.

ATPC: Antiplatelet Trialists' Collaboration; **CI:** Confidence interval; **RR:** Risk ratio

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

[1]Downgraded 1 level for risk of bias
[2]Downgraded 2 levels for imprecision and 1 level for risk of bias

Summary of findings 2. Anti-VEGF compared to laser for branch retinal vein occlusion (BRVO)

Anti-VEGF compared to laser for branch retinal vein occlusion (BRVO)

Patient or population: people with BRVO
Setting: eye hospital
Intervention: anti-VEGF
Comparison: laser

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with laser	Risk with anti-VEGF				
Gain of 15 letters or more of visual acuity	6 months	260 per 1000	543 per 1000 (374 to 793)	RR 2.09 (1.44 to 3.05)	201 (2 RCTs)	⊕⊕⊕ MODERATE[1]	

	12 months	Data not available because participants in sham group received anti-VEGF after 6 months				
Mean change in visual acuity letters measured with a logMAR chart (higher letter score is better visual acuity)	6 months	The mean visual acuity change with laser ranged from 2 to 7 letters	The mean number of letters read with anti-VEGF was 9.63 letters more (7.23 more to 12.03 more)	-	473 (3 RCTs)	⊕⊕⊕ MODERATE[1]
	12 months	Data not available because participants in sham group received anti-VEGF after 6 months				
Mean central retinal thickness (CRT) change at 6 months in microns (lower value is better)		The mean CRT change with laser was −128 microns	The mean CRT change with anti-VEGF was 147.47 microns less (200.19 less to 94.75 less)	-	201 (2 RCTs)	⊕⊕⊕ MODERATE[1]
Adverse outcomes at any time point	Cataract*	1 per 1000	3 per 1000 (0 to 75)	RR 2.97 (0.12 to 71.89)	456 (2 RCTs)	⊕ VERY LOW[2]
	Raised IOP*	No raised IOP was reported in either anti-VEGF (n = 182) or laser (n = 93) groups				⊕ VERY LOW[2]
	APTC events	5 per 1000	4 per 1000 (1 to 37)	RR 0.99 (0.15 to 6.78)	476 (3 RCTs)	⊕ VERY LOW[2]
	Endophthalmitis	No endophthalmitis was reported in either anti-VEGF (n = 284) or laser (n = 192) arms				⊕ VERY LOW[2]
Mean change in quality of life at 12 months on the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) (scored 0 to 100) (higher score is better quality of life)		Not reported				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). Where no events observed in control group, we have used an estimate of 1 per 1000 for illustrative purposes.

ATPC: Antiplatelet Trialists' Collaboration; **CI:** Confidence interval; **RR:** Risk ratio

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

[2]Downgraded 1 level for risk of bias and 2 levels for imprecision

Summary of findings 3. Anti-VEGF compared to steroid for branch retinal vein occlusion (BRVO)

Anti-VEGF compared to steroid for BRVO

Patient or population: people with BRVO
Setting: eye hospital
Intervention: anti-VEGF
Comparison: steroid

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with steroid	Risk with anti-VEGF				
Gain of 15 letters or more of visual acuity	6 months	379 per 1000	633 per 1000 (466 to 802)	RR 1.67 (1.33 to 2.10)	330 (2 RCTs)	⊕⊕⊕⊕ HIGH[1]	
	12 months	338 per 1000	595 per 1000 (460 to 771)	RR 1.76 (1.36 to 2.28)	307 (1 RCT)	⊕⊕⊕⊕ HIGH[1]	
Mean change in visual acuity letters measured with a logMAR chart (higher letter score is better visual acuity)	6 months	The mean visual acuity change with steroid ranged from 9 to 11 letters	The mean number of letters read with anti-VEGF was 8.22 more (5.69 more to 10.76 more)	-	330 (2 RCTs)	⊕⊕⊕⊕ HIGH[1]	
	12 months	The mean visual acuity change with steroid ranged from 6 to 8 letters	The mean number of letters read with anti-VEGF was on average 9.15 letters more (6.32 more to 11.97 more)	-	343 (2 RCTs)	⊕⊕⊕⊕ HIGH[1]	
Mean central retinal thickness (CRT) change at 12 months in microns (lower value is better)		The mean CRT change with steroid ranged from −249 to −306 microns	The mean CRT change with anti-VEGF was 26.92 microns less (65.88 less to 12.04 less)	-	343 (2 RCTs)	⊕⊕⊕ MODERATE[2]	
Adverse outcomes at any time point	Cataract	125 per 1000	22 per 1000 (7 to 75)	RR 0.12 (0.04 to 0.32)	551 (3 RCTs)	⊕⊕⊕ MODERATE[2]	
	Raised IOP	240 per 1000	57 per 1000 (34 to 94)	RR 0.25 (0.16 to 0.40)	673 (4 RCTs)	⊕⊕⊕ MODERATE[2]	

	APTC events	1 per 1000	3 per 1000 (0 to 74)	RR 3.02 (0.12 to 73.55)	587 (3 RCTs)	⊕ VERY LOW[3]
	Endoph-thalmitis	No endophthalmitis was reported in either anti-VEGF (n = 187) or steroid (n = 179) arms.				
Mean change in quality of life at 12 months on the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) (scored 0 to 100) (higher score is better quality of life)		The mean change in quality of life score with steroid was 3.5	The mean change in quality of life score with anti-VEGF was 3.10 high-er (0.22 higher to 5.98 higher)	-	307 (1 RCT)	⊕⊕⊕ MODERATE[2]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__ATPC:__ Antiplatelet Trialists' Collaboration; __CI:__ Confidence interval; __RR:__ Risk ratio

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

[1] One study was judged to be at high risk of attrition bias because participants in the steroid group dropped out of the study due to adverse effects and poor response. We did not downgrade for risk of bias as the direction of the risk of bias is likely to be favouring the steroid group and so the estimate of effect reported here may well be an under-estimate.
[2]Downgraded 1 level for risk of bias (studies were at high risk of attrition bias)
[3]Downgraded 2 levels for imprecision and 1 level for risk of bias

Anmerkung/Fazit der Autoren

The available RCT evidence suggests that treatment of MO secondary to BRVO with anti-VEGF improves visual and anatomical outcomes at six and 12 months.

Key messages The review shows that people with MO due to BRVO benefit from treatment with anti-VEGF with an increased chance of improved vision at six and 12 months when compared with no treatment, laser or steroid injection.

3.2 Systematische Reviews

Santhakumaran S et al., 2022 [10].

Efficacy and Safety of Aflibercept Therapy for Diabetic Macular Edema: A Systematic Review and Meta-Analysis

Fragestellung

To assess the real-world efficacy and safety of aflibercept for the treatment of diabetic macular edema (DME).

Methodik

Population:

Patients with macular edema

Intervention:

- Aflibercept

Komparator:

- Another treatment (laser photocoagulation, bevacizumab, ranibizumab)

Endpunkte:

- Primary outcomes included changes in BCVA and CMT.
- Secondary outcomes consisted of safety, particularly ocular adverse events, Antiplatelet Trialists' Collaboration (APTC)-defined adverse events (myocardial infarction, stroke, or vascular death), serious/systematic adverse events, and death.

Recherche/Suchzeitraum:

- The search included studies that were written in English or French and published before February 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 28 studies

Charakteristika der Population/Studien:

- Patients with macular edema

Qualität der Studien:

- RCTs are inherently of higher quality; therefore, a low risk score for a non-RCT study may only equate to an RCT with some concerns.

Studienergebnisse:

Aflibercept vs. laser photocoagulation

- Aflibercept was more effective than laser photocoagulation functionally (12-month BCVA-weighted mean difference [WMD] = 10.77 letters, P < 0.001; 24 months = 8.12

letters, P < 0.001) and anatomically (12-month CMT WMD = –114.12 µm, P < 0.001; 24 months = –90.4 µm, P = 0.004).

Aflibercept vs. bevacizumab

- Compared to bevacizumab, aflibercept was noninferior at improving BCVA at 12 months (WMD = 1.71 letters, P = 0.34) and 24 months (WMD = 1.58 letters, P = 0.083).
- One study found that aflibercept was more effective than bevacizumab anatomically at 1 and 2 years (P < 0.001 at 12 and 24 months).

Aflibercept vs. ranibizumab

- Compared to ranibizumab, aflibercept rendered a greater improvement in BCVA at 1 year (WMD = 1.76 letters, P = 0.001), but not 2 years (WMD = 1.66 letters, P = 0.072).
- CMT was not significantly different between both therapies at 12 months (WMD = −14.30 µm, P = 0.282) and 24 months (P = 0.08).

Aflibercept compared with dexamethasone

- One study reported greater functional improvement with aflibercept compared with dexamethasone (P = 0.004), but inferiority in reducing CMT (P < 0.001).

Anmerkung/Fazit der Autoren

Aflibercept is a safe and effective therapy option for DME in the clinical setting, performing superiorly to laser photocoagulation. Evidence regarding comparisons with bevacizumab, ranibizumab, and dexamethasone is mixed and limited.

SR u.a. mit Vergleich von aflibercept und ranibizumab.

Zou W et al., 2022 [13].

Comparison of the efficiency of anti-VEGF drugs intravitreal injections treatment with or without retinal laser photocoagulation for macular edema secondary to retinal vein occlusion: A systematic review and meta-analysis

Es liegen weitere SR zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Chen J et al., 2023 [1].

Fragestellung

To compare the efficiency of anti-VEGF drugs intravitreal injections (IVI) treatment with or without retinal laser photocoagulation (LPC) for macular edema (ME) secondary to retinal vein occlusion(RVO).

Methodik

Population:

- Patients with macular edema

Intervention/Komparator:

- anti-VEGF drugs intravitreal injections treatment with or without retinal laser photocoagulation

Endpunkte:

- best corrected visual acuity (BCVA), central macular thickness (CMT), the number of injections and the progress of retinal non-perfusion areas (NPAs)

Recherche/Suchzeitraum:

- Publications were searched on PubMed, Medline, Embase, Cochrane library and Web of science until February 2022.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 20 studies, with a total of 1387 patients

Charakteristika der Population/Studien:

- Patients with macular edema

Qualität der Studien:

- Methodological quality and bias risk assessment showed that there was no high risk of bias in our included studies, while the unclear risk of bias was mainly focused on the allocation concealment and the blinding of outcome assessment.

Studienergebnisse:

- BCVA
  - The results ofrandom effect model analysis($p < 0.00001$,$I2 = 86\%$) showed that IVI is not inferior to IVI + LPC(WMD = 0.12,95%CI = -3.54–3.78,$p = 0.95$), neither in BRVO patients (WMD = -2.01,95%CI = -4.37–0.34,$p = 0.09$),nor in CRVO patients(WMD = 5.82,95%CI = -3.65–15.29,$p = 0.23$)
- CMT
  - The fixed effect model analysis ($p = 0.27$, $I2 = 16\%$) demonstrated that there was no significant difference in CMT between IVI + LPC group and IVI group (WMD = -4.40,95%CI = -21.33–12.53,$p = 0.61$),whether in BRVO patients (WMD= -1.84,95%CI= -19.98–16.30,$p = 0.84$) or in CRVO patients (WMD = -21.72,95%CI = -68.89–25.45,$p = 0.37$)
- Number of injections
  - The results of the random effect model analysis ($p < 0.00001$, $I2 = 97\%$) illustrated that there was no significant difference between the IVI + LPC group and the single IVI group (WMD = -1.14,95% CI = -2.51–0.23, $p = 0.10$)
- progress of retinal NPAs
  - The results of the fixed effect model analysis ($p = 0.15$, $I2 = 47\%$) showed that no significant differences were detected in the change of NPAs areas between the combined treatment group and the single IVI group (WMD = 0.01,95%CI = -0.28–0.30, $p = 0.94$)

Anmerkung/Fazit der Autoren

In the treatment of RVO patients with macular edema, the combination of IVI and retinal LPC neither improves BCVA nor reduces CMT significantly compared with the single IVI treatment. However, the combination treatment can decrease the number of intravitreal injections in patients with BRVO, while it is not observed in CRVO patients.

Li X et al., 2022 [5].

The Efficacy and Safety of Dexamethasone Intravitreal Implant for Diabetic MacularEdemaand MacularEdemaSecondaryto Retinal Vein Occlusion: AMeta-Analysis of Randomized Controlled Trials

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Ming S et al., 2020 [6].

Fragestellung

The purpose of this meta-analysis was to evaluate the efficacy and safety of dexamethasone intravitreal implant (DEX) for the treatment of diabetic macular edema (DME) with retinal vein occlusion secondary to macular edema (RVO-ME).

Methodik

Population:

- Patients with diabetic macular edema

Intervention:

- dexamethasone

Komparator:

- anti-VEGF treatment or or sham injections

Endpunkte:

- Effectiveness outcomes were improvement in BCVA and degree of reduction in CST/CRT.
- Safety outcomes were adverse drug reactions. The safety outcomes were incidence ofadverse drug reactions, cataract occurrence or exacerbation, high intraocular pressure, subconjunctival hemorrhage

Recherche/Suchzeitraum:

- searched until March 2022

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

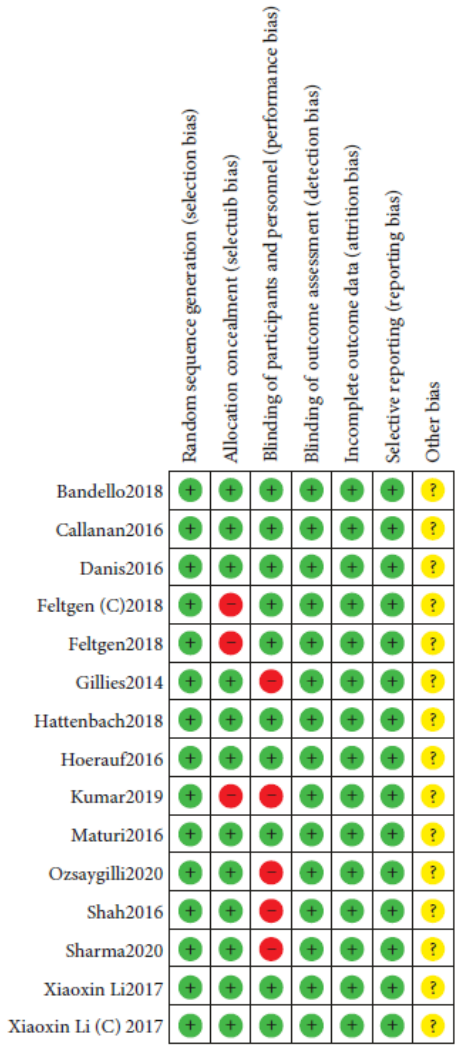
Anzahl eingeschlossener Studien:

- 13 RCTs (a total of3206 patients, with 1573 in the trial group and 1633 in the control group).

Charakteristika der Population/Studien:

- Patients with macular edema

Qualität der Studien:



Studienergebnisse:

BCVA and CRT for DME

- the difference between DEX and anti-VEGF in the BCVA improvement rate was not statistically significant (P = 0.15)
- DEX treatment of DME was significantly better than anti-VEGF treatment in terms of CRT reduction (MD=−72.35, 95% CI: −115.0–29.69, P = 0.0009).

BCVA and CRT for RVO-ME

- DEX treatment of RVO-ME was associated with an improvement in best corrected visual acuity (BCVA) (MD=−9.08, 95% CI: −10.89–7.27, P< 0.00001) and central retinal thickness (CRT) (MD= 93.47, 95% CI: 28.55–159.39, P = 0.005).

Adverse Reactions

- The safety study showed that the risk of cataract from RVO-ME (OR= 5.06, 95% CI: 1.96 to 13.06, P = 0.0008) and the incidence ofhigh intraocular pressure (OR= 6.67, 95% CI: 3.46 to 12.86, P< 0.00001) were significantly higher with DEX than with anti-VEGF therapy.

- The risk of cataract from DME (OR=4.70, 95% CI: 2.10 to 10.54, P = 0.00022) was significantly higher with DEX than with anti-VEGF therapy (OR= 4.70, 95% CI: 2.10 to 10.54, P = 0.0002). The incidence of high IOP (OR= 13.77, 95% CI: 4.96 to 38.18, P< 0.00001) was significantly higher with DEX than with anti-VEGF therapy.

Anmerkung/Fazit der Autoren

In patients with DME and RVO-ME, DEX was more efficacious but slightly less safe than anti-VEGF therapy.

3.3 Leitlinien

Flaxel CJ et al., 2020 [2].

American Academy of Ophthalmology

Retinal Vein Occlusions Preferred Practice Pattern

Zielsetzung/Fragestellung

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Literature searches to update the PPP were undertaken in March 2018 and June 2019 in PubMed and the Cochrane Library.
- Complete details of the literature searches are available online at www.aao.org/ppp.

LoE/GoR

- 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 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

Empfehlungen

Management: Medical and surgical Management

- Consequences of untreated RVOs and vision loss are an economic burden on patients, their family, and society. Anti-VEGF agents, laser and intravitreal steroids are cost-effective for the management of RVOs. The choice of treatment should be individually tailored based on discussion between the patient, family, and physician.[66,67] The current treatment strategies for BRVO target the sequelae of the venous occlusion (i.e., CME and NVD/NVE) rather than to attempt to treat the occlusion itself.

Empfehlung: anti-VEGF agents ((I++, Good quality, Strong recommendation)

- Clinical trials have evaluated the efficacy of anti-VEGF agents and/or intravitreal corticosteroid injections. Multiple level I studies have demonstrated the efficacy of these agents in the treatment of macular edema associated with BRVO.37-40,51,65 Currently, there are three that are commonly used in these cases: off-label bevacizumab and FDA-approved ranibizumab, and aflibercept. The double-masked, multicenter, randomized phase 3 clinical trial BRAVO (Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety) demonstrated efficacy of monthly intravitreal 0.3 or 0.5 mg ranibizumab compared with sham injection in 397 eyes when followed for 6 months. In this trial, monthly intravitreal

ranibizumab injections resulted in a gain of 16 (0.3 mg) to 18 letters (0.5 mg) compared with a gain of 7.3 letters in the sham group at month 6; 55% (0.3 mg) to 61% (0.5 mg) of ranibizumab-treated eyes gained at least 15 letters from baseline compared with 29% in the sham group.38 After 6 months, all eyes were eligible for injections of ranibizumab 0.5 mg as required until month 12. Eyes randomized to initial sham injection and then eligible for ranibizumab 0.5 mg after 6 months demonstrated vision improvement but did not achieve the level of vision gain compared with those eyes that were randomized to ranibizumab initially—demonstrating that delay in treatment can be deleterious.42 The benefits of ranibizumab seen at 6 months were generally maintained by month 12.37 The HORIZON trial included all patients who completed the BRAVO trial and entered an open-label multicenter extension trial. Patients were followed quarterly for 12 months with repeat injections of 0.5 mg ranibizumab, used at the investigator's discretion.51 Approximately half of the eyes in HORIZON achieved resolution of edema and 80% had visual acuity of better than or equal to 20/40. However, approximately half of the eyes enrolled in the HORIZON extension study received grid laser photocoagulation surgery at some point during the study period. These studies used ranibizumab, whereas other smaller, level II studies have demonstrated the efficacy of bevacizumab for BRVO-associated macular edema.39,40,65 The VIBRANT trial was a randomized double-masked phase 3 trial that demonstrated the efficacy of aflibercept over grid laser treatment for macular edema in BRVO.36 Two systematic reviews between 2013 and 2016 have confirmed the efficacy of anti-VEGF injections for treatment of macular edema associated with RVO with minimal side effects.68,69 (I++, Good quality, Strong recommendation)

- In general, the use of topical povidone iodine is recommended before all intravitreal injections, whereas the use of routine antibiotic eye drops is not recommended.70 Severe adverse effects of intravitreal injections are uncommon and include infectious endophthalmitis, cataract formation, retinal detachment, and elevated IOP. There are possible systemic risks associated with anti-VEGF treatment; however, a meta-analysis demonstrated no evidence of increased arterial thromboembolic events associated with anti-VEGF treatment.71 Intraocular pressure elevations are particularly common with the use of intravitreal corticosteroids and the corticosteroid implants. In conclusion, because of the favorable risk-to-benefit profile, anti-VEGF agents are the preferred initial therapy for treatment of macular edema related to BRVO. Either corticosteroids and/or grid laser treatment should be considered when there is a failure to respond or an inadequate response.
- Several randomized controlled trials have also shown the efficacy of anti-VEGF agents in treating macular edema with CRVO.45,48,52,72 The Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE) showed a doubling of the number of letters read following intravitreal ranibizumab compared with sham injections and a decrease in macular edema by OCT imaging.48 In the Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (COPERNICUS) study, intravitreal aflibercept was compared with sham injections; there was a 15-letter gain in 56% of the treated eyes compared with 12% of sham injections.45 Similar findings were found in the General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye (GALILEO) study.52 Intravitreal bevacizumab was compared with sham injections in a randomized trial that found a 15-letter gain in 60% of the treated eyes compared with 20% for sham injections.49 Subsequent studies, including 3 systematic reviews, have also supported the efficacy of anti-VEGF for treatment of macular edema secondary to CRVO.42,43,73-75 (I++, Good quality, Strong recommendation)

- The Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) comparison of aflibercept to bevacizumab for macular edema from CRVO showed that aflibercept was similar to bevacizumab in mean visual acuity at 6 months (primary outcome).76 From months 6 to 12, patients in SCORE2 were then stratified based on their response to the original monthly treatment as good, poor, or marginal response. Those with a good response were then given the original treatment drug monthly or on a treat-andextend protocol basis. Patients in the treat-and-extend protocol received about one to two fewer injections compared with the monthly regimen. However, because of the widths of the confidence intervals on visual acuity at 12 months, caution is advised before concluding that the two regimens yield similar visual outcomes.77 For eyes classified as poor responders to aflibercept at 6 months, dexamethasone rescue was used.77 Aflibercept was used for eyes with a marginal response to bevacizumab.77

Empfehlung: Steroide (I+, Good quality, Strong recommendation)

- There is a role for intravitreal steroids such as triamcinolone, dexamethasone and other corticosteroids that have been shown to be efficacious for macular edema associated with CRVO, yet there are known associated risks of cataracts and glaucoma.56,72,78 The SCORE study for BRVO evaluated the use of two doses of intravitreal corticosteroids (triamcinolone 1 mg and 4 mg) versus macular grid laser therapy in 411 eyes randomized to one of the three treatment arms in a 1:1:1 fashion and followed for 12 months.41 After 1 year, approximately one-third of eyes in the laser treatment group, one-third of eyes in the triamcinolone1-mg group, and one-third of eyes in the triamcinolone 4-mg group gained 15 or more letters. The mean gain in best-corrected visual acuity was 4 to 5 letters in all groups; however, patients in either of the corticosteroid groups were more likely to develop cataract or elevated IOP than those who received laser treatment.
- The SCORE recommendations for BRVO were to consider macular grid laser treatment in eyes with BRVO and perfused macular edema leading to vision loss because the efficacy was similar in all treatment arms.
- The SCORE CRVO trial included 271 people aged 68 years on average.56 Seventy-three percent of patients with CRVO had high blood pressure and 23% percent had diabetes. Patients in the corticosteroid medication groups received an average of two injections in the first 12 months of the study. After 1 year, 27% of patients in the 1-mg group and 26% of patients in the 4-mg group experienced a substantial visual gain of 3 or more lines of visual acuity. Only 7% of patients in the observation group experienced a similar visual gain. Therefore, patients in the corticosteroid treatment groups were much more likely to have a substantial visual gain at 1 year. These results persisted up to 2 years.
- However, participants who received the 4-mg dose had the highest rates of cataract formation, cataract surgery, and elevated IOP within the eye, indicating a preference for the 1-mg dose.56
- The GENEVA study evaluated the use of the intravitreal dexamethasone implant (Ozurdex®, Allergan, Inc., Irvine, CA) in two doses compared with sham injection in eyes with either a CRVO or a BRVO.79 The study included pooled data from 1131 patients, 34% with CRVO and 66% with BRVO, and showed that in the BRVO eyes treatment with either the 0.35-mg or the 0.7-mg dose implant had no efficacy at 6 months. However, there was significant visual acuity gain at 90 days that was lost at 6 months. Results from an open-label extension beyond 6 months were similar to the initial study, showing visual acuity gains up to 90 days, then loss of a treatment effect at 1 year.72 Cataract formation and elevated IOP were seen more frequently at 1 year than at 6 months (16% had an elevated IOP of 25 mmHg or greater). The dexamethasone implant was FDA approved in 2009 for the treatment of macular edema due to CRVO and BRVO.

- The COBALT study has shown that with retreatment using the dexamethasone implant as often as every 4 months, significant visual acuity gains can be achieved for eyes with macular edema secondary to a BRVO.80 In fact, mean visual acuity improvement was 18.6 ± 12.9 and 15.3 ± 15.0 letters at 6 and 12 months, respectively. There was a rapid response, with approximately 70% of maximum treatment response seen at 1 week. Incidence of IOP elevation was 18% and cataract incidence was 16% at one year.
- A third corticosteroid implant, fluocinolone, has also been shown to be beneficial in the treatment of BRVO-associated macular edema up to 3 years following injection. There were improvements in both edema and visual acuity,81 but fluocinolone is not yet approved by the FDA for this indication. Glaucoma and cataract formation were reported side effects in this study.
- A Cochrane systemic review questioned the results of SCORE because of incomplete outcome data and the GENEVA study because of selective reporting and found that there was insufficient evidence to determine if steroids are beneficial or not.82 (I+, Good quality, Strong recommendation) A meta-analysis found no difference in visual improvement for treatment of macular edema from CRVO with bevacizumab, ranibizumab, aflibercept and triamcinolone. However, steroid and IOP risks associated with steroids make anti-VEGF more favorable as initial therapy.78 (I+, Good quality, Strong recommendation)

<u>Empfehlung: Laser Photocoagulation (kein Empfehlungsgrad angegeben)</u>

- The BVOS first demonstrated the efficacy of grid laser photocoagulation surgery for macular edema due to BRVO. Patients with BRVO who presented with a visual acuity of 20/40 or worse due to perfused BRVO (retained macular perfusion on FA) with macular edema were randomized to either grid-pattern laser photocoagulation surgery or no treatment. There were more patients who gained at least 2 lines of visual acuity from baseline in the laser photocoagulation surgery group than in the untreated group (65% vs. 37%). Nearly twice as many treated eyes had final visual acuity outcomes greater than 20/40 when compared with untreated eyes. This finding led to the recommendation that grid laser treatment should be considered for eyes with BRVO, macular perfusion, and macular edema with a visual acuity of 20/40 or worse.30 However, anti-VEGF results in more improvement in visual acuity (see above) than laser and should be the preferred treatment unless there are contraindications to its use. Further, treatment for macular edema should not be delayed. Patients in whom monthly follow-up is difficult may also be managed more easily with laser photocoagulation surgery, with follow-up 3 months after laser. Sectoral PRP is still recommended for neovascularization when complications such as vitreous hemorrhage or iris neovascularization occur.57 Most recently, clinical trials have shown no added benefit for macular grid or peripheral scatter laser photocoagulation surgery for BRVO. The 2-year BRIGHTER83 and the 4-year RETAIN84 studies demonstrated that adding laser to ranibizumab did not result in a better visual outcome or reduce the need for treatment. In the RELATE study, scatter laser to peripheral ischemic areas did not decrease the macular edema.85
- The Central Vein Occlusion Study (CVOS) did not show any value of focal photocoagulation for macular edema in patients with CRVO.17 For patients with iris or angle neovascularization, the CVOS recommended complete peripheral PRP.17 Currently, anti-VEGFs are being used as an adjunct to treat iris or angle neovascularization. There is no phase 3 clinical trial evidence for this usage.

Referenzen:

37. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology. 2011;118(8):1594-1602.
38. Campochiaro PA, Heier JS, Feiner L, et al. BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1102-1112.
39. Russo V, Barone A, Conte E, Prascina F, Stella A, Noci ND. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. Retina. 2009;29(4):511-515.
40. Yilmaz T, Cordero-Coma M. Use of bevacizumab for macular edema secondary to branch retinal vein occlusion: a systematic review. Graefes Arch Clin Exp Ophthalmol. 2012;250(6):787-793.
41. Scott IU, Ip MS, VanVeldhuisen PC, et al. SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. Arch Ophthalmol. 2009;127(9):1115-1128.
42. Ehlers JP, Kim SJ, Yeh S, et al. Therapies for Macular Edema Associated with Branch Retinal Vein Occlusion: A Report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(9):1412-1423.
43. Yeh S, Kim SJ, Ho AC, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology. Ophthalmology. 2015;122(4):769-778.
44. Chatziralli IP, Jaulim A, Peponis VG, Mitropoulos PG, Moschos MM. Branch retinal vein occlusion: treatment modalities: an update of the literature. Semin Ophthalmol. 2014;29(2):85-107.
45. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. Ophthalmology. 2012;119(5):1024-1032. Erratum in: Ophthalmology 2012;1119:2204.
46. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1124-1133.
47. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema
secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol. 2013;155(3):429-437.
48. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology. 2011;118(10):2041-2049.
49. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. Ophthalmology. 2012;119(6):1184-1189.
50. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. Ophthalmology. 2012;119(12):2587-2591.
51. Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology. 2012;119(4):802-809.
52. Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013;97(3):278- 284.
53. Kriechbaum K, Michels S, Prager F, et al. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: a prospective study. Br J Ophthalmol. 2008;92(4):518-522.
54. Prager F, Michels S, Kriechbaum K, et al. Intravitreal bevacizumab (Avastin) for macular oedema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial. Br J Ophthalmol. 2009;93(4):452-456.
55. Zhang H, Liu ZL, Sun P, Gu F. Intravitreal bevacizumab for treatment of macular edema secondary to central retinal vein occlusion: eighteen-month results of a prospective trial. J Ocul Pharmacol Ther. 2011;27(6):615-621.
56. Ip MS, Scott IU, VanVeldhuisen PC, et al. SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. Arch Ophthalmol. 2009;127(9):1101-1114.
57. Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion: a randomized clinical trial. Arch Ophthalmol. 1986;104(1):34-41.
58. Frank RN, Hoffman WH, Podgor MJ, et al. Retinopathy in juvenile-onset diabetes of short duration. Ophthalmology. 1980;87(1):1-9.
59. Davis MD, Bressler SB, Aiello LP, et al. Diabetic Retinopathy Clinical Research Network Study Group. Comparison of time-domain OCT and fundus photographic assessments of retinal thickening in eyes with diabetic macular edema. Invest Ophthalmol Vis Sci. 2008;49(5):1745-1752.

60. Rispoli M, Savastano MC, Lumbroso B. Capillary network anomalies in branch retinal vein occlusion on optical coherence tomography angiography. Retina. 2015;35(11):2332-2338.
61. Kashani AH, Lee SY, Moshfeghi A, Durbin MK, Puliafito CA. Optical coherence tomography angiography of retinal venous occlusion. Retina. 2015;35(11):2323-2331.
62. Thomas AS, Thomas MK, Finn AP, Fekrat S. Use of the Ischemic Index on Widefield Fluorescein Angiography to Characterize a Central Retinal Vein Occlusion as Ischemic or Nonischemic. Retina. 2019;39(6):1033-1038.
63. Yannuzzi LA, Rohrer KT, Tindel LJ, et al. Fluorescein angiography complication survey. Ophthalmology. 1986;93(5):611-617.
64. Sunness JS. The pregnant woman's eye. Surv Ophthalmol. 1988;32(4):219-238.
65. Ehlers JP, Fekrat S. Retinal vein occlusion: beyond the acute event. Surv Ophthalmol. 2011;56(4):281-299.
66. Smiddy WE. Economic considerations of macular edema therapies. Ophthalmology. 2011;118(9):1827-1833.
67. Suner IJ, Margolis J, Ruiz K, Tran I, Lee P. Direct medical costs and resource use for treating central and branch retinal vein occlusion in commercially insured working-age and Medicare populations. Retina. 2014;34(11):2250-2258.
68. Regnier SA, Larsen M, Bezlyak V, Allen F. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis. BMJ Open. 2015;5(6):e007527.
69. Song WT, Xia XB. Ranibizumab for macular edema secondary to retinal vein occlusion: a metaanalysis of dose effects and comparison with no anti-VEGF treatment. BMC Ophthalmol. 2015;15:31.
70. Parke DW, II, Coleman AL, Rich WL, III, Lum F. Choosing Wisely: five ideas that physicians and patients can discuss. Ophthalmology. 2013;120(3):443-444.
71. Cheng JW, Cheng SW, Lu GC, Wei RL. Effect of intravitreal anti-vascular endothelial growth factor therapy on the risk of arterial thromboembolic events: a meta-analysis. PLoS One. 2012;7(7):e41325.
72. Haller JA, Bandello F, Belfort R, Jr., et al. Ozurdex GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology. 2011;118(12):2453-2460.
73. Braithwaite T, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. Cochrane Database Syst Rev. 2014(5):CD007325.
74. Ford JA, Clar C, Lois N, et al. Treatments for macular oedema following central retinal vein occlusion: systematic review. BMJ Open. 2014;4(2):e004120.
75. Zhou S, Gao J, Xu X. Antivascular endothelial growth factors in the treatment of macular oedema secondary to central retinal vein occlusion: a meta-analysis. Clin Exp Ophthalmol. 2014;42(7):637- 649.
76. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. JAMA. 2017;317(20):2072-2087.
77. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of monthly vs treat-and-extend regimens for individuals with macular edema who respond well to anti-vascular endothelial growth factor medications: secondary outcomes from the SCORE2 randomized clinical trial. JAMA Ophthalmol.2018;136(4):337-345.
78. Ford JA, Shyangdan D, Uthman OA, Lois N, Waugh N. Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis. BMJ Open. 2014;4(7):e005292.
79. Haller JA, Bandello F, Belfort R, Jr., et al. Ozurdex GENEVA Study Group. Randomized, shamcontrolled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010;117(6):1134-1146.
80. Yoon YH, Kim JW, Lee JY, et al. Dexamethasone intravitreal implant for early treatment and retreatment of macular edema related to branch retinal vein occlusion: the multicenter COBALT study. Ophthalmologica. 2018;240(2):81-89.
81. Jain N, Stinnett SS, Jaffe GJ. Prospective study of a fluocinolone acetonide implant for chronic macular edema from central retinal vein occlusion: thirty-six-month results. Ophthalmology. 2012;119(1):132-137.
82. Gewaily D, Muthuswamy K, Greenberg PB. Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion. Cochrane Database Syst Rev. 2015(9):CD007324.
83. Tadayoni R, Waldstein SM, Boscia F, et al. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the BRIGHTER study. Ophthalmology. 2017;124(12):1778-1787.
84. Campochiaro PA, Sophie R, Pearlman J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. Ophthalmology. 2014;121(1):209-219.
85. Campochiaro PA, Hafiz G, Mir TA, et al. Scatter photocoagulation does not reduce macular edema or treatment burden in patients with retinal vein occlusion: the RELATE trial. Ophthalmology. 2015;122(7):1426-1437.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2023) am 26.04.2023

#	Suchfrage
1	MeSH descriptor: [Macular Edema] explode all trees
2	(macula* AND (edema OR oedema)):ti,ab,kw
3	MeSH descriptor: [Retinal Vein Occlusion] explode all trees
4	(retinal AND vein AND occlu*):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	#5 with Cochrane Library publication date from Apr 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 26.04.2023

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 edema[mh]
2	macula*[tiab] AND (edema[tiab] OR oedema[tiab])
3	retinal vein occlusion[mh]
4	retinal[tiab] AND vein[tiab] AND occlu*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR

#	Suchfrage
	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])
7	(#6) AND ("2018/04/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT "The Cochrane database of systematic reviews"[Journal]
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 26.04.2023

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

#	Suchfrage
1	macular edema[mh]
2	macula*[tiab] AND (edema[tiab] OR oedema[tiab])
3	retinal vein occlusion[mh]
4	retinal[tiab] AND vein[tiab] AND occlu*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2018/04/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 27.04.2023

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

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

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

Referenzen

1. **Chen J, Wang H, Qiu W.** Intravitreal anti-vascular endothelial growth factor, laser photocoagulation, or combined therapy for diabetic macular edema: a systematic review and network meta-analysis. Front Endocrinol (Lausanne) 2023;14:1096105.
2. **Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, et al.** Retinal vein occlusions Preferred Practice Pattern. Ophthalmology 2020;127(2):288-320.
3. **Gao L, Zhao X, Jiao L, Tang L.** Intravitreal corticosteroids for diabetic macular edema: a network meta-analysis of randomized controlled trials. Eye Vis (Lond) 2021;8(1):35.
4. **Gao S, Zhang Y, Li X, Ge G, Duan J, Lei C, et al.** Comparative efficacy of pharmacotherapy for macular edema secondary to retinal vein occlusion: a network meta-analysis. Front Pharmacol 2021;12:752048.
5. **Li X, Xi X.** The efficacy and safety of dexamethasone intravitreal implant for diabetic macular edema and macular edema secondary to retinal vein occlusion: a meta-analysis of randomized controlled trials. J Ophthalmol 2022;2022:4007002.
6. **Ming S, Xie K, Yang M, He H, Li Y, Lei B.** Comparison of intravitreal dexamethasone implant and anti-VEGF drugs in the treatment of retinal vein occlusion-induced oedema: a meta-analysis and systematic review. BMJ Open 2020;10(6):e032128.
7. **Pranata R, Vania A, Vania R, Victor AA.** Intravitreal ranibizumab versus dexamethasone implant in macular edema due to branch retinal vein occlusion: Systematic review and meta-analysis. Eur J Ophthalmol 2021;31(4):1907-1914.
8. **Qiu XY, Hu XF, Qin YZ, Ma JX, Liu QP, Qin L, et al.** Comparison of intravitreal aflibercept and dexamethasone implant in the treatment of macular edema associated with diabetic retinopathy or retinal vein occlusion: a meta-analysis and systematic review. Int J Ophthalmol 2022;15(9):1511-1519.
9. **Rittiphairoj T, Mir TA, Li T, Virgili G.** Intravitreal steroids for macular edema in diabetes. Cochrane Database of Systematic Reviews [online]. 2020(11):Cd005656. URL: http://dx.doi.org/10.1002/14651858.CD005656.pub3.
10. **Santhakumaran S, Salimi A, Brunetti VC, Galic J.** Efficacy and safety of aflibercept therapy for diabetic macular edema: a systematic review and meta-analysis. J Curr Ophthalmol 2022;34(2):133-147.
11. **Shalchi Z, Mahroo O, Bunce C, Mitry D.** Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database of Systematic Reviews [online]. 2020(7):Cd009510. URL: http://dx.doi.org/10.1002/14651858.CD009510.pub3.
12. **Veritti D, Sarao V, Soppelsa V, Lanzetta P.** Managing diabetic macular edema in clinical practice: systematic review and meta-analysis of current strategies and treatment options. Clin Ophthalmol 2021;15:375-385.
13. **Zou W, Du Y, Ji X, Zhang J, Ding H, Chen J, et al.** Comparison of the efficiency of anti-VEGF drugs intravitreal injections treatment with or without retinal laser photocoagulation for macular edema secondary to retinal vein occlusion: a systematic review and meta-analysis. Front Pharmacol 2022;13:948852.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in

Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-107

Verfasser	
Name der Institution	Deutsche Ophthalmologische Gesellschaft (DOG), Berufsverband der Augenärzte Deutschlands e.V. (BVA), Retinologische Gesellschaft (RG)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	14. Mai 2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Behandlung von erwachsenen Patienten mit einer Visusbeeinträchtigung aufgrund eines Makulaödems infolge eines retinalen Venenverschlusses (RVV) (Venenastverschluss [VAV] oder Zentralvenenverschluss [ZVV])
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? Die Behandlungsoptionen sind zuletzt ausführlich in der Stellungnahme der augenärztlichen Fachgesellschaften dargestellt worden (1). Folgende Therapieoptionen für die Therapie des Makulaödems bei retinalem Venenverschluss (RVV) mit fovealer Beteiligung kommen in Frage: • Intravitreale operative Medikamentenapplikation (IVOM) mit VEGF-Inhibitoren (*Aflibercept, Bevacizumab*, Ranibizumab*) beim Zentralvenenverschluss (ZVV) oder Venenastverschluss (VAV). • Intravitreale operative Medikamentenapplikation (IVOM) mit Steroiden (*Triamcinolon**) und Steroid-Implantaten (*Dexamethason*) beim ZVV und VAV • Lasertherapie (*focal/GRID laser*) beim VAV **Bevacizumab* und *Triamcinolon* stellen eine *off-label*-Behandlung dar. Grundsätzlich sollen alle Patienten über die verschiedenen Therapiemodalitäten, insbesondere über die jeweilige Visusprognose, Behandlungsfrequenzen und Komplikationshäufigkeiten informiert werden. Es ist zu beachten, dass verschiedene Untersuchungen wie die Bestimmung des bestkorrigierten Visus, die Spaltlampenuntersuchung der vorderen Augenabschnitte die stereoskopische Untersuchung der gesamten Netzhaut in Mydriasis, die Fluoreszeinangiographie und die optische Kohärenztomographie (OCT) erforderlich sind, um die Indikation, d.h. Chancen und Risiken der Behandlung im Einzelfall zu bewerten. Die Behandlung eines Makulaödems mit fovealer Beteiligung beim RVV mit intravitrealen Medikamenten soll nur dann erfolgen, wenn aufgrund des Ausgangsbefunds eine positive Beeinflussung des funktionellen (und morphologischen) Befunds erwartet werden kann. Diese Einschätzung betrifft vor allem ältere Befunde, da frische Verschlüsse in der Regel gut auf die Behandlung ansprechen und therapiert werden sollten.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „Patienten mit Visusbeeinträchtigung infolge eines Makulaödems mit fovealer Beteiligung nach einem RVV“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Folgende Faktoren sollten in der Entscheidung berücksichtigt werden:

Visusbeeinträchtigung

Eine Visusbeeinträchtigung kann bei Patienten mit RVV durch die Folgen der Durchblutungsstörung, aber auch durch andere Augenerkrankungen bedingt sein. Dabei ist es nicht immer einfach, den Anteil unterschiedlicher Ursachen für eine Sehverschlechterung zu bewerten. Während in den meisten Zulassungs- und Wirksamkeitsstudien andere Erkrankungen des Auges ausgeschlossen waren, werden im klinischen Alltag auch Patienten behandelt, die z.B. Linsentrübung, Oberflächen-Benetzungsstörung, ein Glaukom oder Glaskörperblutung aufweisen können.

Eine IVOM-Therapie soll nach den Empfehlungen der augenärztlichen Fachgesellschaften dann erfolgen, wenn eine positive Beeinflussung des funktionellen (und morphologischen) Befundes aufgrund des Befundes erwartet werden kann. Bei frischen Verschlüssen ist das in der Regel der Fall. In den Zulassungsstudien wurden Patienten mit einer Verschlussdauer bis zu 6 Monaten eingeschlossen, weshalb diese Krankheitsdauer für die Erstbehandlung zugrunde gelegt werden kann.

Ein wichtiges Instrument, um die Beeinträchtigung der zentralen Netzhaut zu bewerten, ist die OCT-Untersuchung. Es sollte nur dann eine Behandlung initiiert werden, wenn ein zystoides Makulaödem im Bereich der Fovea nachweisbar ist, welches die Sehschärfenreduktion erklärt. Das Ödem kann am besten mit der OCT nachgewiesen und die Höhe ausgemessen werden. Da bei allen vaskulären Erkrankungen neben der Ödemhöhe auch immer eine Abschattung durch Blutungen oder zentrale Gesichtsfeldausfälle durch Ischämien auftreten können, korreliert die Ödemhöhe nicht immer mit der Sehleistung.

Linsenstatus und Alter

Der Zustand der Linse und das Alter haben einen Einfluss auf die mögliche Naheinstellungsreaktion (Akkommodation). Weil intraokulare Steroide ein Fortschreiten bzw. das Auftreten einer relevanten Katarakt bewirken, sollten diese Präparate zurückhaltend bei jungen Menschen mit erhaltener Akkommodation bzw. eigener Linse gewählt werden, da es durch eine Katarakt-Operation zum Verlust der Akkommodation kommt (1). Daher sind entsprechende Hinweise auch den Fachinformationen von Ozurdex® erhalten.

Glaukom

Ein Glaukom oder eine okuläre Hypertension gelten als wichtige okuläre Risikofaktoren für die Entstehung eines RVV und sollten auch am 2. Auge entsprechend behandelt werden. Nach der Gabe von Steroiden in den Glaskörperraum kam es teilweise zu einer Erhöhung des Augeninnendruckes, sodass Patienten mit augendrucksenkenden Augentropfen oder in seltenen Fällen mit einer Glaukom-Operation behandelt werden müssen, um einen irreversiblen Glaukomschaden zu verhindern. Die Wahrscheinlichkeit für erhöhte Augendruckwerte nach der Gabe von Steroiden wird zusätzlich durch eine schon vorbekannte Glaukom-Erkrankung erhöht. Daher müssen Hinweise auf erhöhte Augendruckwerte oder ein vorbestehendes Glaukom beachtet werden, um die Patienten über das Nebenwirkungsprofil ausreichend aufklären zu können (1).

Begleiterkrankungen und systemische Therapie
RVV-Patienten weisen in der Regel ein ungünstiges kardiovaskuläres Risikoprofil auf und haben ein erhöhtes Risiko, vaskuläre Folgeerkrankungen zu erleiden (1). Deshalb ist die internistische Abklärung eine wesentliche Säule in der Behandlung von RVV-Patienten. Unabhängig davon soll das Makulaödem frühzeitig mittels IVOM behandelt werden, um die Gefahr einer Chronifizierung zu minimieren. Es ist nicht davon auszugehen, dass eine systemische Therapie von Risikofaktoren einen Einfluss auf die Höhe des Makulaödems besitzt, ebenso haben die IVOM-Medikamente keinen gesicherten Einfluss auf kardiovaskuläre Erkrankungen (2).

Retinale Ischämie
Bei der Behandlung der zentralen Netzhautveränderung darf die Beurteilung und ggf. Behandlung der Netzhautperipherie nicht außer Acht gelassen werden. Auch bei den retinalen Venenverschlüssen kann es zu schweren retinalen Ischämien kommen, die in der Folge zu Neovaskularisationen und Glaskörperblutungen führen können. Deshalb soll der Ischämiegrad mittels Fluoreszeinangiografie bestimmt und bei Nachweis einer relevanten Ischämie mit Laserkoagulation behandelt werden. Die Grenze, ab der eine Laserung empfohlen wird, betrifft bei einem VAV circa fünf und beim ZVV circa zehn Papillenflächen. Der Ischämiegrad sollte wiederholt beurteilt werden, die erste Fluoreszeinangiografie ist innerhalb der ersten 6 Monate nach Verschlussereignis empfehlenswert.

Behandlungslast
Da es sich bei einem RVV um ein akutes Ereignis mit einem meist klar wahrnehmbaren Beginn handelt, ist eine intensive Behandlung vor allem innerhalb des ersten Jahres empfehlenswert, um die Gefahr einer Chronifizierung zu reduzieren. Durchschnittlich sind im ersten Behandlungsjahr ca. 9 IVOM erforderlich (1). Aber auch in den Folgejahren ist mit einer regelmäßigen und oft dauerhaften IVOM-Therapie zu rechnen.

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.)

Innerhalb der Gruppe der VEGF-Inhibitoren (Ranibizumab, Bevacizumab, Aflibercept) gibt es keine Unterschiede, die zu einer bevorzugten Empfehlung führen. In allen Vergleichsstudien gehen die Autoren von einer Gleichwertigkeit der medikamentösen Behandlung aus (3–6).
Das Glukokortikoid Dexamethason hat im Vergleich zu Ranibizumab einen gleichwertigen initialen Effekt (7,8). Allerdings sollten Steroide bei Vorliegen einer okulären Hypertension oder eines Glaukoms nur zurückhaltend eingesetzt werden, da ein Druckanstieg nicht vorhersagbar ist und wirksame Alternativen zur Verfügung stehen. Auch bei noch vorhandener Akkommodation werden Steroide wegen der kataraktogenen Wirkung nur bei mangelnder Wirkung von VEGF-Inhibitoren eingesetzt. Für Triamcinolon gibt es deutlich weniger aussagekräftige Daten, es spielt bei der Behandlung nur eine untergeordnete Rolle.
Die fokale zentrale Laserbehandlung (focal/ GRID-Laser) hatte vor der IVOM-Ära einen Stellenwert bei Patienten mit VAV und einem zystoidem Makulaödem, das älter als 3 Monate war (9). Der visusverbessernde Effekt beim Makulaödem konnte in den 80-er Jahren beim VAV, nicht aber beim ZVV nachgewiesen werden (10). Die fokale Laserkoagulation des Makulaödems bei VAV führt zur Narbenbildung und hat im Vergleich zur IVOM mit VEGF-Inhibitoren sowie auch additiv als initiale Behandlung keinen zusätzlichen Effekt. Sie wird deshalb heute nur noch in Einzelfällen angewendet, meist bei chronischen Verläufen.

Referenzliste:

1. Berufsverband der Augenärzte Deutschlands e. V. (BVA), Deutsche Ophthalmologische Gesellschaft (DOG), Retinologische Gesellschaft e. V. (RG): Stellungnahme von BVA, DOG und RG zur intravitrealen Therapie des visusmindernden Makulaödems bei retinalem Venenverschluss: Therapeutische Strategien, Stand 24.04.2018. Ophthalmol 2018; 115: 842–54.

2. Reibaldi M, Fallico M, Avitabile T, u. a.: Risk of Death Associated With Intravitreal Anti-Vascular Endothelial Growth Factor Therapy: A Systematic Review and Meta-analysis. JAMA Ophthalmol 2020; 138: 50–7.

3. Vader MJC, Schauwvlieghe A-SME, Verbraak FD, u. a.: Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Retinal Vein Occlusion: The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) study, a Randomized Trial. Ophthalmol Retina 2020; 4: 576–87.

4. Scott IU, Oden NL, VanVeldhuisen PC, u. a.: Month 24 Outcomes After Treatment Initiation With Anti-Vascular Endothelial Growth Factor Therapy for Macular Edema Due to Central Retinal or Hemiretinal Vein Occlusion: SCORE2 Report 10: A Secondary Analysis of the SCORE2 Randomized Clinical Trial. JAMA Ophthalmol 2019; .

5. Hykin P, Prevost AT, Sivaprasad S, u. a.: Intravitreal ranibizumab versus aflibercept versus bevacizumab for macular oedema due to central retinal vein occlusion: the LEAVO non-inferiority three-arm RCT. Health Technol Assess Winch Engl 2021; 25: 1–196.

6. Shalchi Z, Mahroo O, Bunce C, Mitry D: Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev 2020; 7: CD009510.

7. Hoerauf H, Feltgen N, Weiss C, u. a.: Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study. Am J Ophthalmol 2016; 169: 258–67.

8. Hattenbach L-O, Feltgen N, Bertelmann T, u. a.: Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B). Acta Ophthalmol (Copenh) 2018; 96: e10–8.

9. Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands zur Therapie des Makulaödems beim retinalen Venenverschluss. Ophthalmologe 2010; 107: 583–96.

10. BVOS: Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. Am J Ophthalmol 1984; 98: 271–82.