Review Article

Anti-vascular endothelial growth factor therapies in ophthalmology

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ABSTRACT

Background: Retinal diseases, including neovascular age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion, are leading causes of vision loss worldwide. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies has dramatically changed the management of these conditions, offering targeted treatment that can preserve and even improve vision. We aimed to provide a comprehensive review of the development, clinical applications, and emerging indications of anti-VEGF therapies in ophthalmology, including biosimilar agents.

Methods: A comprehensive literature search was conducted in PubMed/MEDLINE for English-language articles published up to 31 July 2025. Additional sources were identified through manual screening of reference lists. Included studies spanned various designs: clinical trials, meta-analyses, observational studies, and preclinical research. Keywords used in the search strategy included terms such as "anti-VEGF therapy", "biosimilar pharmaceuticals", "intravitreal and intrastromal anti-VEGF injections", "retinal diseases" including "macular degeneration" and "retinal neovascularization", "ranibizumab", and "bevacizumab", as well as relevant MeSH terms where applicable.

Results: Anti-VEGF agents have transformed the management of retinal diseases such as neovascular age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity. Newer agents such as brolucizumab and faricimab offer prolonged durability and enhanced anatomic outcomes, while biosimilars provide cost-effective alternatives. Anti-VEGF therapy has also shown promise in off-label or emerging indications such as neovascular glaucoma, corneal neovascularization, and other retinal or choroidal disorders including secondary macular edema and/or macular neovascularization associated with various forms of uveitis, diffuse choroidal hemangioma in Sturge-Weber Syndrome, hereditary retinal disorders such as fundus flavimaculatus, Coats-Like retinitis pigmentosa, Peripherin-2-associated retinopathy, immune checkpoint inhibitor use, radiation retinopathy, retinitis pigmentosa, Bietti crystalline dystrophy, autosomal recessive bestrophinopathy, melanocytoma-associated macular neovascular membrane, Best disease, Wyburn-Mason syndrome, choroidal osteoma, peripheral exudative hemorrhagic chorioretinopathy, traumatic choroidal rupture, torpedo maculopathy, optic disc melanocytoma, type 2 proliferative macular telangiectasia, and Coats disease. High-dose formulations and innovative delivery systems are under active investigation to reduce the treatment burden and extend dosing intervals.

Conclusions: Anti-VEGF therapies have revolutionized the field of ophthalmology, providing sight-saving treatment for a range of retinal diseases that were once considered untreatable or inevitably blinding. Today, anti-VEGF drugs are the go-to option for managing neovascular retinal disorders, thanks to their proven efficacy, favorable safety profile, and transformative impact on modern eye care.

KEYWORDS

vascular endothelial growth factor, vegf, intravitreal injection, ziv-aflibercept, vegf-trap, avastin, bevacizumab-awwb, lucentis, ranibizumab, brolicuzumab, faricimab, retina, pathological neovascularization, diabetic retinopathies, retinal neovascularization, optic disc neovascularization, age-related macular degeneration, choroid neovascularization, corneal neovascularizations

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INTRODUCTION

Vascular Endothelial Growth Factor (VEGF) is a fundamental cytokine mediating endothelial cell proliferation, vascular permeability dynamics, and vessel wall integrity [1]. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have significantly transformed the field of ophthalmology [2]. In December 2004, the U.S. Food and Drug Administration (FDA) approved Pegaptanib (Macugen®; Bausch and Lomb), a PEGylated aptamer that selectively targets the VEGF165 isoform, effectively inhibiting VEGF-A-induced endothelial cell proliferation and vascular leakage [3]. It received approval for the treatment of nAMD [4, 5]. Although pegaptanib was employed in the management of nAMD, it demonstrated less potency compared to other anti-VEGF agents. This reduced efficacy is likely related to its selective binding to a single VEGF isoform [6].

Bevacizumab (Avastin; Genentech, South San Francisco, CA), initially received FDA approval in 2004 for the treatment of metastatic colorectal cancer. The off-label use of bevacizumab in ophthalmology was initiated in 2005, following the unexpected yet compelling evidence that systemic intravenous administration of the drug was effective in treating neovascular age-related macular degeneration (nAMD) [7, 8]. Shortly thereafter, in 2006, ranibizumab (Lucentis; Genentech) was approved for managing nAMD, marking a major advancement in retinal disease therapy [9]. The landscape of anti-VEGF treatments further evolved in 2011 with the FDA approval of aflibercept (Eylea; Regeneron, Tarrytown, NY) [9].

Brolucizumab 6 mg (Beovu®; Novartis) received FDA approval on 8 October 2019 [10]. However, initial post-marketing reports revealed instances of serious vision loss due to intraocular inflammation and occlusive retinal vasculitis [11, 12].

Next, on 28 January 2022 faricimab 6 mg (Vabysmo®; Roche/Genentech) was approved by the FDA for treating nAMD and diabetic macular edema (DME) [13]. The introduction of faricimab marked a significant advance in retinal therapy, offering dual inhibition of VEGF-A and Angiopoietin-2, both pivotal for the occurrence of macular neovascularization. This mechanism allows for broader disease control by addressing both neovascular growth and vascular remodeling [14].

One of the main challenges with current anti-VEGF-A therapies is the need for frequent injections, which places a significant burden on patients and healthcare systems. To reduce the burden, newer treatment strategies have focused on extending the intervals between doses [15]. These strategies include brolucizumab, faricimab, high-dose aflibercept (8 mg), the Port Delivery System (PDS) (Susvimo), and investigational gene therapies. Clinical trials have shown that brolucizumab given every 2 or 3 months, and faricimab given in intervals of up to 16 weeks, are comparable in efficacy to aflibercept given every 8 weeks [13, 16].

Aflibercept 8 mg was approved after trials showed that dosing every 12 or 16 weeks was as effective at 48 weeks as the 2-mg dose given every 8 weeks for nAMD and DME [17]. The PDS is a surgically implanted, refillable ocular device engineered to provide sustained intravitreal delivery of a specialized ranibizumab formulation. However, following its approval the device was withdrawn from the market and manufacturing issues have yet to be resolved [15, 18].

The aim of this comprehensive review is to provide an in-depth overview of VEGF's role in ocular disease mechanisms and to assess the clinical impact and future directions of anti-VEGF treatment strategies in ophthalmology.

METHODS

A comprehensive literature review was conducted using the PubMed/MEDLINE database to identify relevant studies published up to 31 July 2025. The search strategy combined anatomical and imaging-related terms, incorporating Medical Subject Headings (MeSH) when appropriate to enhance specificity. Inclusion criteria were limited to full-text articles published in English. The reference lists of the selected studies were manually screened to capture further pertinent publications. The review encompassed a broad spectrum of study designs, including clinical trials, systematic and meta-analyses, narrative reviews, observational research, case series, and preclinical animal studies. Keywords used in the search strategy included terms such as "anti-VEGF therapy", "biosimilar pharmaceuticals", "intravitreal and intrastromal anti-VEGF injections", "retinal diseases" including "macular degeneration" and "retinal neovascularization", "ranibizumab", and "bevacizumab", as well as relevant MeSH terms where applicable.

RESULTS and DISCUSSION

Table 1 summarizes the characteristics of anti-VEGF drugs used in ophthalmology [7, 15, 19–42]. Biosimilars, which closely resemble the licensed biological drugs in both form and activity, hold promising potential for improving care in retinal diseases [43]. Table 2 summarizes biosimilar anti-VEGF agents used in ophthalmology [15, 20, 22, 28–31, 43, 44]. Table 3 summarizes major anti-VEGF clinical trials in ophthalmology [2, 8, 13, 16, 17, 18, 46–86].

Table 1. Comparative overview of anti-VEGF agents used in ophthalmology [7, 15, 19–42]

Agents	Structure and Mechanism	Molecular Weight	Clinical Dose	Ocular Half-life	Systemic Half-life	FDA Approval for Ocular Use	Indications	Notes
Bevacizumab (Avastin®)	Humanized monoclonal IgG1 antibody against VEGF-A	~149 kDa	1.25 mg	9.82 days	18.7 days	Off-label use since ~2006	- nAMD - DME - RVO - NVG	- Cost-effective - Off-label
Ranibizumab (Lucentis®)	Fab fragment of humanized IgG1 antibody targeting VEGF-A	~48 kDa	0.5 mg	7.19 days	~2 hours	nAMD-2006 RVO-2010 DME-2012 Myopic CNV-2017	- nAMD - DME - RVO - Secondary ME - Secondary CNV - DR - ROP	- First FDA approved anti-VEGF for eye diseases
Aflibercept (Eylea®)	Fusion protein (VEGFR1/2 extracellular domain + Fc region) inhibiting VEGF-A, VEGF-B, PlGF	97–115 kDa	2 mg	7.13 days	5–6 days	nAMD-2011 RVO-2012 DME-2014	- nAMD - DME - RVO - DR - ROP - Myopic CNV	- Longer durability compared to ranibizumab - Can cause sterile inflammation
Aflibercept (Eylea HD®)	Fusion protein (VEGFR1/2 extracellular domain + Fc region) inhibiting VEGF-A, VEGF-B, PlGF	97–115 kDa	8 mg	7.13 days	5–6 days	2023	- nAMD - DME	- Longer durability compared to ranibizumab - Can cause sterile inflammation
Brolucizumab (Beovu®)	Single-chain antibody fragment targeting VEGF-A	26 kDa	6 mg	~57 h	4–5 days	2019	- nAMD - DME	- Smallest molecule - Long durability - Can cause retinal vasculitis
Faricimab (Vabysmo®)	Bispecific monoclonal antibody targeting VEGF-A and Angiopoietin-2	150 kDa	6 mg	7.5 days	7.5 days	2022	- nAMD - DME	- First bispecific antibody in ophthalmology - Four monthly injection - Can cause retinal vasculitis
Conbercept (Lumitin)	Recombinant fusion protein (VEGFR1/2 extracellular domain + Fc); targets VEGF-A, B, PlGF	142 kDa	0.5 mg	4.5 days	4.5 days	2013 (only in China)	- nAMD - DME - RVO	- Available in China - Phase 3 trials halted in US

Abbreviations: VEGF, vascular endothelial growth factor; FDA, Food and Drug Administration; Ig, immunoglobulin; kDa, kilodalton; mg, milligram; nAMD, neovascular age-related macular degeneration; DME, diabetic macular edema; RVO, retinal vein occlusion; NVG, neovascular glaucoma; CNV, choroidal neovascularization; ME, macular edema; DR, diabetic retinopathy; ROP, retinopathy of prematurity; US, United States; VEGFR, vascular endothelial growth factor receptor; PlGF, placental growth factor; Fc region, Fragment crystallizable region; h, hours.

Table 2. Approved biosimilars of anti-VEGF agents [15, 20, 22, 28–31, 43, 44]

Drug	Biosimilar	Approval Authority	Year
Ranibizumab	Razumab® (Intas Pharmaceuticals Ltd.)	DCGI, India	2015
	Ranizurel® (Reliance Life Sciences)	DCGI, India	2020
	Byooviz® (SB11; Ranibizumab-nuna; Samsung Bioepis, trademark of Genentech Inc.)	FDA, US; EMA, Europe	2021
	Ranieyes® (Lupin Limited)	DCGI, India	2021
	Cimerli® (Formycon, Bioeq, Coherus Biosciences)	FDA, US; EMA, Europe	2022
	Ongavia® (Teva Pharmaceutical Industries Ltd)	UKMHRA, UK	2022
	Ranivisio® (Bioeq, the Polpharma Biologics Group joint venture company)	EMA, Europe	2022
	Ximluci® (STADA Arzneimittel AG,Almanya and Xbrane Biopharma)	EMA, Europe; UKMHRA, UK	2022
Bevacizumab	BCD-021® (JSC BIOCAD)	Russian Regulatory Body	2015
	RTXM83 (mAbxience Research SL)	Argentina Regulatory Body	2016
	Cizumab® (Hetero Drug)	DCGI, India	2016
	BevaciRel® (Reliance Life Sciences)	DCGI, India	2016
	Krabeva®(Biocon, a Bangalore-based biopharmaceutical company)	DCGI, India	2017
	Zybev® (Zydus Cadila Pharmacokinetics)	DCGI, India	2017
	Abevmy® (Mylan Pharmaceuticals Pvt Ltd)	DCGI, India	2017
	Bevatas® (Intas Pharmaceuticals Ltd)	DCGI, India	2017
	ABP215 Mvasi, Mvasi® (bevacizumab-awwb) (Amgen, Thousand Oaks; Allergan)	FDA, US EMA, Europe EC, Europe	2017 2017 2018
	Zirabev ® (Bevacizumab-bvzr, Pfizer Inc.)	FDA, US; EMA, Europe	2019
	Aybintio® (Samsung Bioepis Co., Ltd.)	EC, Europe	2020
	Onbevzi® (Samsung Bioepis Co., Ltd.)	EMA, Europe	2020
	Alymsys® (Amneal Pharmaceuticals LLC)	FDA, US	2022
	Vegzelma® (Celltrion Inc.)	FDA, US	2022
Aflibercept	Yesafili® (Biocon Pharmaceuticals)	EC, Europe FDA, US	2023 2024
	Opuviz® (Samsung Bioepis Co., Ltd.)	FDA, US	2024
	Ahzantive® (Formycon AG/Klinge Biopharma GmBH)	FDA, US; EMA, Europe	2024
	Enzeevu® (Sandoz)	FDA, US	2024
	Afqlir® (Sandoz)	EC, Europe; EMA, Europe	2024
	Afilivu® (Samsung Bioepis Co., Ltd.)	MFDS, Republic of Korea	2024
	Zhuochuming® (Qilu Pharmaceutical Co.)	NMPA, China	2024
	Tyalia® (CinnaGen)	Approved in Iran	2024
	Eydenzelt® (Celltrion Inc.)	MFDS, Republic of Korea EMA, Europe	2024 2025
	Pavblu® (Amgen, Inc. Pharmaceutical company)	FDA, US EMA, Europe	2024 2025
	Skojoy® (Amgen, Inc. Pharmaceutical company)	EMA, Europe	2025

Abbreviations: VEGF, vascular endothelial growth factor; DCGI, Drug Controller General of India; FDA, Food and Drug Administration; US, United States; EMA, European Medicines Agency; UKMHRA, United Kingdom Medicines and Healthcare Products Regulatory Agency; UK, United Kingdom; EC, European Commission; MFDS, Ministry of Food and Drug Safety; NMPA, National Medical Products Administration.

Table 3. Major clinical trials of anti-VEGF agents in ophthalmology [2, 8, 13, 16, 17, 18, 46–86]

Drug	Clinical Trial (Year)	Indication	Phase	Study Design	Main Results
Ranibizumab	**MARINA (2006)** [45]	nAMD	-	Monthly 0.3 mg or 0.5 mg ranibizumab vs. sham	Two-year intravitreal ranibizumab treatment improved mean visual acuity and prevented vision loss with low serious adverse event rates in patients with minimally classic or occult MNV from AMD.
	ANCHOR (2009) [46]	nAMD	III	Monthly 0.3 mg or 0.5 mg ranibizumab injection plus sham verteporfin therapy vs. sham injections plus active verteporfin therapy	Ranibizumab was more effective than verteporfin therapy in treating patients with AMD and newly diagnosed, predominantly classic MNV.
	RISE and RIDE (2012) [47]	DME	III	Monthly 0.3 mg or 0.5 mg ranibizumab vs. sham	Ranibizumab injections improved vision-related quality of life in DME patients compared to sham injections.
	READ-3 (2016) [48]	DME	-	Mandatory injections of 0.5 mg ranibizumab vs. 2.0 mg ranibizumab 6 monthly followed by as-needed injections until month 24	2.0 mg ranibizumab offered no additional benefit over 0.5 mg.
	PAGODA (2025) [49]	DME	III	Ranibizumab, 100 mg/mL, via PDS with refill exchanges every 24 weeks (PDS Q24W) vs. monthly 0.5 ranibizumab	The PDS with ranibizumab 100 mg/mL offers an effective and durable treatment option for DME, with dosing every six months and a favorable safety profile.
	PAVILION (2025) [50]	moderately severe to severe NPDR without center-involved DME	-	Ranibizumab, 100 mg/mL, via PDS with refill exchanges every 36 weeks (PDS Q36W) vs. control	At one year, PDS Q36W significantly improved diabetic retinopathy severity scale outcomes and reduced vision-threatening complications, though early postoperative BCVA decline, and long-term safety remain important considerations.
	HARBOR (2014) [51]	nAMD	III	Monthly 0.5 mg or 2.0 mg ranibizumab vs. 0.5 mg PRN ranibizumab vs. 2.0 mg PRN ranibizumab	All groups showed similar, meaningful visual acuity gains at 24 months.
	ARCHWAY (2023) [18, 52]	nAMD	III	PDS with ranibizumab 100 mg/ml with fixed 24-week refill-exchanges (PDS Q24W) vs. Monthly 0.5 mg ranibizumab	PDS Q24W demonstrated non-inferior and equivalent efficacy to monthly ranibizumab.
	RAINBOW (2019, 2024) [53, 54]	ROP	-	Single 0.1 mg or 0.2 mg ranibizumab injection vs. laser therapy	In the treatment of ROP, ranibizumab 0.2 mg might be superior to laser therapy, with fewer unfavorable ocular outcomes than laser therapy and with an acceptable 24-week safety profile in very low birthweight infants (<1500 mg). Five-year follow-up confirmed earlier findings, including a continued decrease in high myopia rates with ranibizumab treatment.
	ARTIS (2019) [55]	nAMD and PCV	-	A single dose followed by PRN ranibizumab vs. 3 loading doses followed by PRN ranibizumab	A single dose plus PRN regimen showed non-inferior visual gains compared to three loading doses plus PRN ranibizumab.
	CANTREAT (2020) [56]	nAMD	-	T and E 0.5 mg ranibizumab vs. monthly 0.5 mg ranibizumab	T and E dosing provided vision outcomes comparable to monthly ranibizumab in nAMD over 24 months, achieving significant BCVA gains with reduced treatment burden.
	DRAGON (2020) [57]	nAMD and PCV	IV	Monthly ranibizumab from baseline to month 11, then PRN from month 12 to 23 vs. three monthly ranibizumab doses followed by PRN through month 23	The results supported the use of either ranibizumab monthly or PRN regimens in patients with nAMD, regardless of presence of PCV.
	TREND (2018) [58]	nAMD	IIIb	T and E 0.5 mg ranibizumab vs. monthly 0.5 mg ranibizumab	Ranibizumab 0.5 mg via T and E regimen was non-inferior and clinically comparable to monthly dosing in improving visual acuity from baseline to study end.
	IVAN (2013) [59]	nAMD	-	Injection of 0.5 mg ranibizumab (monthly or PRN) vs. 1.25 mg bevacizumab (monthly or PRN)	Both ranibizumab and bevacizumab demonstrated comparable efficacy. Decreasing retreatment frequency resulted in modest efficacy declines, independent of the drug used.

	PrONTO (2009) [60]	nAMD	-	Three consecutive monthly 0.5 mg ranibizumab during the first year, retreatment with ranibizumab at each monthly visit if any criterion was fulfilled: an increase in OCT-CRT of at least 100 microns or a loss of 5 letters or more. During the second year, the retreatment criteria were amended to include retreatment if any qualitative increase in the amount of fluid detected using OCT.	An OCT-guided variable dosing regimen with intravitreal ranibizumab achieved visual acuity outcomes comparable to phase III trials, with fewer injections needed.
	MINERVA (2018) [61]	MNV (uncommon cause)	III	PRN 0.5 mg ranibizumab vs. PRN sham	Ranibizumab 0.5 mg was effective in treating MNV of varied etiologies by month 2, with no additional safety concerns.
	CRUISE (2011) [2, 62]	CRVO	III	Monthly 0.3 mg ranibizumab vs. monthly 0.5 mg ranibizumab vs. sham	Injection of 0.3 mg or 0.5 mg ranibizumab provided rapid improvement in 6-month visual acuity and macular edema following CRVO, with low rates of ocular and non-ocular safety events.
	RETAIN (2016) [63]	DME	-	T and E 0.5 mg ranibizumab vs. T and E 0.5 mg ranibizumab + laser vs. PRN 0.5 mg ranibizumab	T and E is a feasible treatment option for patients with DME, with a potential to reduce treatment burden.
	RELATE (2015) [64]	RVO	-	0.5 mg vs. 2.0 mg ranibizumab every 4 weeks for 24 weeks and re-randomized to PRN ranibizumab plus laser or ranibizumab alone.	There was no short-term significant benefit from monthly injections of 2.0 mg vs. 0.5 mg ranibizumab injections and no long-term benefit in BCVA, resolution of edema, or number of ranibizumab injections obtained by addition of laser treatment to ranibizumab.
	SHORE (2014) [65]	RVO	-	Monthly 0.5 mg ranibizumab for 7 months, followed by PRN ranibizumab vs. monthly 0.5 mg ranibizumab for 7 months, followed by continued monthly ranibizumab	After edema resolution from 7 or more monthly ranibizumab injections in RVO subjects, visual outcomes at month 15 were excellent and not significantly different in subjects treated PRN versus those who continued monthly injections.
	CRYSTAL (2016 and 2018) [66, 67]	CRVO	IIIb	Patients received ranibizumab 0.5 mg injections (minimum of three) until visual acuity stabilized for three consecutive months, after which further injections were given if monitoring revealed vision loss attributable to disease activity.	An individualized, stabilization criteria-driven dosing regimen of ranibizumab 0.5 mg led to sustained visual acuity gains for up to 24 months in patients with CRVO.
	BRIGHTER (2017) [68]	BRVO	-	Three monthly 0.5 mg ranibizumab followed by PRN vs. 3 monthly 0.5 mg ranibizumab + laser followed by PRN vs. laser with optional 0.5 mg ranibizumab after month 6	The study results confirmed the long-term efficacy and safety profile of PRN dosing driven by individualized visual acuity stabilization criteria using ranibizumab 0.5 mg in patients with BRVO.
	CARE-ROP (2022) [69]	ROP	-	Injection of 0.12 mg ranibizumab vs. 0.2 mg ranibizumab	Ranibizumab was effective in controlling acute ROP and that 24% of the standard adult dose (0.12 mg) appears equally effective as 40% (0.2 mg).
Bevacizumab	**CATT (2011)** [70]	nAMD	-	Injection of 0.5 mg ranibizumab (monthly) vs. 1.25 mg bevacizumab (monthly)	After one year, bevacizumab and ranibizumab demonstrated comparable visual acuity outcomes when administered identically. Ranibizumab given as needed with monthly evaluations achieved vision outcomes equivalent to monthly dosing.
	DRCR.net Protocol T (2016) [71]	DME	-	Injection of 2.0 mg aflibercept vs. 1.25 mg bevacizumab vs. 0.3 mg ranibizumab first 6 months; monthly. Months 6–12; monthly evaluations; treatment paused/resumed per protocol. Months 12–24; visits every 4–16 weeks based on clinical status.	All three anti-VEGF treatments improved vision over two years, with fewer injections needed in the second year. For patients who started with better vision, outcomes were similar across treatments. In those with worse initial vision, aflibercept showed better results than bevacizumab at two years, while its earlier advantage over ranibizumab disappeared.
	SCORE2 (2017) [72]	CRVO	-	Injection of 1.25 bevacizumab every 4 weeks vs. 2.0 mg aflibercept every 4 weeks	Bevacizumab was non-inferior to aflibercept with respect to visual acuity after 6 months of treatment.

	BEAT-ROP (2011) [8]	ROP	-	Injection of 0.625 mg bevacizumab vs. laser therapy	Bevacizumab compared with conventional laser therapy, in infants with stage 3+ ROP showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina.
Aflibercept	**VIEW 1 and 2 (2012)** [73]	nAMD	III	Injection of 0.5 mg ranibizumab every 4 weeks (Rq4) vs. 2.0 mg aflibercept every 4 weeks (2q4) vs. 0.5 mg aflibercept every 4 weeks (0.5q4) vs. 2 mg aflibercept every 8 weeks after 3 initial monthly doses (2q8)	All aflibercept and ranibizumab groups were equally effective in improving and maintaining visual acuity over 96 weeks. The 2q8 aflibercept group achieved similar visual outcomes to ranibizumab with approximately five fewer injections.
	VISTA and VIVID (2015) [74]	DME	III	Laser vs. aflibercept (q4w/q8w)	The visual and anatomical superiority of aflibercept over laser at week 52 was maintained through week 100, with comparable outcomes between the 2 mg every 4 weeks and 2 mg every 8 weeks regimens
	PULSAR (2024) [17]	nAMD	III	Injection of 8 mg aflibercept every 12 weeks, vs. 8 mg aflibercept every 16 weeks vs. 2 mg aflibercept every 8 weeks	Injection of 8 mg aflibercept showed efficacy and safety with extended dosing intervals.
	FIREFLEYE (2024) [75]	ROP	III	Injection of 0.4 mg aflibercept vs. laser therapy	Aflibercept compared with laser therapy did not meet criteria for non-inferiority with respect to the primary outcome of the proportion of infants achieving treatment success at week 24.
	ALTAIR (2020) [76]	nAMD	-	T and E aflibercept with either 2-week adjustments vs. T and E aflibercept with either 4-week adjustments	In treatment-naive exudative AMD, aflibercept delivered through two T and E regimens led to functional and anatomical improvements at week 52, with stability maintained to week 96. No meaningful differences were observed between the 2- and 4-week groups.
	ARIES (2021) [77]	nAMD	IIIb/IV	Patients received 2 mg intravitreal aflibercept at week (W) 0, W4, W8, and W16. At W16, patients were randomized 1:1 to early-start (2W interval adjustments) or late-start (8W intervals until W48 then 2W interval adjustments) T and E.	Early and late T and E regimens of aflibercept led to similar 2-year outcomes in nAMD, with just one injection difference.
	RIVAL (2020) [78]	nAMD	IV	T and E 0.5 mg ranibizumab vs. T and E 2 mg aflibercept	Ranibizumab and aflibercept showed no significant differences in the incidence or progression of macular atrophy over 24 months.
	QUASAR (2024) [79]	RVO	III	Injection of 8 mg aflibercept every 8 weeks following 3 initial monthly doses vs. 8 mg aflibercept every 8 weeks following 5 initial monthly doses vs. 2 mg aflibercept every 4 weeks	Injection of 8 mg aflibercept formulation demonstrated non-inferior vision gains with 8-week dosing intervals compared to monthly 2 mg dosing, with approximately 90 % of patients maintaining extended intervals through 36 weeks.
	COPERNICUS (2014) [80]	CRVO	III	Injection of 2 mg aflibercept every 4 weeks up to week 24, followed by PRN 2 mg aflibercept vs. sham every 4 weeks up to week 24, followed by PRN 2 mg aflibercept	The visual and anatomic improvements after fixed dosing through week 24 and PRN dosing with monthly monitoring from weeks 24 to 52 were diminished after continued PRN dosing, with a reduced monitoring frequency from weeks 52 to 100.
	GALILEO (2014) [81]	CRVO	III	Injection of 2 mg aflibercept every 4 weeks up to week 20, followed by PRN 2 mg aflibercept vs. sham	Aflibercept provided significant functional and anatomic benefits after 52 weeks as compared with sham. The improvements achieved after 6 monthly doses at week 24 largely were maintained until week 52 with as-needed dosing.
	LEAVO (2019) [82]	CRVO	-	Injection of 2 mg aflibercept vs. 0.5 mg ranibizumab vs. 1.25 mg bevacizumab	Aflibercept was non-inferior to ranibizumab. Bevacizumab is an economically attractive treatment alternative and would lead to substantial cost savings
Brolucizumab	**HAWK and HARRIER (2020)** [16]	nAMD	III	Injection of 3 mg brolucizumab vs. 6 mg brolucizumab vs. 2 mg aflibercept	Brolucizumab was non-inferior to aflibercept in visual function at week 48, and >50% of brolucizumab 6 mg-treated eyes were maintained on q12w dosing interval through week 48.

	KESTREL and KITE (2022) [83]	DME	III	Injection of brolucizumab 3 mg/6 mg or aflibercept 2 mg in KESTREL or brolucizumab 6 mg or aflibercept 2 mg in KITE	Brolucizumab 6 mg showed robust visual gains and anatomical improvements with an overall favorable benefit/risk profile in patients with DME.
	MERLIN (2025) [84]	Recalcitrant nAMD	-	Injection of 6 mg brolucizumab every 4 weeks vs. 2 mg aflibercept every 4 weeks	Visual acuity outcomes in previously treated participants with nAMD and persistent retinal fluid receiving brolucizumab 6 mg dosed every 4 weeks were non-inferior to aflibercept 2 mg dosed every 4 weeks, with superior anatomic outcomes.
Faricimab	**TENAYA and LUCERNE (2022) [13]**	nAMD	III	Q16W Faricimab vs. Q8W aflibercept	Faricimab demonstrated non-inferiority to aflibercept. No cases of retinal vasculitis or retinal occlusive events occurred.
	YOSEMITE and RHINE (2022) [85]	DME	III	Q8W faricimab vs. T and E faricimab up to Q16W vs. Q8W aflibercept	Faricimab Q8W demonstrated non-inferior visual outcomes to aflibercept Q8W, with comparable safety profiles.
	BALATON and COMINO (2023) [86]	RVO	III	Monthly injection of 6 mg faricimab up to week 24, followed by faricimab up to week 72 vs. 2 mg aflibercep up to week 24, followed by faricimab up to week 72	Faricimab, administered at a dose of 6 mg, demonstrated comparable efficacy to aflibercept (2 mg) in improving BCVA and reducing central retinal thickness in patients diagnosed with BRVO, CRVO, or hemicentral RVO.

Abbreviations: nAMD, neovascular age-related macular degeneration; mg, milligram; MNV, macular neovascularization; DME, diabetic macular edema; PDS, port delivery system; NPDR, non-proliferative diabetic retinopathy; BCVA, best-corrected visual acuity; PRN, pro re nata; ROP, retinopathy of prematurity; PCV, polypoidal choroidal vasculopathy; T and E, treat and extend; OCT, optical coherence tomography; CRT, central retinal thickness; CRVO, central retinal vein occlusion; RVO, retinal vein occlusion; BRVO, branch retinal vein occlusion; VEGF, vascular endothelial growth factor.

Clinical Ophthalmic Indications

I. Posterior segment

1- Anti-VEGF Therapy in Diabetic Macular Edema and Proliferative Diabetic Retinopathy

Intravitreal anti-VEGF agents are now considered the standard first-line therapy for center-involved DME [87]. Cochrane reviews of randomized controlled trials have provided robust evidence supporting the superiority of anti-VEGF agents over macular laser therapy in the management of center-involved DME [88, 89].

Anti-VEGF therapy for DME resulted in an average improvement of 5 letters in best-corrected visual acuity over a 12-month period in routine clinical practice, beginning from a baseline visual acuity of 59 letters. This visual gain is smaller than those reported in registrational randomized controlled trials, where intravitreal ranibizumab and aflibercept achieved improvements of approximately 10 and 11 letters, respectively [47, 90]. The DRCR.net Protocol T study demonstrated that all three anti-VEGF agents provided similar overall improvements in visual acuity from baseline to 24 months, with a reduced number of injections required in the second year [71].

In a recent randomized controlled trial on initial treatment of DME with bevacizumab, 70% of eyes had to be switched to aflibercept [91]. Significant anatomical improvements were observed after patients with persistent DME, resistant to bevacizumab or ranibizumab, were switched to aflibercept [92].

Brolucizumab, a single-chain antibody fragment, received approval for the treatment of DME in June 2022. The KESTREL and KITE clinical trials demonstrated that brolucizumab was non-inferior to aflibercept in visual outcomes, with a higher proportion of patients achieving a central macular thickness <280 μm [83].

Brolucizumab has a smaller molecular size compared to commercially available ranibizumab and aflibercept. This enables a stronger binding affinity to VEGF compared to the other agents [93]. Faricimab's effectiveness and safety in treating DME were examined in the YOSEMITE and RHINE studies. Results showed that it matched aflibercept in visual outcomes. In both trials, personalized faricimab treatment interval group had fewer monitoring visits and longer dosing intervals, with over half receiving faricimab every 16 weeks at one year, increasing to over 60% by the second year [85].

Aflibercept 8 mg was designed by increasing the concentration of the 2-mg version, with the intention of delivering a higher dose and longer-lasting effects [94]. In non-vitrectomized eyes with DME, a comparative study evaluating 2-mg and 8-mg doses of aflibercept found no significant differences in functional outcomes or anatomical improvements [95]. Following panretinal photocoagulation, vitreous hemorrhage occurs in roughly 32–39% of individuals with proliferative diabetic retinopathy [96]. Intravitreal anti-VEGF injections have recently been reported to offer improved outcomes compared to panretinal photocoagulation in patients diagnosed with proliferative diabetic retinopathy [97, 98] (Figures 1 and 2).

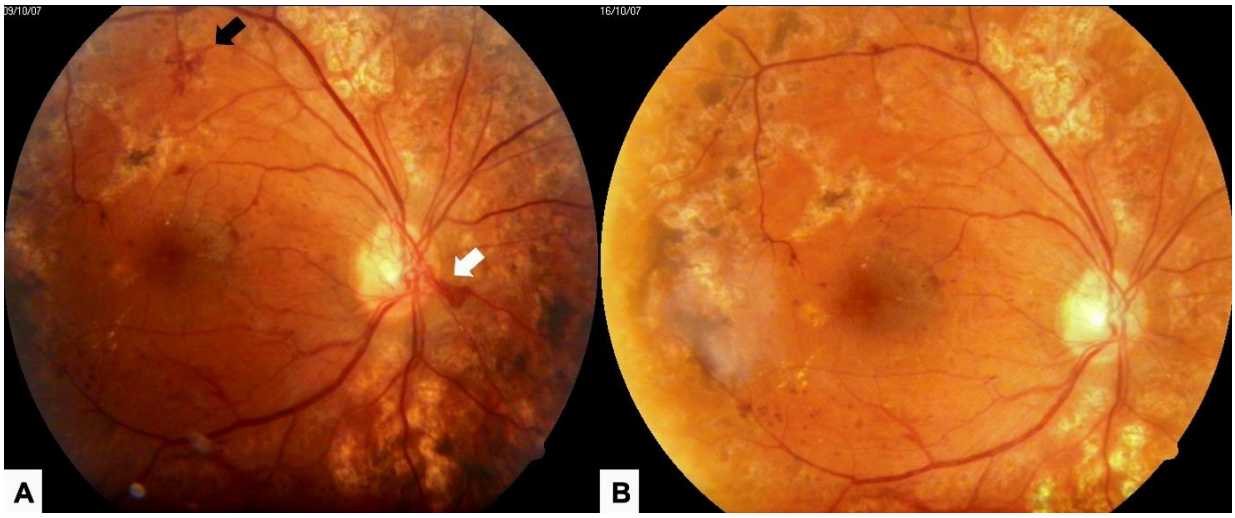

Figure 1. Color fundus (Visucam® 500, Carl Zeiss Meditec AG, Jena, Germany) picture of the right eye of a diabetic patient with previous panretinal photocoagulation taken in 2007 with (A) neovascularization elsewhere (NVE) (black arrow) and neovascularization of the disc (NVD) (white arrow). (B) Both NVE and NVD regressed one week after a single intravitreal injection of bevacizumab (1.25 mg) (Avastin®; Genentech, Inc., South San Francisco, CA, USA).

2- Anti-VEGF Therapy in Neovascular Age-Related Macular Degeneration: Current Approaches and Clinical Outcomes

Over the past 15 years, the introduction of anti-VEGF therapy as the standard treatment for nAMD has led to a 50% reduction in blindness associated with the condition [99]. Several anti-VEGF treatment protocols exist for nAMD, including fixed dosing, treat-and-extend, and pro re nata approaches [100].

Recent real-world studies have shown that anti-VEGF agents bevacizumab, ranibizumab, and aflibercept 2.0 mg are effective treatments for nAMD [101–103]. The recommended regimen consists of three initial monthly doses, then monthly administration of ranibizumab until optimal visual acuity, or dosing of intravitreal aflibercept every two months [104]. Newer therapies for nAMD such as brolucizumab, faricimab, and aflibercept 8 mg have recently yielded similar visual improvements compared to aflibercept 2 mg [13, 16, 17].

Studies have demonstrated that higher doses of anti-VEGF agents can lead to improved anatomical outcomes and enhanced treatment durability [51, 105]. Aflibercept 8.0 mg, designed for greater efficacy and longer-lasting effects, was FDA-approved on 18 August 2023 for treating nAMD. Its enhanced VEGF affinity and estimated half-life support extended dosing intervals up to 16 weeks, following an initial phase of three monthly injections [17]. In the 44-week phase II CANDELA trial with 106 neovascular age-related macular degeneration patients, aflibercept 8.0 mg was evaluated and found to have a safety profile like the 2.0 mg dose when given on the same schedule (three monthly injections plus doses at weeks 20 and 32). The 8.0 mg group showed better anatomical and visual outcomes, with more patients free of fluid in the central subfield by week 16 [106].

Interim data from the PORTAL study suggest that long-term use of the PDS delivering ranibizumab 100 mg/mL maintains stable visual and anatomical outcomes for up to four years and is generally preferred to monthly intravitreal ranibizumab injections in individuals with nAMD [107].

Faricimab was approved for nAMD in the UK by the National Institute for Health and Care Excellence (NICE) in June 2022, after results from the TENAYA and LUCERNE trials showed it provided visual outcomes comparable to aflibercept 2 mg [13]. Dual inhibition of angiopoietin-2 and VEGF-A is thought to synergistically improve vascular stability and reduce neovascularization and inflammation, potentially offering more durable treatment outcomes than VEGF-only therapies [99]. Recent real-world studies have demonstrated that faricimab injections are effective in previously treated nAMD patients, showing improvement or maintenance of visual acuity alongside rapid anatomical improvements [108, 109].

Brolucizumab was approved by the FDA in 2019 for nAMD based on the HAWK and HARRIER studies, which showed it to be as effective as aflibercept, with superior anatomical outcomes and longer injection intervals. However, adverse events related to intraocular inflammation (IOI), including retinal vasculitis with or without occlusion, have been reported [110]. Intraocular inflammation occurred in 4.6% of patients treated with intravitreal brolucizumab in the HAWK and HARRIER phase III clinical trials for nAMD [16].

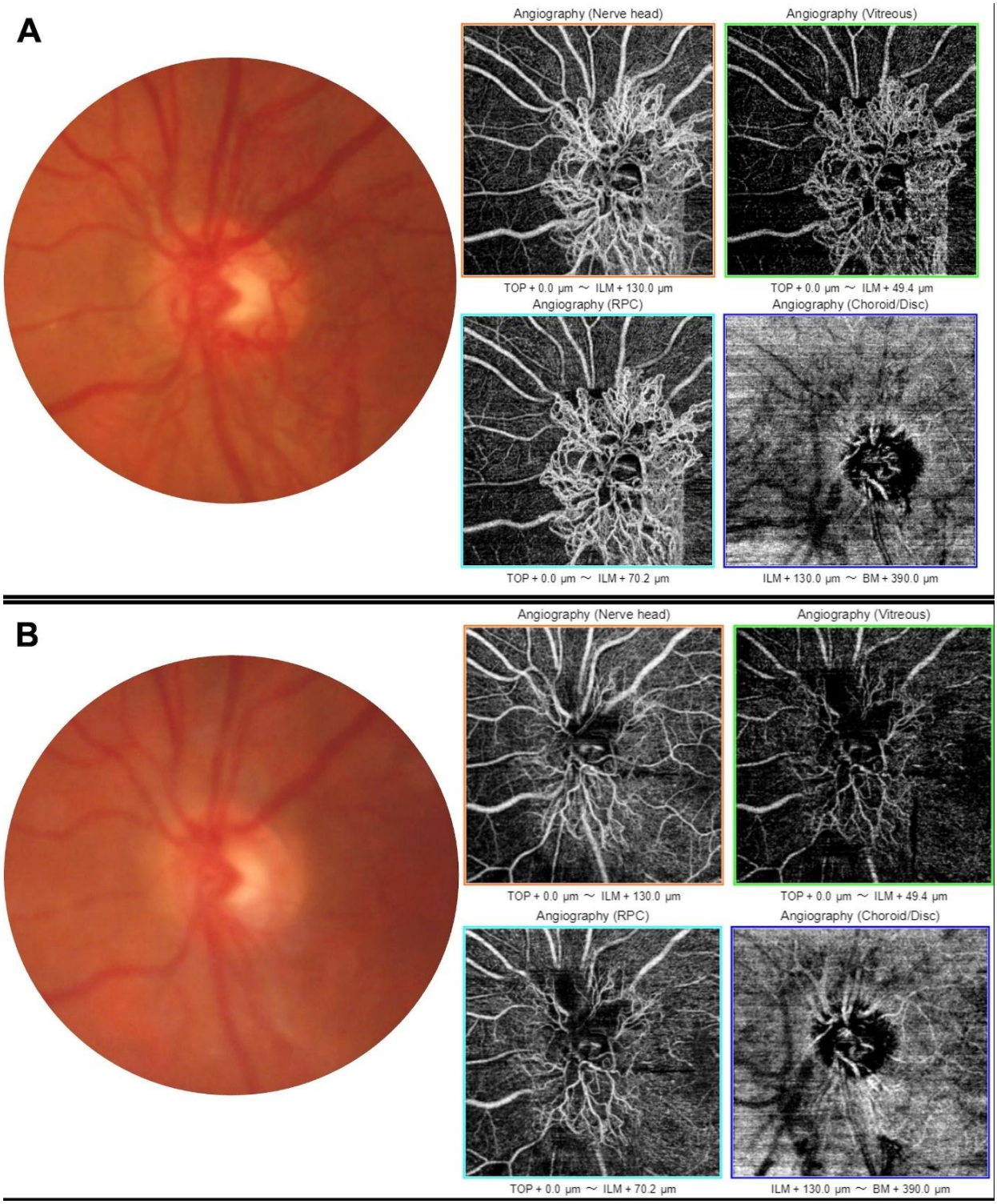

Figure 2. Color fundus photographs (Visucam® 500, Carl Zeiss Meditec AG, Jena, Germany) and swept-source optical coherence tomography angiography (OCTA) (Triton, Topcon Inc., Oakland, New Jersey, USA) images of the optic disc in a patient with diabetes mellitus and proliferative disease before and after the intravitreal aflibercept (2 mg) (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA) injection. (A) Pre-injection images demonstrating the prominent neovascularization of the optic disc on the color fundus photograph, along with pathological vascular proliferation in the nerve head, vitreous, radial peripapillary capillary, and choroid/disc interface slabs on OCTA. (B) One month after a single intravitreal injection of aflibercept, marked regression of the neovascularization and a significant reduction in pathological vascular flow signals across all OCTA slabs are observed.

3- Anti-VEGF Therapy in Myopic Macular Neovascularization

Macular neovascularization is among the most frequent vision-threatening complications of pathologic myopia. If left untreated, myopic macular neovascularization typically results in progressive vision loss and a poor visual prognosis [111].

Anti-VEGF therapy via intravitreal injection is the standard of care for treating myopic macular neovascularization [112]. Numerous clinical trials have demonstrated the efficacy of intravitreal injections of ranibizumab (the RADIANCE study/FDA) [113], bevacizumab, and aflibercept (the MYRROR study) [114–116]. In myopic macular neovascularization, treatment typically follows a pro re nata retreatment approach after the initial injection [117].

NICE approved ranibizumab for myopic macular neovascularization in November 2013 and aflibercept in 2017 [118]. In 2017, conbercept received regulatory approval from the China FDA (National Medical Products Administration [NMPA]) for use in myopic macular neovascularization, highlighting its safety and clinical effectiveness in treating macular neovascularization [119].

4- Anti-VEGF Therapy in Non-Neovascular Age-Related Macular Degeneration Macular Neovascularization

The MINERVA study [61] is the first large-scale, prospective, randomized, double-masked Phase III trial specifically designed to evaluate the efficacy and safety of ranibizumab 0.5 mg in adults with macular neovascularization due to rare causes other than nAMD and pathologic myopia. The study population was stratified into five predefined subgroups based on underlying etiology: idiopathic, angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, and miscellaneous causes. Ranibizumab demonstrated a sustained and clinically meaningful improvement in visual acuity, with a mean gain of +11.0 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 12 months. Subgroup analyses confirmed consistent benefits across all etiologies, with particularly notable outcomes in idiopathic, angioid streak-related, and miscellaneous macular neovascularization. Overall, the findings offer meaningful clinical support for the use of ranibizumab in non-nAMD macular neovascularization, addressing a previously unmet need in the management of these rare entities [61].

5- Anti-VEGF Therapy in Retinal Vein Occlusion

Intravitreal anti-VEGF therapy is commonly employed as the first-line approach for managing macular edema resulting from retinal vein occlusion [42]. Retinal vein occlusion triggers hypoxia and VEGF overproduction, which increases vascular leakage and causes macular edema. Elevated VEGF may also worsen retinal ischemia, further aggravating the disease [120]. By inducing phosphorylation of tight junction proteins, VEGF compromises the integrity of the blood-retinal barrier, leading to fluid leakage and the formation of macular edema. For this reason, anti-VEGF therapies offer a focused and effective treatment option for managing macular edema associated with retinal vein occlusion [121].

Ranibizumab, aflibercept, and bevacizumab are the primary anti-VEGF medications widely prescribed to manage macular edema caused by retinal vein occlusion [122]. The FDA has approved ranibizumab, aflibercept, and faricimab for treating macular edema, including cases related to retinal vein occlusion (Figure 3). However, brolucizumab is not currently authorized for retinal vein occlusion treatment [123, 124].

According to the results of a meta-analysis, studies on central retinal vein occlusion involving ranibizumab, aflibercept, and faricimab reported no significant differences in baseline characteristics such as mean age, gender distribution, ETDRS letter scores, or intraocular pressure [42]. Similarly, in branch retinal vein occlusion comparisons between ranibizumab, aflibercept, and laser or sham controls showed no notable baseline disparities. The primary outcome: improvement in visual acuity at six months demonstrated a clear benefit of anti-VEGF treatment. At both six and twelve months, patients receiving anti-VEGF therapy were more likely to gain over 15 ETDRS letters. The risk of losing more than 15 letters at six months was lower in the anti-VEGF group [42].

In the LEAVO trial [82], 463 patients with macular edema resulting from central retinal vein occlusion were randomized equally to receive bevacizumab, ranibizumab, or aflibercept. Visual acuity gains with aflibercept were shown to be comparable to those achieved with ranibizumab. However, comparison between bevacizumab and ranibizumab yielded inconclusive results, leaving uncertainty as to whether bevacizumab results in inferior visual improvements [82].

Both the BALATON and COMINO studies also found that faricimab (6 mg) matched aflibercept (2 mg) in improving visual acuity and reducing retinal thickness among patients with branch retinal vein occlusion, central retinal vein occlusion, or hemicentral retinal vein occlusion [86].

Anti-VEGF agents are widely accepted as the primary treatment modality for macular edema due to branch retinal vein occlusion [42]. Timely intervention is critical for maximizing visual recovery. Outcome differences among various anti-VEGF agents are minimal. A regimen of monthly intravitreal injections with vigilant surveillance is advised until disease control is achieved [122, 125].

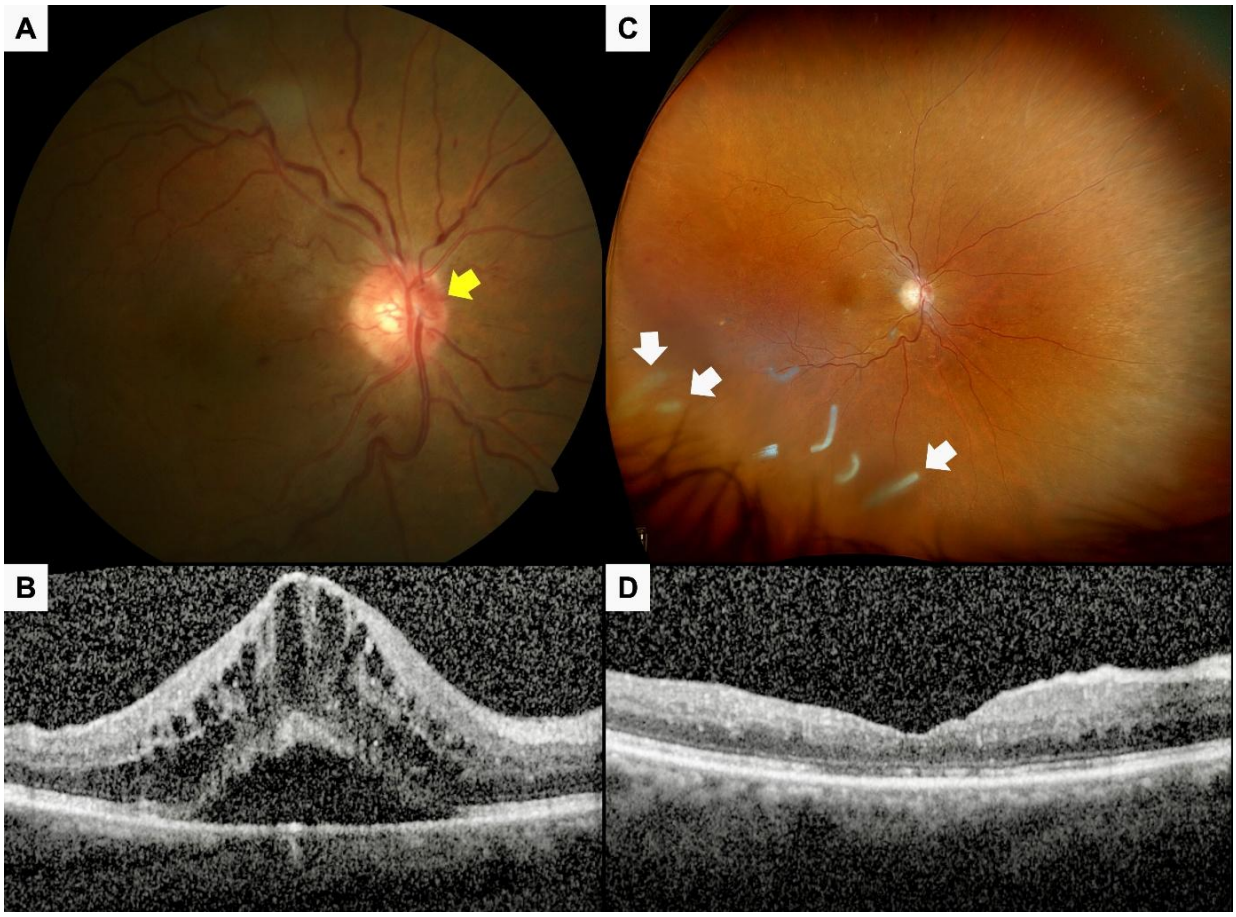

Figure 3. Color fundus image (Visucam® 500, Carl Zeiss Meditec AG, Jena, Germany) (A) showing the optociliary shunt (yellow arrow), a few retinal hemorrhages, and some vascular engorgement; transfoveal spectral-domain optical coherence tomography (OCT) (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) section (B) revealing the cystoid macular edema in a nonischemic type retinal vein occlusion with suboptimal response to three-monthly dexamethasone implants (Ozurdex®; Allergan Inc, Irvine, CA, USA). (C and D) One month after the first intravitreal faricimab (6 mg) injection (Vabysmo®; Roche-Genentech), resolution of the macular edema and remnants of the previous dexamethasone implants were seen in (C) fundus image (Optos California RGB; Nikon, Dunfermline, Scotland) and (D) macular OCT.

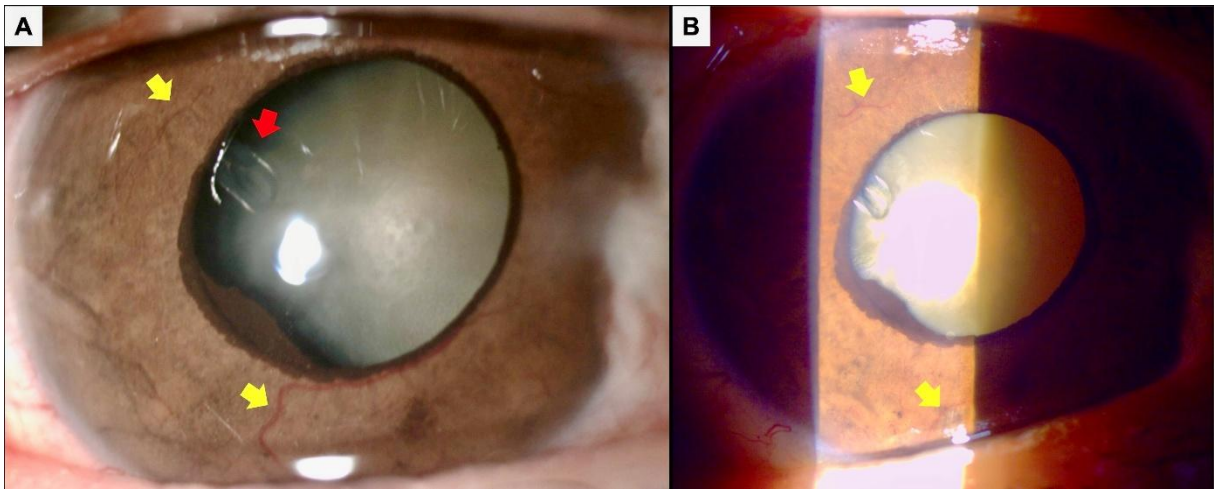

Figure 4. (A) Prominent iris neovascularization (yellow arrows), a dense nuclear cataract, and the tip of the Ahmed glaucoma valve tube implanted in the sulcus (red arrow) on the anterior segment photograph (Model DC-3, Topcon Corporation, Tokyo, Japan) of a male patient with neovascular glaucoma. (B) Marked regression of iris neovascularization 9 days after a single intravitreal injection of ranibizumab (0.5 mg) (Lucentis®, Genentech Inc., San Francisco, CA, USA) (Courtesy of Professor Gul Arikan).

6- Anti-VEGF Therapy in Retinopathy of Prematurity

Anti-VEGF drugs are becoming more widely used to treat retinopathy of prematurity. Several agents have been studied for their potential benefits in this condition, including bevacizumab, ranibizumab, aflibercept, conbercept, and pegaptanib [126]. To date, bevacizumab remains the most widely studied intravitreal anti-VEGF agent for the treatment of retinopathy of prematurity [127, 128]. In preterm infants, its systemic half-life can extend to approximately 21 days [129]. The accepted standard dose of bevacizumab for the treatment of retinopathy of prematurity is 0.625 mg administered in 0.025 mL [126].

One of the landmark studies highlighting the efficacy of intravitreal bevacizumab in treating retinopathy of prematurity was the BEAT-ROP trial [8], which provided early evidence supporting its use in Zone I and posterior Zone II disease. The trial demonstrated a significantly lower recurrence rate in Zone I with intravitreal bevacizumab compared to conventional laser therapy [8]. Similarly, the RAINBOW study [54] established the effectiveness of intravitreal ranibizumab in managing retinopathy of prematurity among very low birth weight infants, offering another viable anti-VEGF treatment alternative to laser therapy [54]. Among anti-VEGF therapies, ranibizumab is considered preferable in premature infants because of its reduced serum half-life, which may lower the risk of systemic exposure [126]. Bevacizumab, administered at doses of 0.625 mg and 0.325 mg, was the most frequently reported anti-VEGF agent used. It was followed by ranibizumab, commonly given at 0.2 mg and 0.1 mg [130].

In February 2023, the FDA granted approval for intravitreal aflibercept as a treatment option for retinopathy of prematurity in infants [131]. FIREFLEYE was a 24-week, phase III open-label randomized trial comparing intravitreal aflibercept (0.4 mg) with laser therapy in infants with advanced retinopathy of prematurity [75]. After 24 weeks, aflibercept had a success rate of 85.5%, while laser had 82.1%. In Zone I disease, the success rate was 70.8% for aflibercept and 64.4% for laser. However, aflibercept did not meet the official criteria to be considered "not worse than" laser therapy [75].

II. Anterior Segment

1- Anti-VEGF Therapy in Neovascular Glaucoma and Its Role in Glaucoma Surgery

Neovascular glaucoma represents a secondary glaucoma subtype caused by ischemic changes in ocular structures [132]. Persistent hypoxia and ischemia in the eye promote the expression and distribution of angiogenic factors like VEGF and inflammatory cytokines such as IL-6. This cascade facilitates pathological neovascularization and fibrovascular membrane formation over critical anterior segment structures, obstructing aqueous outflow and leading to elevated intraocular pressure [133]. Anti-VEGF therapies have marked a breakthrough in the treatment of neovascular glaucoma. However, due to their brief duration of action they are insufficient as sole treatment options [134].

Scarring of the filtration channel, an important factor in bleb dysfunction, has been linked to VEGF activity, positioning it as a promising target for intervention [135]. Anti-VEGF drugs like bevacizumab are used during needling to maintain outflow but may cause adverse effects [136]. Sun et al. [136] achieved an 81.25% success rate with subconjunctival injection of conbercept after needling, comparable to prior results obtained using anti-metabolites alongside needle revision [136].

The Ahmed valve includes a pressure-responsive mechanism that allows fluid drainage only within an intraocular pressure range of 8–14 mmHg, helping to prevent overdrainage after surgery. This makes it a more suitable option than standard trabeculectomy for treating neovascular glaucoma [137, 138]. Given VEGF's pivotal role in promoting angiogenesis and fibroblast activation, intravitreal administration of anti-VEGF agents has been suggested as an adjunctive treatment for neovascular glaucoma [139]. Preoperative use has been associated with rapid regression of neovessels in the iris and angle, leading to reduced intraoperative bleeding, a lower incidence of postoperative hyphemia and fibrovascular occlusion of the drainage tube, and improved surgical outcomes with the Ahmed Glaucoma Valve [140] (Figure 4).

Ranibizumab and bevacizumab have proven effective in slowing neovascular growth and minimizing leakage in eye diseases involving abnormal vessel formation [141]. Several studies have evaluated how safe and effective preoperative intravitreal bevacizumab is in managing neovascular glaucoma [142, 143]. Intraocular bevacizumab can reduce neovessels in the angle, lower intraocular pressure, and decrease aqueous VEGF levels [144]. Klettner and Roider [145] found that ranibizumab was more effective than bevacizumab at inhibiting VEGF *in vitro* [145]. Only a small number of studies have investigated the application of intravitreal ranibizumab in neovascular glaucoma patients receiving Ahmed Glaucoma Valve implants [146–149]. Kaushik et al. [137] assessed the effect of administering ranibizumab alongside initial Ahmed Glaucoma Valve implantation on intraocular pressure over a three-year follow-up. Both the group receiving Ahmed Glaucoma Valve implantation with adjunctive intravitreal ranibizumab and the group treated with Ahmed Glaucoma Valve alone demonstrated a significant reduction in intraocular pressure after three years [137].

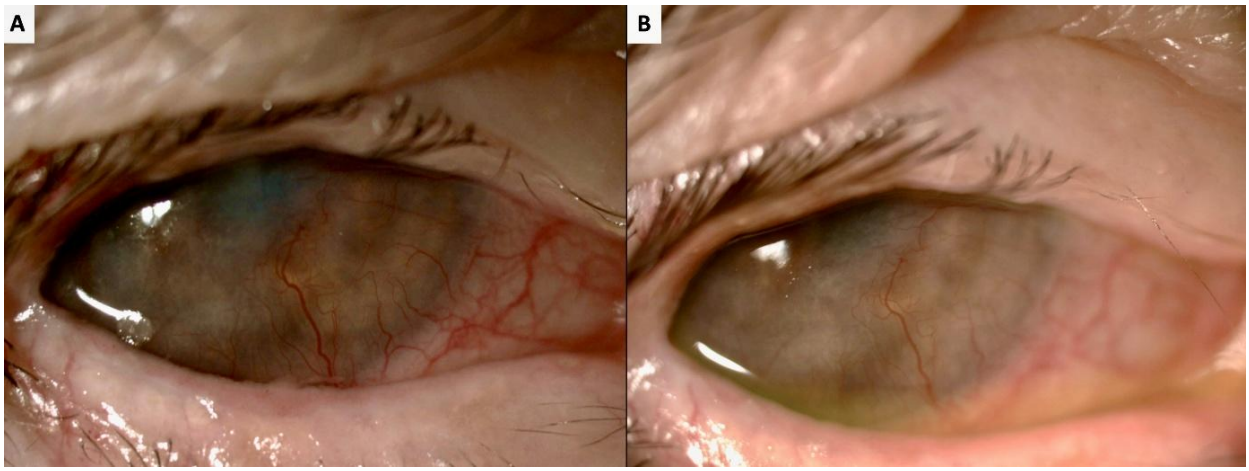

Figure 5. Anterior segment photographs (Model DC-3, Topcon Corporation, Tokyo, Japan) of an 82-year-old male patient with herpetic keratouveitis demonstrating corneal neovascularization in the inferonasal peripheral cornea of the right eye prior to (A) and after (B) a single subconjunctival aflibercept (2 mg) (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA) administration, showing marked regression of the corneal neovascularization. (Courtesy of Professor Canan Asli Utine)

2- ***Anti-VEGF Therapy in Corneal Neovascularization***

Corneal neovascularization refers to the abnormal growth of blood vessels from the limbus into the normally avascular cornea, compromising its transparency and significantly impairing visual acuity. It can be triggered by various causes, including infections, chemical burns, trauma, autoimmune disorders, prior corneal surgeries, prolonged contact lens use, and other inflammatory stimuli [150].

Corneal neovascularization is commonly managed in its early phase with topical steroid therapy. Once the condition progresses, treatment choices are scarce and usually involve surgery, which tends to have a poor prognosis or no viable options at all [151]. More recently, off-label use of anti-VEGF therapies has emerged as a treatment option for corneal neovascularization, expanding beyond their approved indications [152]. Experimental studies show that locally-administered anti-VEGF via topical, subconjunctival, intrastromal, or intraocular routes can reduce neovascularization by approximately 15–20%, while clinical studies report reductions ranging from 36% to 61% [153–157] (Figure 5).

Inhibition of VEGF signaling disrupts key processes like endothelial cell survival, proliferation, and migration, thereby halting the development of pathological neovascularization in the cornea [158]. Bevacizumab is often administered to the cornea via compounded topical solutions (commonly 5 mg/ml, 5x/day) as well as subconjunctival or intrastromal injections [159, 160]. Its use in early anti-VEGF studies targeting corneal neovascularization showed potential; however, the overall effectiveness was likely diminished due to the molecule's high molecular weight, which hinders epithelial permeability and drug diffusion [161]. Topical absorption of bevacizumab is often limited by the eye's natural barriers, yet can penetrate a vascularized cornea more effectively [160, 162]. Subconjunctival injections can improve drug delivery, but they may also cause localized side effects. Both approaches present certain drawbacks, including the high cost of compounded eye drop formulations and the risk of systemic exposure following subconjunctival administration [155, 163].

Ranibizumab possesses potent antiangiogenic activity, concurrently inhibiting hemangiogenesis and lymphangiogenesis, thereby underscoring its promise as a therapeutic agent in corneal neovascularization [164]. Topical administration of a 1% ranibizumab solution is shown to reduce the area occupied by mature neovessels and decrease vessel diameter, without inducing significant changes in vessel length [165]. In animal models, early subconjunctival injection following alkali injury effectively suppressed new vessel formation in the cornea. It significantly lowered VEGF levels in multiple ocular tissues, including the cornea, conjunctiva, aqueous humor, and iris [166]. Successful treatment of corneal neovascularization has also been reported with topical administration and intrastromal injection [167, 168].

Topical administration of aflibercept in concentrations of 0.1% and 0.01% is shown to significantly suppress corneal neovascularization and VEGF expression in a rabbit model where corneal neovascularization was induced by suturing [169]. In a separate experimental setting a single subconjunctival injection of aflibercept administered at the time of corneal transplantation led to a notable reduction in donor-derived vascularization and enhanced graft survival in a high-risk murine model [170].

Conbercept is a novel anti-VEGF agent consisting of a humanized soluble VEGF receptor protein. This fusion protein effectively neutralizes all VEGF-A, VEGF-B, VEGF-C isoforms, as well as PlGF, demonstrating a particularly strong affinity for VEGF-A165 [171]. Du et al. [172] demonstrated that both subconjunctival and intrastromal injections of conbercept significantly suppress the initiation and progression of corneal neovascularization, although they do not fully reverse the condition, regardless of whether treatment occurs during the early or late stages [172].

III. Miscellaneous Indications

Beyond their well-established indications, anti-VEGF agents have also been utilized in a variety of less common or emerging ophthalmic conditions, such as retinal neovascularization secondary to rickettsial retinitis [173]; submacular hemorrhage associated with pathological myopia or angioid streaks [44]; idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome [174]; disc neovascularisation due to direct carotid cavernous fistula [175]; occlusive retinal vasculitis [176]; non-arteritic anterior ischemic optic neuropathy [177]; and choroidal metastasis (combined with photodynamic therapy) [178].

In addition, anti-VEGF therapy has been reported in cases of secondary macular edema and/or macular neovascularization associated with various forms of uveitis [179–181], diffuse choroidal hemangioma in Sturge-Weber Syndrome [182], hereditary retinal disorders such as fundus flavimaculatus [183], Coats-Like retinitis pigmentosa [184], Peripherin-2-associated retinopathy [185], immune checkpoint inhibitor use [186], radiation retinopathy [187], retinitis pigmentosa [188], Bietti crystalline dystrophy [189], autosomal recessive bestrophinopathy [190], melanocytoma-associated macular neovascular membrane [191], and Best disease [192].

Other reported indications include Wyburn-Mason syndrome [193], choroidal osteoma [194], peripheral exudative hemorrhagic chorioretinopathy [195], traumatic choroidal rupture [196], torpedo maculopathy [197], optic disc melanocytoma [198], type 2 proliferative macular telangiectasia [199], and Coats disease [200], all complicated by macular edema and/or macular neovascularization.

This review summarizes current knowledge on anti-VEGF therapies, drawing on diverse clinical and real-world evidence. Its main strengths include the comprehensive scope, attention to both established and emerging treatments, and relevance to everyday practice. As a narrative review it may be subject to selection bias, and variability among studies limits direct comparisons. With ongoing advances in the field, continual updates will be essential to maintain its clinical relevance.

CONCLUSIONS

Literature underscores the expanding therapeutic potential of anti-VEGF agents in the management of rare and complex retinal and choroidal pathologies. Anti-VEGF treatments are effective and generally safe, and their use is growing as new ways of delivering them are developed. These advances help improve patient outcomes and quality of life. As research continues to improve treatment plans and new versions of these drugs become available, anti-VEGF therapy will become even more important and remain a key part of future eye care.

ETHICAL DECLARATIONS

Ethical approval: This narrative review received ethical approval at the departmental level of the Faculty of Medicine, Dokuz Eylul University, Izmir, Turkiye. All figures presented were obtained from the patient documentation archives of our unit and informed consent was obtained from each patient before inclusion in the review.

Conflict of interest: None.

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