

Effects of anti-VEGF on peripapillary retinal nerve fiber layer and papillary/peripapillary blood circulation in retinopathies (Review)

HONGWEI WANG¹, RENFENG DING¹, WENYA JIANG¹, SIYI LI¹, YIJUAN WU¹,
JUNFENG MAO¹, YANAN CHEN¹, PENG SUN² and MENGQI SHI^{3,4}

¹Department of Ophthalmology, Jingjiang People's Hospital Affiliated to Yangzhou University, Taizhou, Jiangsu 214500, P.R. China;

²Department of Ophthalmology, The Jiamusi Center Hospital, Jiamusi, Heilongjiang 154002, P.R. China; ³Department of Ophthalmology,

Taizhou Fourth People's Hospital, Taizhou, Jiangsu 225300, P.R. China; ⁴Department of Clinical Medicine, Medical College,

Yangzhou University, Yangzhou, Jiangsu 225009, P.R. China

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Abstract. Vascular endothelial growth factor (VEGF) is an endothelial cell-specific angiogenic factor. VEGF is involved in vasodilatation, nerve protection and retinal development and maturation. Over-expression of VEGF is closely associated with retinopathies, such as retinal vein occlusion, diabetic retinopathy, age-related macular degeneration and diabetic macular edema. Intravitreal injections of anti-VEGFs are widely used in the treatment of retinopathies to reduce the angiogenesis and the macular edema. Hypothetically, repeated anti-VEGF injections for retinopathies should interfere with the neuroprotective function of VEGF and might induce the vasoconstriction with a subsequent decrease in the ocular perfusion. These two could affect the optic nerve. The peripapillary retinal nerve fiber layer (p-RNFL) thinning and the decreased papillary/peripapillary blood circulation can show the optic nerve damage earlier. In the present review, the effects of anti-VEGFs on p-RNFL and papillary/peripapillary blood circulation in retinopathies were comprehensively summarized and analyzed to explore whether the anti-VEGFs cause damages to the optic nerve. The present review provided a detailed evaluation and analysis of the changes in p-RNFL thickness, papillary/peripapillary blood circulation and intraocular pressure and the correlations between these changes with the number and type of anti-VEGFs in 3,078 affected eyes and 520 fellow eyes with retinopathies. The present review sought to establish a foundation for the intravitreal

administration of anti-VEGFs and efficacy monitoring of the possible side effects on the optic nerve.

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Correspondence to: Ms. Mengqi Shi, Department of Ophthalmology, Taizhou Fourth People's Hospital, 99 Gulou North Road, Taizhou, Jiangsu 225300, P.R. China
E-mail: wangyutingwangxin@163.com

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1. Introduction

Vascular endothelial growth factor (VEGF), a secreted 46 kDa glycoprotein, is an endothelial-cell-specific angiogenic factor (1). Although initially considered to be endothelial-cell-specific, VEGF is involved in the development and maturation of neural tissue, including the retina (2). Retinal pigment epithelial (RPE) cells and astrocytes in the retinal

ganglion cell layer can secrete VEGF (3). In the normal adult retina, VEGF is expressed in the absence of active neovascularization and plays a role in the function of adult retina neuronal cells (4). Upregulation of VEGF occurs in several retinopathies associated with ischemia in the retina. Upregulated intraocular VEGF expression leads to vitreous hemorrhage, neovascular glaucoma and even retinal detachment, with subsequent loss of vision (5). Intravitreal injections of anti-VEGFs are widely used in the treatment of retinopathies to reduce angiogenesis and macular edema. Hypothetically, repeated treatment with anti-VEGFs for retinopathies should interfere with the neuroprotective function of VEGF (6). Additionally, long-term studies have suggested that, besides the short-term intraocular pressure (IOP) elevation, anti-VEGF injections can also lead to long-term elevations in IOP (7,8) and repeated episodes of IOP spikes can lead to glaucoma-like progression (9). Given that multiple anti-VEGF injections are often required due to the chronic course of retinopathies, the cumulative long-term effect of IOP elevation may affect the optic nerve (7).

Damage to the optic nerve leads to changes in the peripapillary and intrapapillary regions of the optic nerve head (known as the papillary region or optic disc) (10). In patients with optic nerve damage, peripapillary retinal nerve fiber layer (p-RNFL) thinning occurs earlier prior to other manifestations, such as loss of vision or functional visual field defects (11). Therefore, measurement of p-RNFL thickness is a more sensitive method for detecting early optic nerve damage. Anti-VEGFs are effective not only for resolving macular edema, but also for vasoconstriction (12). Thus, it can be hypothesized that the therapeutic anti-VEGFs may induce vasoconstriction in the papillary/peripapillary vessels, resulting in a subsequent decrease in ocular perfusion. The restrained blood flow induces alterations to the extracellular matrix in the optic nerve and retina, which leads to progressive optic nerve degeneration and loss of vision (13). In the present review, two indicators that show optic nerve damage, p-RNFL thickness and papillary/peripapillary blood circulation, are discussed in detail.

Multiple databases were searched and no reviews were found on this topic. Previous reviews have focused on the resolution of macular edema and the changes in the macular RNFL by anti-VEGFs. The novelty of the present review lay in its comprehensive discussion of the effects of anti-VEGF on p-RNFL and papillary/peripapillary blood circulation to explore whether the anti-VEGFs cause damage to the optic nerve.

2. Pathogenicity of VEGF upregulation in retinopathies

Retinal ischemia is a fundamental pathological factor associated with retinopathies, such as retinal vein occlusion (RVO), diabetic retinopathy (DR), age-related macular degeneration (AMD) and diabetic macular edema (DME). Upregulation of VEGF secreted by human RPE cells is a fundamental cause of abnormal angiogenesis (14) and is also considered to be one of the pathogenic causes of numerous retinopathies.

Pathogenicity of oxidative stress/reactive oxygen species (ROS)-mediated imbalances between VEGF and pigment epithelium-derived factor (PEDF). Reduction/oxidation (redox) imbalances, which are caused by imbalances in

pro-oxidant/antioxidant reactions increase oxidative stress (OS), resulting in retinopathies; ROS are one of the most important oxidants (15). RPE cells secrete a variety of cytokines, including VEGF (an angiogenic stimulator) and PEDF (an angiogenic inhibitor) (14,16). Physiologically, in the retina, there is a balance between PEDF and VEGF, which is essential for retinal health. VEGF-induced angiogenesis is normally inhibited by PEDF (17). An increased VEGF/PEDF ratio can lead to retinopathies (18). In a model of ischemia-induced retinal neovascularization, the retina shows a 5-fold increase in VEGF and a 2-fold decrease in PEDF, compared with the age-matched controls (16). Advanced glycation end product (AGE), a senescent macro-protein derivative, formation of which is accelerated in patients with diabetes, elicits OS and induces vascular inflammation and is therefore involved in retinopathies (19,20). PEDF inhibits AGE-induced retinal vascular hyperpermeability and angiogenesis by blocking the generation of ROS and subsequent ROS-mediated upregulation of VEGF (21). These findings suggest that an imbalance between angiogenic stimulators and inhibitors contributes to retinopathies.

Pathogenicity of VEGF-mediated inflammation. Inflammation is a critical factor in the pathogenesis of certain retinopathies (14). Endoplasmic reticulum (ER) stress is an inducer of the inflammatory response, which can cause AMD via the interaction of C-reactive protein (CRP) and serum amyloid P protein (14). CRP is an inflammatory biomarker and risk factor for AMD (22). VEGF contributes to the inflammatory process following laser-induced retinopathy (23). In human RPE cells, CRP can induce VEGF and interleukin-8 (IL-8) expression (24). The increased level of inflammation occurs in proliferative DR eyes with larger non-perfusion areas and the expression of IL-8 positively correlates with the non-perfusion area (25). Inflammatory mediators [such as VEGF, hypoxia-inducible factor (HIF)-1 α , IL-8 and others] are markedly increased (4-10-fold) compared with the control retina in laser-induced retinopathy (23). Additionally, there is upregulation of VEGF and IFN- γ -inducible protein-10 (IP-10), characteristic inflammatory cytokines present in the aqueous humor of patients with AMD (26,27). These indicate that the VEGF pathway is involved in retinal inflammation and damage and plays a role in the inflammation-induced pathogenesis of retinopathies.

VEGF upregulation and hypoxia/ischemia. DR and RVO are the two most common ischemic retinopathies and upregulation of VEGF further aggravates retinal ischemia and hypoxia, commonly leading to loss of vision (28). Noninvasive perfusion measurement data have suggested that the decreased choroidal circulation and subsequent hypoxia/ischemia can aggravate the pathogenesis of AMD (29-31). In human RPE cells, ER stress upregulates the expression of VEGF via the actions of activating transcription factor (ATF) (32,33). Furthermore, the excessive proteasomal inhibition generates ER stress and induces the expression of VEGF, HIF-1 α and angiopoietin-2 to support neovascularization in AMD (34). Hypoxia is also an efficient inducer of VEGF expression (35). VEGF, as an HIF-1 α -regulated angiogenic mediator, and HIF-1 α are upregulated in the retinal tissue of DR (36).

VEGF upregulation and its association with other factors. VEGF upregulation in retinopathies is also associated with other factors that collectively affect the pathological process, leading to increased VEGF levels. The missense mutation in R345W of fibulin-3 protein causes an accumulation of a misfolded protein within the ER and the retention of the protein in the ER stimulates ER stress, resulting in upregulation of VEGF in human RPE cells (37). Alternatively, increased levels of homocysteine (an ER stressor) are involved in wet AMD (w-AMD) (38). Homocysteine is a toxic metabolite that induces ER stress in the liver in patients who abuse alcohol (39). Notably, excessive alcohol consumption is also considered to be a risk factor for AMD (40). Homocysteine can activate the protein kinase R-like ER kinase (PERK)/ATF4 pathway, which is an important component of ER stress, inducing upregulation of VEGF expression in human RPE cells (32). OS induces the upregulation of ATF4 via arsenite (an oxidative stressor) in human RPE cells (14). Upregulation of ATF4 is sufficient to activate the VEGF promoter (32). These findings suggest that the homocysteine/arsenite induces the expression of VEGF via an ATF4-dependent mechanism.

3. Types of anti-VEGF and ocular side effects

Types of anti-VEGFs. The commonality among w-AMD, DME, DR and RVO is the vascular permeability and pathological neovascularization induced by VEGF. Intravitreal injections of anti-VEGFs can resolve macular edema, subretinal fluid and neovascularization (12). Although anti-VEGFs were initially developed as a cancer treatment, bevacizumab was first approved by U.S. Food and Drug Administration (FDA) in 2004 for colon cancer treatment (41); however, they are now widely used in various retinopathies, including RVO, DR, AMD and DME. Bevacizumab, a humanized monoclonal antibody with a molecular weight of 149 kDa, has been used in ophthalmology since 2005 as an off-label therapy (42). Pegaptanib, an anti-VEGF drug used in certain retinopathies (w-AMD), was approved by the FDA in 2004 (41). Ranibizumab, approved by the FDA in 2006 for w-AMD, contains the Fab fragment of a humanized IgG1 κ isotype murine monoclonal antibody and has a molecular weight of 48 kDa, almost three times smaller than bevacizumab (43). Aflibercept, with a molecular weight of 115 kDa, was approved by the FDA in 2011 (42).

Recently introduced anti-VEGF drugs for retinopathies include brolocizumab and faricimab. Brolocizumab was approved by the FDA in 2019. Brolocizumab is a single-chain humanized antibody fragment, designed to bind VEGF-A (43,44). Faricimab, a bispecific heterodimeric monoclonal human antibody, has a greater molecular weight than bevacizumab and was approved by the FDA for DME and w-AMD in 2022 (45). Due to their shorter presence on the market, they have not yet been extensively used and studied.

Ocular side effects of anti-VEGF treatments. Intraocular inflammation is a primary ocular adverse effect associated with anti-VEGF therapies (46). The incidence of significant ocular inflammation following ranibizumab injection for AMD ranges from 1.4-2.9%, whereas the incidence following bevacizumab injection is comparatively lower, between 0.09-0.4% (47). An acute increase in IOP is relatively common

immediately after an anti-VEGF injection, with most studies reporting spontaneous normalization of IOP within several hours (42,48,49). The incidence of rhegmatogenous retinal detachment post-anti-VEGF injections is low, ranging from 0-0.67% (47,50). Of note, there was no statistically significant difference in the occurrence of rhegmatogenous retinal detachment and retinal tear between eyes treated with anti-VEGF treatments and the control group (46).

Following bevacizumab injection, rare ocular side effects include anterior ischemic optic neuropathy in w-AMD and angioid streaks in pseudoxanthoma elasticum (51,52), central retinal artery occlusion (RAO) and RVO in central RVO, AMD and proliferative DR (53) and hemorrhagic macular infarction in central RVO (54), acute retinal ischemic changes in diabetic rubeosis (55) and sixth nerve palsy (56). Among 4,069 injections (ranibizumab or aflibercept) administered for the treatment of DME (464 cases), w-AMD (187 cases) or RVO (156 cases), only 18 cases (0.44%) exhibited transient central RAO, including four severe cases (ranibizumab: two cases, aflibercept: two cases) (57).

4. Methods of literature retrieval and summary of retrieved literature

Methods of literature retrieval. The literature search was conducted on January 1, 2025, using PubMed, Clinicalkey (Elsevier), SpringerLink, Cochrane Library and CNKI databases. The search used combinations of the following search terms: (anti-VEGF OR aflibercept OR bevacizumab OR ranibizumab OR brolocizumab OR faricimab) AND (papillary OR circumpapillary OR juxtapapillary OR intrapapillary OR optic disk OR optic nerve head OR optic papilla) AND (p-RNFL OR blood flow OR blood vessel OR capillary OR microvascular OR microcirculation). Filters applied included human studies and articles were initially screened based on the titles or abstracts. The inclusion criteria were: i) Original research articles and ii) participants included were aged over 18 years. Case reports were excluded.

Summary of retrieved literature. Studies that assessed p-RNFL thickness using optical coherence tomography angiography (OCTA) and blood circulation parameters using laser speckle flowgraphy (LSFG) [measuring mean blur rate (MBR), relative flow volume (RFV) and blowout score], Canon laser blood flowmeter (CLBF; measuring vessel diameter), scanning laser Doppler flowmetry (SLDF; measuring blood flow) and OCTA [measuring vessel density (VD), vessel length density (VLD), capillary volume (CV), perfusion density (PD) and perfusion index (PI, or flux index)] were included. All studies included in the present review involved patients with RVO, DR, AMD or DME. Previous studies and clinical trials examining the effects of anti-VEGF treatments on p-RNFL and papillary/peripapillary blood circulation are summarized in Tables I and II, respectively. The studies included in the present review encompass an analysis of 3,077 affected eyes treated with anti-VEGF treatments for retinopathies, as detailed in Tables I and II. The underlying mechanisms for the effects of anti-VEGF treatments on p-RNFL and papillary/peripapillary blood circulation are illustrated in Figs. 1 and 2, respectively.

Table I. A summary of studies targeting effects of anti-VEGF on p-RNFL in patients with retinopathies.

First author, year	Eye disease or other therapy	No. of eyes	Follow up (months)	Age of patients (year)	Anti-VEGF: number of injections	Effect on p-RNFL (μm) (Pre/Post-injection)	(Refs.)
Viggiano <i>et al.</i> , 2024	w-AMD with type 1 or type 2 MNV	35	2 to 5 min post-injection	78.10±10	IVA: -	100.9±18.8/98.6±17.4	(75)
Zhuang <i>et al.</i> , 2024	w-AMD with type 1 or type 2 MNV	68	3	64.87±6.99	Conbercept, IVR, IVA: 3	115.90±2.32/112.17±1.57	(102)
Boltz <i>et al.</i> , 2024	w-AMD	66	-	83.4±0	Anti-VEGF: more than 50 (prior 12.58)	-90.62±0	(66)
Viggiano <i>et al.</i> , 2023	non-proliferative DR with DME	IVA: 32 DEX-I: 33	Short-term	IVA: 64.3±5.7 DEX-I: 67.2±8.9	IVA: -	IVA: 96.8±8.8/97.4±9.13 DEX-I: 97.1±9.11/98.2±9.6	(114)
Zivkovic <i>et al.</i> , 2023	w-AMD	135	24	65±15	IVB: 12.4±2.4	87.6±12.2/86.2±12.6	(77)
Türkseven <i>et al.</i> , 2023	w-AMD	Group1: 19 Group2: 21	Short-term	Group1: 79.0±6.6 Group2: 77.9±7.2	IVR, IVA: 2.79±1.03 IVR, IVA: 35.52±17.00	Group1: -80.7±9.1 Group2: -86.0±8.6	(85)
Dikmetas <i>et al.</i> , 2023	w-AMD DME	AMD: 36 DME: 40 Control: 34	1	AMD: 70.7±8.8 DME: 65.5±8.4 Control: 63.7±11.2	IVR, IVA, IVB: 1	AMD: 101.2±17.3/99.5±16.9 DME: 96.8±16.0/95.4±20.8 Control: 92.0±16	(60)
Buyukavsar <i>et al.</i> , 2023	w-AMD	43	0.5±3.6	75.6±7.6	IVA: 5.4±1.6 (3+PRN)	97.1±15.2/95.1±14.3 (3rd month)/ 98.19±12.3 (10rd month)	(168)
Jun <i>et al.</i> , 2023	w-AMD	22 19 (fellow)	3	67.77±5.95 67.63±4.08	IVBr (1 injection) because of poor response	IVBr: 99.47±14.19/98.86±14.73 97.22±12.19/96.94±12.65	(62)
Liu <i>et al.</i> , 2022	Branch RVO with macular edema	24 24 (fellow)	4	55.50±7.86	IVR: 3+PRN	132.04±16.86/121.50±14.25 120.04±17.04/121.83±18.16	(154)
Gunay and Esenulku, 2022	w-AMD	34	12	75.59±6.85	IVA: 6.0±1.8(3+PRN)	92.52±7.69/ 92.04±10.07	(6)
Sun J <i>et al.</i> , 2022	Branch RVO with macular edema	18 30	3	55.39±9.29 53.60±6.54	Anti-VEGF3	118.00±10.44/104.94±13.86 107.50±9.37	(155)
Moleiro <i>et al.</i> , 2022	Central RVO(24) Branch RVO(40)	24 40	9	58.00±18.90 70.15±10.15	Anti-VEGF+Corticoid: 5.69±2.68, 6.17±2.21	187.00±53.33/112.13±35.242 110.95±34.23/94.63±18.20	(127)
Wichrowska <i>et al.</i> , 2022	unilateral w-AMD non-advanced d-AMD	104	-	Female: 73.23±7.60 Male: 71.71±7.13	IVB: 1.02±2.91 IVR: 0.96±2.98 IVA: 9.29±8.19	An increase of p-RNFL in the nasal quadrant of the optic disc by 0.536 μm for each additional injection	(58)
Khodabande <i>et al.</i> , 2021	DME or w-AMD. Other therapy: ACP	58	4	62.9±10.0	Group 1: IVB: 3 Group 2: IVB (ACP): 3	Group 1: 110±19/111±18 Group 2: 115±19/115±19	(80)

Table I. Continued.

First author, year	Eye disease or other therapy	No. of eyes	Follow up (months)	Age of patients (year)	Anti-VEGF: number of injections	Effect on p-RNFL (μm) (Pre/Post-injection)	(Refs.)
Tan <i>et al</i> , 2021	Branch RVO with macular edema	47	6	55.80±10.03 55.31±9.31	Anti-VEGF: 3	102.67±1.43/99.44±1.47 Control: 99.77±1.54	(156)
Ahn <i>et al</i> , 2021	w-AMD	IVR: 29 IVA: 29	12	IVR: 70.86±8.56 IVA: 73.00±9.10	IVR: 4.93±1.39 IVA: 4.69±1.31	IVR: 101.03±15.07/99.32±14.07 IVA: 97.39±18.61/94.54±17.71	(68)
Wang <i>et al</i> , 2021	w-AMD d-AMD: fellow eye	108	46.8±42.0 (range: 0.5-44)	79.7±7.3	IVB, IVR, or IVA: mean 29	w-AMD: -87.3±9.6 Fellow eye: 89.0±7.5 (d-AMD)	(86)
Valverde-Megias <i>et al</i> , 2019	w-AMD	20	96	83±1.4	IVR	105.6±10.7/96.5±2.1	(63)
Roohipour <i>et al</i> , 2019	proliferative DR Other therapy: PRP	9 (fellow) IVB+PRP:32 PRP: 32	10	83.1±2.5 53.2±6.6 53.5±6.7	21±2.8 IVB+PRP: 1 (26 eyes) - 2 (6 eyes)	103.2±7.9/92.9±3.2 102.8±28/101.3±20.2 104.9±17.1/102.7±9.9	(118)
Jampol <i>et al</i> , 2019	proliferative DR	Total: 146	24	Mean 52 Mean 50	IVR 33 eyes < 9, 39 eyes ≥ 9	IVR: 96.8±18.2/85.3±15.2 PRP: 96.8±19.3/95.2±18.9	(119)
Gómez-Mariscal <i>et al</i> , 2019	w-AMD DME, RVO	29	3 or 24	76.8±6.9 76.9±6.6	IVA or IVR: 3 or 6	Treated: 99.6±6.0/97.3±5.5 Untreated: 97.3±6.5/97.0±5.2	(92)
Rud'ko <i>et al</i> , 2019	w-AMD with POAG	24 (fellow) IVR: 42 IVA: 20	-	-	IVR: 3 IVA: 3	Significant decrease of p-RNFL thickness in the temporal quadrant	(108)
Yang <i>et al</i> , 2017	DR with DME DR without DME	50 90	6	68.2±13.1 67.4±13.0	IVB: -	DME: 126.4±34.7/117.6±28.8 No DME: 100.7±17.0/102.1±12.1	(112)
Soheilian <i>et al</i> , 2017	w-AMD or DME Other therapy: ACP	44 42	3	Group A: 64.9±5 Group B: 67.8±4.5	IVB: 1	IVB: 85.3±5.6/82.8±6 IVB+ACP: 85.6±5/86±5.3	(81)
Bitirgen <i>et al</i> , 2017	w-AMD	66 25	-	67.91±7.29 66.24±7.24	IVR: 8.9±5.0 (range 3-20)	94.83±6.60/95.52±10.10 95.84±13.75	(69)
Ranjbar <i>et al</i> , 2017	w-AMD Other therapy: SRT	35	12	76.23±7.05	IVA or IVR: 19.29 ± 6.92	No significant p-RNFL thinning 97.23±12.55/95.29±12.07	(94)
Kopić <i>et al</i> , 2017	w-AMD+POAG DME+POAG	AMD+ POAG: 30 DME+ POAG: 30	24	Over 18	IVB: minimum of 4	77.27±12.48/76.46±16.40 84.90±16.41/81.10±16.08	(109)
Enders <i>et al</i> , 2017	w-AMD Other therapy: ACP	44 32	32.3±12.9 30.0±16.3	76.8±7.8 75.0±6.5	IVR or IVA: 16.6±7.1 IVR, IVA or IVB: 16.2±5.8	ACP: 61.41±7.2/61.57±7.7 Non-ACP: 58.34±6.0/56.19±6.8	(93)
Zucchiatti <i>et al</i> , 2017	w-AMD	24	12	76±7.8	IVR: 3+PRN	81.9±9.9/84.6±15.5	(71)
El-Ashry <i>et al</i> , 2015	w-AMD	30	1	77.6±0	IVR: 3	90.8±18.43/91±15.31	(72)

Table I. Continued.

First author, year	Eye disease or other therapy	No. of eyes	Follow up (months)	Age of patients (year)	Anti-VEGF: number of injections	Effect on p-RNFL (μ m) (Pre/Post-injection)	(Refs.)
Yau <i>et al</i> , 2015	w-AMD d-AMD	29 29	Mean 47.9	Mean 81.1	Anti-VEGF: mean 23.1	w-AMD: mean 95.0 d-AMD (fellow eye): mean 89.9	(111)
Demirel <i>et al</i> , 2015	w-AMD	29 29 (fellow)	38.96±15.49	73.92±6.1 71.87±4.1	IVR: 13.88±3.81	92.3±7.7/92.46±8.1 Fellow eye: 91.83±7.9	(70)
Parlak <i>et al</i> , 2015	w-AMD	22 22 (fellow)	12	66.3±8.8	IVR: 3+PRN (mean 4.86)	101.4±14.2/99.9±14.5 99.1±8.8/96.2±9.5	(64)
Entezari <i>et al</i> , 2014	w-AMD	18	24 weeks	76.1±1.6	IVB: 2	89±21/87±23	(76)
Hwang <i>et al</i> , 2014	DR with DME DR without DME	42 53	1	55.7±11.4 55.8±11.9	IVB: 1	DME: 134.8±39.7/119.7±28.9 No DME: 98.1±12.2	(110)
Sobacı <i>et al</i> , 2013	w-AMD	IVB: 35 IVR: 30	IVB: 14.05±2.6 IVR: 13.6±2.1	IVB: 69.1±7.7 IVR: 68.0±7.5	IVB: 5.1±1.3 IVR: 6.3±1.9	IVB: 105.8±8.1/104.6±8. IVR: 105.3±6.9/104.6±8.4	(73)
Martinez-de-la-Casa <i>et al</i> , 2012	w-AMD	49 27 (fellow)	12	79.2±7.0 77.2±6.5	IVR: 4.8±1.6	105.7±12.2/100.2±11.0 101.8±11.6/100.5±10.8	(61)
Horsley <i>et al</i> , 2010	w-AMD	41	27.0±9.7 20.1±3.6 27.1±4.2	79.2±8.7	IVP, IVB, IVR: 16.0±5.5 IVR: 13.4±3.6 IVB, IVR: 17.7±3.7	Group 1: 92.4±15.2/93.8±15.2 Group 2: 91.7±16.4/97.6±13.7 Group 3: 96.4±12.9/95.4±13.5	(74)

IVA, aflibercept; IVB, bevacizumab; IVR, ranibizumab; IVBr, brolicizumab; IVP, pegaptanib; PRN, ro re nata; PRP, panretinal photocoagulation; MNV, macular neovascularization; DEX-I, dexamethasone implant; POAG, primary open angle glaucoma; ACP, anterior chamber paracentesis; SRT, stereotactic radiotherapy; RVO, retinal vein occlusion; DR, diabetic retinopathy; w-AMD, wet age-related macular degeneration; DME, diabetic macular edema; p-RNFL, peripapillary retinal nerve fiber layer; VEGF, vascular endothelial growth factor.

Table II. Summary of studies targeting effects of anti-VEGF on papillary/peripapillary blood circulation in patients with retinopathies.

First author, year	Eye disease/other therapy	No. of eyes	Follow up Scanning area	Age of patients/ Controls	Anti-VEGF: number of injections	Impact indicators on blood flow (%) (Pre/Post-injection)	(Refs.)
Viggiano <i>et al.</i> , 2024	w-AMD with type 1 or type 2 MNV	35	2 to 5 min RPC	78.10±10	IVA: -	VD: 46.6±4.9/46.9±4.8	(75)
Mizukami <i>et al.</i> , 2024	DME	IVA: 20 IVF: 15	1 month PPA, ONH	68.7±10.8 69.7±12.3	IVA or IVF: 1	MBR (Artery, IVA): 13.6±3.1/11.7±3.0 MBR (Artery, IVF): 16.7±3.5/14.6±3.8 MBR (Vein, IVA): 14.7±6.1/13.0±4.6 MBR (Vein, IVF): 16.3±5.5/15.2±2.8	(162)
Zhuang <i>et al.</i> , 2024	w-AMD with type 1 or type 2 MNV	68	3 months RPC	64.87±6.99	Conbercept, IVR, IVA: 3	VD: 50.08±0.49/50.24±0.54	(102)
Zeng <i>et al.</i> , 2024	proliferative DR nonproliferative DR	187 101	3 months PPA, ONH	58.34±15.78 46.79±19.30	IVA: -	CV: no significant changes in the IVA treatment group	(142)
Viggiano <i>et al.</i> , 2023	non-proliferative DR with DME	IVA: 32 DEX-I: 33	Short-term RPC	64.3±5.7 67.2±8.9	IVA: -	VD (IVA): 46.93±3.16/47.17±3.70 VD (DEX-I): 48.12±4.17/49.04±4.23	(114)
Türkseven <i>et al.</i> , 2023	w-AMD	Group 1: 19 Group 2: 21	Short-term PPA	Group 1: 79.0±6.6 Group 2: 77.9±7.2	IVR, IVA: 2.79±1.03 IVR, IVA: 35.52±17.00	PI: 0.392±0.049 PI: 0.377±0.042 PD: decreased 0.515±0.02 PD: decreased 0.556±0.03	(85)
Helmy <i>et al.</i> , 2023	proliferative DR Other therapy: PRP	IVR: 25 PRP: 25	3 months RPC	IVR: 46.84±8.39 PRP: 51.24±9.4	IVR: 3	VD: increased 1.45±2.59 VD: 46.14±4.12/decreased 2.16±3.55	(147)
Kato <i>et al.</i> , 2023	w-AMD	IVBr: 10 IVA: 11	30 minutes ONH	IVBr: 75.7±6.8 IVA: 72.3±9.5	IVBr or IVA: 1	MBR: 42.0±4.4/37.5±5.0 MBR: 44.8±11.4/40.4±10.7	(132)
Liu <i>et al.</i> , 2022	Branch RVO	24 24 (fellow)	4 months RPC	55.50±7.86	IVR: 3+PRN	VD: 45.88±4.29/48.65±4.33 (%) VD: 50.10±4.38/51.97±4.51 (%)	(154)
Sun <i>et al.</i> , 2022	Branch RVO with macular edema	18 30	3 months RPC	55.39±9.29 53.60±6.54	Anti-VEGF: 3	VD: 42.36±8.2/39.54±8.23 VD (fellow eye): 38.13±8.16	(155)
Tan <i>et al.</i> , 2021	Branch RVO with macular edema	47 47 (fellow)	6 months RPC	55.80±10.03 55.80±10.03	Anti-VEGF: 3	VD: 45.85±1.68/46.96±1.53 VD: 48.04±1.70	(156)
Arumuganathan <i>et al.</i> , 2021	DR or RVO	DR: 12 RVO: 17	5 min PPA, ONH	DR: 58.62±15.07 RVO: 70.19±10.91	IVA or IVR: 18.08±19.65 24.56±16.15	VD: decreased 0.006±0.03 VD: decreased 0.003±0.04 VLD: decreased 0.240±1.12 VLD: decreased 0.106±1.24	(7)
Asano <i>et al.</i> , 2021	Branch RVO with macular edema	24 24 (fellow)	6 months ONH	67.1±11.9	IVR: -	Vessel MBR: 40.2±8.5/41.2±7.3 Vessel MBR (fellow eye): 41.0±8.3	(158)

Table II. Continued.

First author, year	Eye disease/other therapy	No. of eyes	Follow up Scanning area	Age of patients/ Controls	Anti-VEGF: number of injections	Impact indicators on blood flow (%) (Pre/Post-injection)	(Refs.)
Barash <i>et al</i> , 2020	5 retinal diseases	40	Immediately RPC, ONH	60.6±11.82	IVB (37 eyes): - IVA (3 eyes): -	PD (ONH): decreased 3.3% PD (RPC): decreased 2.9%	(140)
Mursch-Edlmayr <i>et al</i> , 2020	w-AMD	20 20 (fellow)	3 months ONH	75.1±8.2	IVA: 3 previous: 3	MBR (versus baseline): -12.9±7.1 MBR: -1.1±31.4	(133)
Toto <i>et al</i> , 2020	DME	20	1 month PPA, ONH	65.4±6.5	IVR: 1	MBR (ONH): 46.1/39.7 MBR (Vein, mean): 20.9/20.6 RFV (Vein, mean): 306.8/259.1 MBR (Artery, mean): 20.9/16.0 RFV (Artery, mean): 269.5/199.7	(161)
Mursch-Edlmayr <i>et al</i> , 2019	w-AMD	20 20 (fellow)	45 min ONH	75.1±8.2	IVA: 1	MBR (microvasculature) 3.4±12.0 (Fellow eye: -1.5±17.4) MBR (big vessel) -27.4±16.5 (Fellow eye: -9.0±17.7)	(134)
Nicolai <i>et al</i> , 2019	Central RVO with macular edema	18 18 (fellow)	4 months RPC	56.09±16.47	IVR: 3	VD: 43.84±1.74/45.58±2.86 VD: 51.12±1.85/51.27±2.82	(157)
Nagasato <i>et al</i> , 2016	macular edema due to central RVO	31	6 months ONH	mean 66.9 (ranged from 40 to 83)	IVB, IVR: 3.52±0.88	Vessel MBR: 34.8±11.2/32.9±12.2	(159)
Fontaine <i>et al</i> , 2011	w-AMD	18	Mean 16.5 weeks PPA	71.8±7.9	IVB 3	Arterial diameter (µm) 122.5±14.5/117.2±13.7 Artery blood flow (µl/min) 11.0±3.5/10.0±2.7 Artery blood flow velocity (mm/min) 30.6±6.6/30.5±5.3	(131)

IVA, affibercept; IVB, bevacizumab; IVR, ranibizumab; IVF, faricimab; IVBr, brolicizumab; VEGF, vascular endothelial growth factor; RPC, radial peripapillary capillary; PPA, peripapillary area; ONH, optic nerve head; VD, vessel density; MBR, mean blur rate; VLD, vessel length density; PD, perfusion density; PI, perfusion index (or flux index); CV, capillary volume; RFV, relative flow volume; BOS, blowout score; RVO, retinal vein occlusion; DR, diabetic retinopathy; w-AMD, wet age-related macular degeneration; DME, diabetic macular edema; DEX-I, dexamethasone implant; PRP, panretinal photocoagulation; MNV, macular neovascularization.

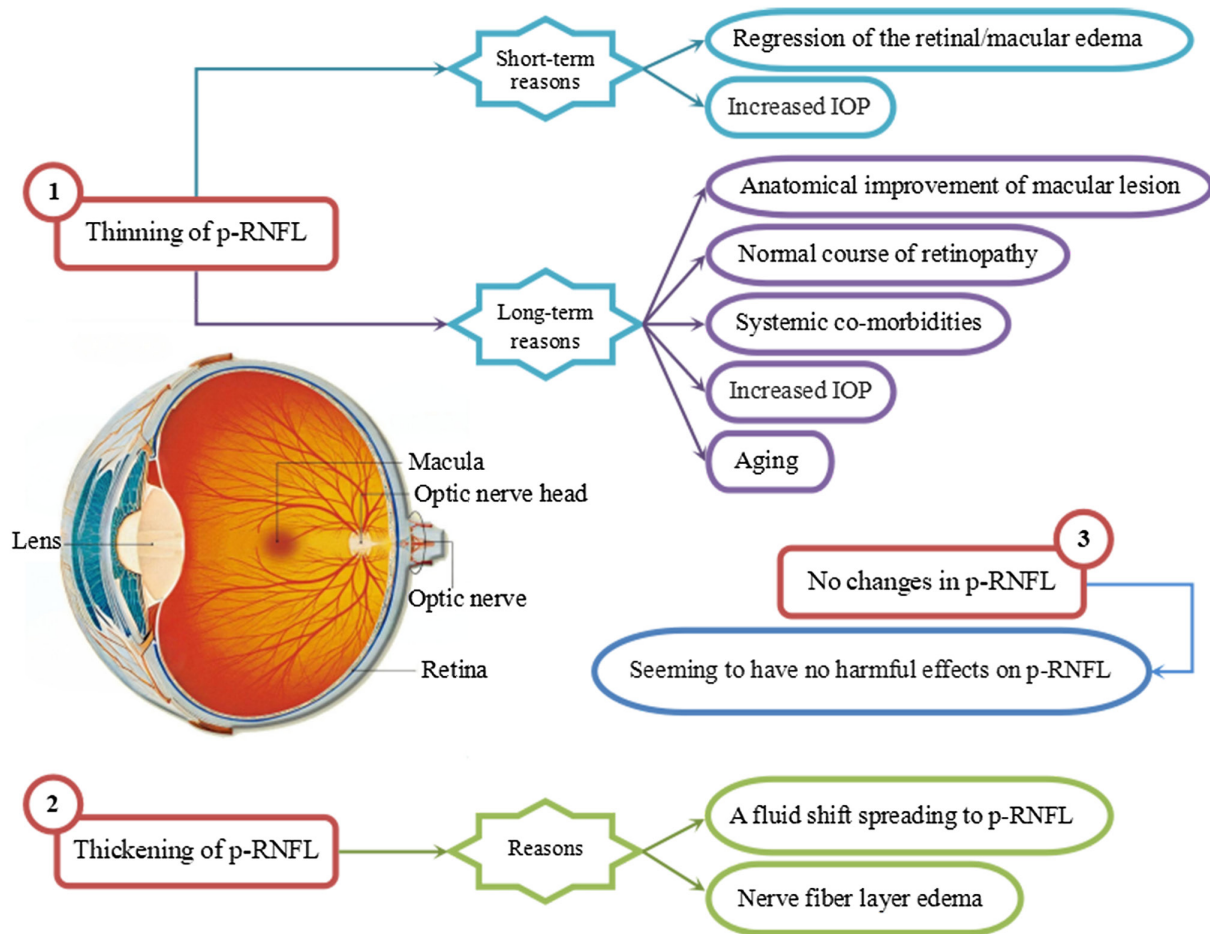


Figure 1. A schematic representation of reasons for effects of anti-VEGF on p-RNFL. The figure was created using the word drawing tool (Eye structure from Baidu). VEGF, vascular endothelial growth factor; p-RNFL, peripapillary retinal nerve fiber layer; IOP, intraocular pressure.

5. Effects of anti-VEGF on p-RNFL in w-AMD

With increasing life expectancy, the prevalence of patients with AMD is increasing. By 2030, it is projected that 243.4 million individuals will be affected by AMD (58). In the early stages of development of AMD, patients with w-AMD typically exhibit a thicker p-RNFL compared with healthy eyes (59), probably due to the potential fluid shift from macular edema to the p-RNFL (60).

Effects of ranibizumab monotherapy on p-RNFL. Martinez de-la-Casa *et al* (61) reported significant p-RNFL thinning in patients treated with ranibizumab over 12 months, compared with an untreated control group. Although IOP elevation was observed, no statistical correlations were found between changes in the outer macular ring and changes in p-RNFL (61). It appears unlikely that post-injection p-RNFL thinning is secondary to changes in reduced macular edema possibly extending to the peripapillary region. IOP fluctuations induced by anti-VEGF treatments could potentially damage the p-RNFL (62). Subsequent continuation of this study revealed the long-term effects (8-year follow-up) of ranibizumab on p-RNFL, with statistically significant thinning observed in both the treated and control groups (63). Of note, IOP remained unchanged throughout the study (63). Parlak *et al* (64) also observed significant thinning in the affected eyes treated

with ranibizumab, with no significant change in IOP over 12 months. The p-RNFL thickness decreased with age at a rate of $-0.21 \mu\text{m}/\text{year}$ (65). Advanced age in patients with w-AMD is associated with a significant decrease in p-RNFL thickness (66) and higher stages of w-AMD are associated with a thinner p-RNFL (67). These studies suggest that aging and the natural progression of w-AMD may contribute to p-RNFL thinning. Additionally, unexpected p-RNFL thinning in the untreated fellow eyes was reported by Valverde-Megías *et al* (63) and Parlak *et al* (64), indicating a potential systemic effect of anti-VEGF on untreated fellow eyes. Another study indicated a significant decrease in p-RNFL thickness in treated eyes over 12 months, with no significant difference in the fellow eyes (68). The authors attributed the thinning of p-RNFL thickness to the anatomical improvement of macular lesions, although a direct effect of ranibizumab on decreased p-RNFL could not be excluded.

Given that ranibizumab may affect fellow eyes of in patients with w-AMD via systemic circulation, certain studies included age-matched healthy subjects as controls. Long-term follow-up revealed no statistically significant differences in p-RNFL thickness (69,70) and IOP (70) between treated, fellow and healthy eyes. Therefore, p-RNFL thinning in fellow eyes may not be associated with a systemic effect of ranibizumab on untreated fellow eyes. The absence of p-RNFL thinning due to ranibizumab has also been reported

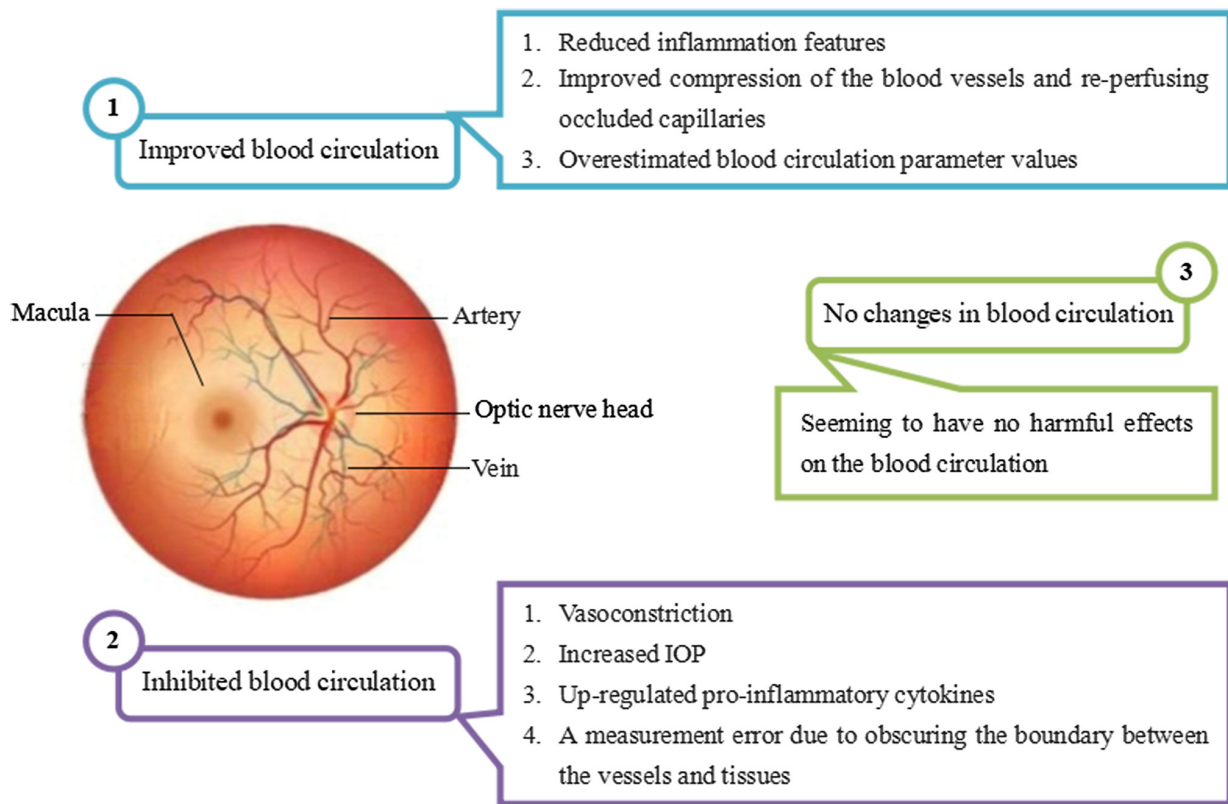


Figure 2. A schematic representation of reasons for effects of anti-VEGF on papillary/peripapillary blood circulation. The figure was created using the word drawing tool (Eye structure from Baidu). VEGF, vascular endothelial growth factor; IOP, intraocular pressure.

by Zucchiatti *et al* (71) over 12 months, El-Ashry *et al* (72) over 1 month and Sobacı *et al* (73) over a mean of 14 months. Notably, Horsley *et al* (74) reported an increase of $5.88 \mu\text{m}$ in the p-RNFL thickness during a follow-up of 20.1 ± 3.6 months despite no statistical difference ($P=0.35$) and there were no sustained IOP elevations for any of the patients with w-AMD. This suggests that ranibizumab may not affect p-RNFL in w-AMD.

Effects of aflibercept monotherapy on p-RNFL. The safety of aflibercept in relation to p-RNFL thickness has been evaluated in both long-term and short-term studies. Following aflibercept injections, a significant reduction in p-RNFL thickness was observed in treated eyes over a 12-month period, with no significant changes in intraocular pressure (IOP) (68). Additionally, no significant differences in p-RNFL thickness and IOP were noted in the fellow eyes (68), suggesting that aflibercept does not affect fellow eyes through systemic circulation. Within 2-5 min post-injection, aflibercept induces immediate p-RNFL thinning, particularly in the nasal region and increases IOP, with a significant negative correlation between increased IOP and p-RNFL thinning (75). The IOP spike immediately following anti-VEGF injections may compromise the integrity of the p-RNFL (71), with the nasal p-RNFL being particularly susceptible to IOP fluctuations. Furthermore, the nasal sector p-RNFL is less affected by macular edema in w-AMD prior to anti-VEGF injection (75), potentially making it a more accurate indicator of damage caused by anti-VEGF injections leading to increased IOP, thereby justifying the significant thinning of p-RNFL in the nasal sector. In contrast to the aforementioned

studies, Gunay *et al* (6) reported no significant changes in p-RNFL thickness in patients with w-AMD with macular edema over 12 months and no significant change in IOP was observed. Thus, the p-RNFL thinning attributed to the reduction of macular edema and increased IOP following aflibercept injections contradicts the findings of Gunay *et al* (6).

Effects of bevacizumab monotherapy on p-RNFL. Regarding the effects of bevacizumab monotherapy on p-RNFL, Entezari *et al* (76) found a significant reduction in p-RNFL thickness in patients with w-AMD at 12 weeks, which returned values that were comparable to baseline values at 24 weeks. Furthermore, IOP elevation returned to baseline values within 30-60 min in most patients receiving two injections of bevacizumab (76), indicating that fewer bevacizumab injections and short-term IOP increases were probably insufficient to cause p-RNFL damage. However, another prospective study involving 135 patients with w-AMD found no statistical differences in p-RNFL thickness after 12.4 ± 2.4 bevacizumab injections over 24 months (77). Similarly, Sobacı *et al* (73) observed no changes in p-RNFL after 5.1 ± 1.3 bevacizumab injections over a mean period of 14 months, although IOP was statistically different compared with baseline values. These studies suggest that a greater number of bevacizumab injections do not result in significant p-RNFL damage.

AMD and DME are among the most common causes of blindness in adults. Several macular diseases are prevalent in the elderly and thus, conditions such as AMD and DME can occur concurrently (78). The standard treatment for DME

and w-AMD involves anti-VEGF injections (79). Due to the chronic nature of w-AMD and DME, standard treatment regimens typically recommend multiple injections during the first year of treatment (80). Additionally, the duration of effectiveness of anti-VEGF agents is limited (81), necessitating repeated injections to maintain therapeutic effects. A transient and acute volume-related IOP increase is commonly observed following an anti-VEGF injection (82). Although the incidence of delayed and sustained IOP is low after a single or multiple anti-VEGF injections (83), an acute increase in IOP may cause loss of p-RNFL (81). Prophylactic anterior chamber paracentesis (ACP) combined with anti-VEGF treatments offers an effective alternative for preventing the acute rise in IOP (84). Thus, it is important to determine whether an anti-VEGF injection and the transient elevation in IOP adversely affect p-RNFL thickness in patients with w-AMD and DME.

In two short-term studies conducted by Khodabande *et al* (80) and Soheilian *et al* (81), patients with w-AMD or DME were randomly assigned to one of two groups: A group that was not treated with prophylactic ACP and the other which was treated with prophylactic ACP. The two studies consistently found that IOP was markedly higher in patients without ACP compared with those with prophylactic ACP following bevacizumab injections and no significant p-RNFL thinning was observed in patients with prophylactic ACP. However, the studies diverged in their conclusions regarding p-RNFL thickness changes in patients without ACP. Soheilian *et al* (81) reported significant p-RNFL thinning in patients without ACP, whereas Khodabande *et al* (80) found no significant thinning in this group. This discrepancy may be attributed to the older age and thinner baseline p-RNFL in the study by Soheilian *et al* (81) compared with those in the study by Khodabande *et al* (80) (66.4±4.9 vs. 62.9±10 years; 85.3±5.6 vs. 110±19 μm , respectively), potentially rendering them more susceptible to IOP fluctuations. Overall, ACP appears to mitigate acute IOP elevation and offers a certain degree of protection to the p-RNFL.

Effects of a combination of anti-VEGFs on p-RNFL. Regarding the effects of a combination of anti-VEGF treatments on p-RNFL, no statistically significant differences in p-RNFL thickness were observed among patients with w-AMD treated with ranibizumab alone (over 20.1±3.6 months; 13.4±3.6 injections), a combination of ranibizumab and bevacizumab (over 27.1±4.2 months; 17.7±3.7 injections), or a combination of ranibizumab, bevacizumab and pegaptanib (over 27.0±9.7 months; 16.0±5.5 injections) (74). Recent investigations have explored the correlation between the number of anti-VEGF injections and p-RNFL thickness. No significant effect on p-RNFL was observed in patients with w-AMD following a combination of anti-VEGF treatments (5-50 injections) (66,85). However, a study by Wang *et al* (86) with an extended follow-up period (46.8±42.0 months) suggested a dose-response relationship between the number of injections (a combination of bevacizumab, ranibizumab and aflibercept; 3-138 injections) and p-RNFL thinning, which became more pronounced after ~30 injections and 50 months of treatment. These findings indicate that prolonged treatment duration and a higher number of injections may be required to detect damage to the p-RNFL caused by active w-AMD.

Progressive optic neuropathy, characterized by a deficit in p-RNFL and corresponding thinning of the neuroretinal rim tissue, can lead to progressive visual field defects (87,88). Thinning of both p-RNFL and Bruch's membrane opening minimum rim width (BMO-MRW) occurs in early progressive optic neuropathy (89). Moreover, a decrease in the minimum rim area precedes reductions in p-RNFL and visual field loss (90). Theoretically, BMO-MRW serves as a sensitive marker for evaluating the effects of anti-VEGF injections on the optic nerve head. BMO-MRW markedly decreases with an increasing number of anti-VEGF injections, while no significant effect on p-RNFL is observed (66). It appears that BMO-MRW is affected earlier than p-RNFL following long-term anti-VEGF injections, suggesting that BMO-MRW may be a more sensitive marker than p-RNFL. Given the relative lack of literature on this topic, further studies with larger sample sizes are required to draw more concrete conclusions. BMO-MRW declines with age at a rate of -1.34 $\mu\text{m}/\text{year}$ and the association with age is stronger with BMO-MRW than with p-RNFL thickness (65). Therefore, the decrease in BMO-MRW after anti-VEGF injections may not necessarily be drug-induced, but is instead likely age-induced.

A significant yet transient elevation in IOP immediately following anti-VEGF administration is relatively common. Typically, IOP returns to baseline levels within 30 min to several hours post-injection (42,48,49,91). The prevalence of sustained IOP increase ranges from 3.4-11% (92). ACP offers a less painful and effective alternative to mitigate the acute rise in IOP following anti-VEGF administration (84). Theoretically, regular administration of ACP may reduce IOP spikes post-anti-VEGF administration, thereby preventing repeated stress on the p-RNFL. In patients with w-AMD who do not receive ACP, the loss in p-RNFL thickness (-2.16±3.60 μm) is markedly greater than in those who receive ACP regularly (93). The p-RNFL thickness declines with age at a rate of -0.21 $\mu\text{m}/\text{year}$ (65). Patients with w-AMD who do not receive ACP experience a loss of -0.86 $\mu\text{m}/\text{year}$ in p-RNFL thickness after an average of 2.5 years (93). This indicates a greater loss of p-RNFL thickness in long-term anti-VEGF injections for w-AMD than the age-related p-RNFL loss. Furthermore, there is a negative correlation between temporal p-RNFL and IOP following a combination of anti-VEGF injections (94). This suggests that higher IOP measurements are associated with a greater decrease in p-RNFL thickness, indicating that p-RNFL thickness loss is due to IOP spikes rather than age. In patients with w-AMD or DME treated with more than six ranibizumab or aflibercept injections, a significant acute and transient IOP increase is observed 5 min post-injection and significant p-RNFL thinning is observed by the third month (92). Additionally, similar immediate post-injection changes, such as IOP increases, are observed after 1 year (92). This suggests that repeated anti-VEGF injections could lead to irreversible changes in the optic nerve head structures. It appears that IOP elevation may be associated with p-RNFL thinning. The p-RNFL thickness may also be influenced by other factors, such as macular edema, in patients with w-AMD or DME treated with a combination of anti-VEGF treatments. The p-RNFL thickness in these retinopathies affecting the macula is greater than in age-matched control eyes (59). Although changes in p-RNFL thickness are markedly associated

with changes in central macular thickness in patients with DME, no such association exists in patients with AMD (60). Whether changes in macular edema in patients with w-AMD or DME affect p-RNFL thickness following a combination of anti-VEGF injections and to what extent, remains unclear.

Stereotactic radiotherapy (SRT) is a novel adjuvant approach for treating w-AMD (95). The mean number of anti-VEGF injections decreases by nearly 50% during the 12 months following SRT compared with the preceding year, while visual acuity improves (96). A single dose of SRT markedly reduces the need for anti-VEGF injections over 2 years without compromising visual acuity (97). Morphological changes only affect the outer retinal layers following SRT (96). It is necessary to investigate whether SRT, in conjunction with decreased anti-VEGF injections, affects p-RNFL thickness. It has been demonstrated that SRT in conjunction with ranibizumab and aflibercept does not lead to significant changes in p-RNFL thickness over 12 months in patients with w-AMD (94). Radiation of SRT can induce microvascular changes; however, only 1% of affected eyes exhibit a worsening of vision (97). Therefore, SRT may be a potential first step in preventing a worsening of vision as a result of a decrease in anti-VEGF injections. A combination of anti-VEGFs and SRT is thus a novel direction for the treatment of w-AMD.

Radial peripapillary capillaries (RPC) constitute the vascular network located within the RNFL (98). The relationship between RPC density and p-RNFL thickness has been extensively investigated in both healthy individuals (99) and those with pathological peripapillary retinas (100). A study suggested that there was a positive correlation between RPC-VD and p-RNFL thickness (101). However, a recent study by Zhuang *et al* (102) reported significant negative associations between transient reductions in RPC-VD and increases in p-RNFL thickness, primarily in the nasal regions, 1 week after treatment with a combination of conbercept, aflibercept and ranibizumab. These increases in p-RNFL thickness may be attributed to nerve fiber layer edema. Given that both RPC-VD and p-RNFL thickness returned to baseline values within 1-3 months post-injection, it appears that nerve fiber layer edema contributes to these negative correlations.

Brolucizumab has recently been approved for the treatment of w-AMD (103). It offers the potential for greater tissue penetration compared with earlier anti-VEGF agents and can deliver higher molar doses than larger molecules (104,105). Patients with refractory w-AMD who exhibit poor responses to other anti-VEGF treatments are often transitioned to brolucizumab. No significant changes in p-RNFL thickness have been observed within 3 months following a single brolucizumab injection, which is subsequently followed by a combination of aflibercept, bevacizumab and ranibizumab (3-37 injections) (62). However, a significant decrease in temporal p-RNFL thickness is noted 1 month after the brolucizumab injection, with this reduction dissipating after 3 months as macular edema increases (62). Therefore, the decrease in temporal p-RNFL thickness following brolucizumab injection in patients with w-AMD may be associated with improvements in macular edema. A single brolucizumab injection appears to be safe concerning p-RNFL damage in patients with intractable w-AMD.

6. Effects of anti-VEGF on p-RNFL in w-AMD concomitant with primary open-angle glaucoma (POAG)

POAG is a chronic optic neuropathy characterized by the thinning of p-RNFL (106). Elevated IOP is associated with an increased risk of POAG (107). Regular measurements of p-RNFL thickness are crucial for patients with POAG. Patients with POAG concomitant with w-AMD or DME are at risk of vision loss. Consequently, certain studies have investigated whether anti-VEGF treatments lead to further decreases in p-RNFL thickness and elevated IOP in these patients. Following a combination of aflibercept and ranibizumab, patients with w-AMD concomitant with POAG exhibited no changes in IOP; however, a statistically significant thinning of p-RNFL in the temporal quadrant was observed (108). This thinning of p-RNFL was attributed to the reduction of macular edema. A decrease in p-RNFL thickness was also observed in patients with w-AMD and POAG, as well as those with DME and POAG, following bevacizumab injections over 12 months (109). A more pronounced reduction in p-RNFL thickness was observed in patients with DME and POAG (109). Generally, p-RNFL thickness increases in patients with DME and this increment is associated with the degree of macular edema (110). In patients with DME and POAG, the p-RNFL is often thicker than in those with w-AMD and POAG. This increased thickness may account for the more pronounced post-injection changes in p-RNFL thickness. Consequently, ranibizumab, aflibercept and bevacizumab are considered safe therapeutic options for patients with w-AMD concomitant with POAG. Given that patients with POAG typically exhibit a compromised p-RNFL and that patients with w-AMD often present with a thinner p-RNFL, the potential alterations in p-RNFL thickness induced by anti-VEGF treatments warrant attention. Therefore, it is prudent to closely monitor p-RNFL thickness during anti-VEGF injections in patients with w-AMD, particularly those with DME and POAG.

7. Effects of anti-VEGF on p-RNFL in treated eyes with w-AMD and in the fellow eyes of patients with dry AMD

AMD is categorized into two types: W-AMD and dry AMD (d-AMD). While no effective treatment has been identified for d-AMD, w-AMD is successfully managed with anti-VEGF therapies (109). To compare p-RNFL thickness in treated w-AMD eyes with that in fellow d-AMD eyes, several studies have been conducted. However, the results of these studies vary. Wichrowska *et al* (58) reported that post-injection p-RNFL thickness in treated w-AMD eyes was 6.16 μm thinner (not statistically significant) compared with untreated fellow d-AMD eyes, with an increase in p-RNFL thickness observed in the nasal quadrant of the papillary region. Conversely, a study by Yau *et al* (111) indicated that post-injection p-RNFL thickness in treated w-AMD eyes was markedly greater than in non-treated fellow d-AMD eyes, with a notable increase in the temporal RNFL in the treated group. The authors attributed this to a fluid shift, spreading to the p-RNFL, due to macular thickening. Post-injection changes in p-RNFL thickness in the temporal quadrant markedly correlate with changes in central macular thickness (60). In patients with DR with macular edema, the p-RNFL was

significantly thicker compared with a control group (temporal quadrant: 117.1 ± 43.3 vs. 81.2 ± 13.8 μm ; nasal quadrant: 87.6 ± 22.1 vs. 70.8 ± 11.2 μm) (112). Furthermore, macular edema predominantly affected temporal and nasal p-RNFL thicknesses in patients with DME (110). The fluid shift associated with macular edema may extend to the temporal and nasal p-RNFL, explaining the observed thickening in different p-RNFL quadrants.

8. Effects of anti-VEGF on p-RNFL in DR

DME is the leading cause of visual impairment in patients with diabetes mellitus (113). DME and macular ischemia are primary contributors to DR-associated visual loss (114). Previously, focal/grid laser photocoagulation was the standard treatment (115), but its use is now primarily restricted to non-center-involved DME cases (116). Current treatment options for DME include anti-VEGF injections or dexamethasone implants (114). The p-RNFL thickness is generally greater in patients with DME than in age-matched controls and this increase markedly correlates with the degree of macular edema and peripapillary retinal thickness (59,60,112). Therefore, p-RNFL thickness measurements may be influenced by these conditions following anti-VEGF treatment in DR.

The post-injection p-RNFL thickness in patients with DR and macular edema is markedly reduced (110,112), with the most pronounced reduction observed in the temporal sector (110). This thinning of the p-RNFL may be attributed to changes in macular tomography following the resolution of macular edema (110). Given that p-RNFL thickness is strongly influenced by macular edema, the observed changes may not accurately reflect the actual gain or loss of p-RNFL in patients with DR with macular edema. However, Viggiano *et al* (114) reported no statistically significant changes in p-RNFL thickness and IOP fluctuations in patients with DR treated with anti-VEGF and dexamethasone. However, the authors did not specify whether macular edema was resolved post-anti-VEGF treatment, leaving it unclear whether the unchanged p-RNFL thickness and IOP were due to unresolved macular edema.

While panretinal photocoagulation (PRP) remains the standard treatment for proliferative DR, anti-VEGF injections have gained popularity as an adjunctive treatment for proliferative DR. PRP and anti-VEGF injections have both been associated with p-RNFL thinning in several studies (61,102). The effect of DME on p-RNFL thickness has been noted, with patients exhibiting a thicker p-RNFL, indicative of inner retinal edema (110,112). Consequently, the thinning of p-RNFL following anti-VEGF treatment could be due to the resolution of inner retinal edema. Significant p-RNFL thinning after proliferative DR treatment may be attributed to axonal loss secondary to PRP treatment (117). Studies have reported on the combined effects of PRP and anti-VEGF on p-RNFL. Unlike patients treated solely with PRP, where p-RNFL thickness is markedly greater than baseline, no significant p-RNFL changes were observed in patients with DR treated with both PRP and anti-VEGF injections (118). The thickening of p-RNFL could be associated with PRP-induced intra-retinal inflammation, which increases capillary permeability and results in axonal edema due to cytokine release (117). Elevated

levels of inflammatory factors are detected in the proliferative DR eyes with larger non-perfusion areas (25). These findings suggest that anti-VEGF injections may mitigate the effects of PRP and protect p-RNFL. Proliferative DR eyes treated with anti-VEGFs exhibit greater p-RNFL thinning than those treated with PRP after 2 years (119). Although diabetic retinal thickening is typically attributed to outer retinal edema, the inner retina, including p-RNFL, may also become edematous (110,112). Therefore, a reduction in nerve fiber layer edema (inner retina) could contribute to p-RNFL thinning in patients treated with anti-VEGFs (119). The p-RNFL consists of the axons of retinal ganglion cells that form nerve fiber bundles converging upon the optic nerve head (120). There is a weak negative association between p-RNFL thickness and visual field in DR patients treated with anti-VEGFs (thinner retina, less field loss), whereas a positive association (thinner retina, more field loss) is observed in patients treated with PRP. (119). Thus, a loss of axons may be responsible for the p-RNFL thinning in patients treated with PRP. In patients treated with anti-VEGF injections, it is also possible that the damage to the axons is not sufficient to influence the visual field function. Therefore, it is not possible to rule out that the p-RNFL thinning could be associated with the loss of axons after anti-VEGF treatment.

9. Effects of anti-VEGF on p-RNFL in RVO

RVO is the second most common retinal vascular disorder, after DR (121). RVO impairs vision and induces macular edema (122) and is categorized into branch and central RVOs based on the location of the vascular obstruction (123). Although various factors contribute to vision loss in RVO, macular edema secondary to RVO is the predominant cause (124). The p-RNFL thickness in eyes affected by RVO is associated with central macular thickness (125). Consequently, retinal edema is typically observed in the early stages of RVO, leading to an increase in p-RNFL thickness in the affected eyes (126). Studies examining the relationship between p-RNFL thickness and retinal/macular edema in patients with RVO have demonstrated that both p-RNFL and central macular thickness are elevated following the acute event in both branch and central RVO due to the ensuing acute edema, with significant reductions observed after anti-VEGF injections (127). Pre- and post-injection p-RNFL thickness is notably greater in patients with central RVO compared with those with branch RVO (127). Patients with central RVO-associated macular edema generally experience more severe vision loss than those with branch RVO, with deterioration often persisting despite treatment (128). Therefore, central RVO is likely to result in more severe and extensive edema than branch RVO, leading to a markedly thicker p-RNFL in patients with central RVO compared with those with branch RVO, both before and after anti-VEGF treatment.

Risk factors for RVO include systemic diseases that cause vascular abnormalities, such as hypertension and diabetes (125,126). Increased attention has been directed towards the unaffected fellow eye in patients with RVO. The reduction in p-RNFL thickness is markedly greater in the fellow eyes of patients with RVO than in healthy individuals over time, following an initial increase due to retinal

edema (120,129). Age and concurrent systemic comorbidities, such as hypertension, should be considered as factors contributing to the decrease in p-RNFL thickness over time in the fellow eyes of patients with RVO (126). Additionally, p-RNFL thickness is markedly thinner in the fellow eyes of patients with central RVO compared with those of patients with branch RVO and healthy individuals over time, suggesting that the fellow eyes of patients with central RVO are more susceptible to p-RNFL damage (125). These findings indicate that the p-RNFL of the fellow eyes of patients with RVO is prone to damage, necessitating increased attention to the fellow eye when administering anti-VEGF treatments.

10. Effects of anti-VEGF on papillary/peripapillary blood circulation in w-AMD

In patients with w-AMD, the VD values decrease in both affected and unaffected eyes compared with healthy individuals (130). A number of studies have documented changes in blood circulation parameters in the papillary/peripapillary regions of patients with w-AMD following anti-VEGF treatment, including reductions in peripapillary VD (102), peripapillary arterial diameter (131), peripapillary pulsatility index (PI) (85), MBR (132-134), peripapillary arteriolar blood flow and blood flow velocity (131) and peripapillary PD (85).

A significant association has been identified between peripapillary VD and p-RNFL thickness in healthy individuals, while a negative association between age and peripapillary VD is observed in the peripapillary region (135). Due to their distinct pattern and distribution, RPC may be more susceptible to IOP than other retinal capillaries (99). Consequently, several studies have been conducted to examine changes in p-RNFL and RPC following anti-VEGF injections. A notable reduction in peripapillary VD in RPC and an increase in p-RNFL thickness, particularly in the nasal regions, are observed 1 week after anti-VEGF injections for w-AMD. Subsequently, over 1-3 months, peripapillary VD and p-RNFL thickness generally returned to baseline values (102). w-AMD is considered not only an exudative vascular event but also a chronic inflammatory disease of the retina (136). The overexpression of VEGF and IP-10 characterizes the inflammatory cytokine profile in the aqueous humor of patients with w-AMD (26,27). IP-10 is implicated in the pathogenesis of w-AMD (137) and functions as a pro-inflammatory cytokine (138). Following anti-VEGF treatment, IP-10 levels increase (26). A transient p-RNFL edema is observed post-anti-VEGF treatment for w-AMD (102), potentially representing an early manifestation of inflammation. Given the strong association between a decrease in PRC-VD and an increase in p-RNFL thickness, the p-RNFL edema may be a response to the reduction in PRC-VD (102).

A number of studies have examined alterations in MBR following anti-VEGF injections for w-AMD. Post-injection, the MBR of the optic nerve head in w-AMD patients is markedly reduced after 30 min (132), 45 min (134) and 1 week (133), with these reductions persisting throughout a 3-month follow-up period (133). In the peripapillary retinal region, the arteriolar diameter markedly decreases in patients with w-AMD; however, arterial blood flow does not exhibit significant changes (131). It remains unclear whether the

measurement of a non-significant change in blood flow, despite a significant effect on arteriolar diameter, is attributable to the technical limitations of CLBF and SLDF. With the marked post-injection decreases in MBR, IOP notably increased in the treated eyes and return to baseline values after 30 min; however, the MBR at the optic nerve head and the region of large vessels was markedly reduced for up to 60 min (134). Conversely, other studies have reported that significant decreases in MBR in the treated eyes were accompanied by a stable IOP (102) and the peripapillary PD and PI were not associated with post-injection IOP (85). Furthermore, considering that the optic nerve head can autoregulate its blood flow in response to experimental changes in ocular perfusion pressure induced by IOP elevations (132), the changes in papillary/peripapillary blood circulation parameters in patients with w-AMD could reflect the direct pharmacologic effects of anti-VEGFs on the vasculature of the papillary/peripapillary regions. These effects could potentially disrupt the normal morphological and functional characteristics of blood vessels in these regions (102). These findings warrant further investigation into the potentially adverse effects of anti-VEGF treatment on papillary/peripapillary microcirculation, particularly in vulnerable eyes. No changes in MBR have been observed in the untreated fellow eyes of patients with w-AMD following anti-VEGF injection (133,134), suggesting no potential effect of anti-VEGF on the untreated fellow eye via the systemic route. Additionally, the peripapillary blood circulation parameters are not associated with the number of anti-VEGF injections (85) or the types of anti-VEGF treatments (132).

11. Effects of anti-VEGF on papillary/peripapillary blood circulation in DR

Anti-VEGFs are short-acting drugs and a single anti-VEGF injection is generally not sufficient for the elimination of retinopathies (139). An acute rise of IOP appears to be relatively common immediately after anti-VEGF injection, with most studies indicating the spontaneous normalization of IOP within 30 min to several hours (42,48,49,91). Short-term IOP spikes have been reported to range from 49 mmHg (7) to 72 mmHg (140), but can be as high as ≥ 90 mmHg (8) after an anti-VEGF injection. Given the need for frequent injections, particularly in patients with DR, there are reports of long-term IOP increases. During a follow-up of >12 months, anti-VEGF injections are associated with sustained IOP elevations and this is likely due to the administration of multiple injections (141). The repeated episodes of IOP spikes might lead to glaucoma-like progression (9). An acute increase in IOP and a reduction in peripapillary perfusion density occur immediately after an anti-VEGF injection in patients with DR (140). With the increase in IOP (a maximum of 49 mmHg), it is not common to see changes in VLD and VD during a short-term follow-up (7). Furthermore, IOP spikes in patients who have received multiple anti-VEGF injections may resolve after a day (7). This suggests that multiple anti-VEGF injections can lead to persistent increased IOP. However, the question of whether the post-injection acute IOP increase is associated with the decreased peripapillary perfusion remains to be causally determined. Therefore, an elevated IOP due to anti-VEGF

injections remains a concern, despite its generally favorable safety profile (8).

A transient but significant decrease in peripapillary CV is observed in patients with DR 1-2 weeks after anti-VEGF injections, suggesting that anti-VEGF treatments have a transient inhibitory effect on the peripapillary distribution, which gradually diminishes over time (142). Although anti-VEGF treatments reduce angiogenic drive and neovascularization (1), they do not cause a reorganization of the retinal microcirculation distribution. This may explain a key limitation of current anti-VEGF treatments: Their short-lived effects (139). In a rabbit model, anti-VEGF treatments suppressed vascular leakage for 8-10 weeks, before recurrence of leakage to pre-treatment levels (143). Symptoms frequently recur as soon as the effect of anti-VEGF treatments wears off. This leads to the need for frequent anti-VEGF injections. Furthermore, no correlation is observed between the decreases in the peripapillary CV distribution and the improvements in the best-corrected visual acuity 3 months post-injection (142). This suggests that anti-VEGF treatment improves visual acuity primarily by promoting the resolution of macular edema rather than changing peripapillary CV distribution.

PRP has been established for >40 years as an effective treatment for high-risk proliferative DR (144). However, PRP can cause several complications, such as visual field defects, decreased visual acuity (145), epiretinal membrane formation, macular edema (146), retinal detachment and vitreous hemorrhage (144). Anti-VEGF treatments were found to be superior to PRP after a 2-year follow-up (144). An RPC-VD increase is observed in patients with proliferative DR treated with anti-VEGF and a decrease was found in those treated with PRP (147). Moreover, the visual acuity gain was higher in patients treated with anti-VEGF than in those treated with PRP (147). Thus, anti-VEGF markedly improves proliferative DR compared with the negative effect of PRP on RPC-VD.

12. Effects of anti-VEGF on papillary/peripapillary blood circulation in RVO

VD of RPC in the fellow and affected eyes in patients with RVO is markedly lower than that in the normal subjects (148). In different retinal layers, eyes affected by RVO compared with the unaffected eyes and the unaffected fellow eyes as compared with the eyes of the healthy subjects, showed a lower VD (149). Macular edema secondary to branch RVO is a common retinal vascular condition that causes severe visual loss. Several therapies have been introduced to treat edema, such as anti-VEGF treatments (127), laser photocoagulation (150), intravitreal or sub-Tenon's injection of triamcinolone acetonide (151) and pars plana vitrectomy (152). At present, anti-VEGF treatments are the strongest evidence-based therapy, reaching evidence level I (153).

Prior to treatment, the RPC-VD in patients with branch RVO is lower than that in the fellow eyes (154-156) and the RPC-VD in the fellow eyes is lower than in normal subjects (155,156). Additionally, before treatment, the p-RNFL thickness in patients with branch RVO is greater than that in the fellow eyes (154-156), while the p-RNFL thickness in the fellow eyes is reduced compared with normal subjects (154,156). This suggests that the microvasculature of the unaffected fellow eyes

also exhibits ischemic changes and alterations in the p-RNFL are already present. Consequently, greater attention should be directed towards the prevention of complications in the unaffected fellow eye and the management of systemic diseases. However, there are instances where no significant difference in p-RNFL thickness is observed between the fellow eyes and those of normal subjects (155), indicating that macular edema may not yet have affected the p-RNFL. Following anti-VEGF injections, a significant decrease in p-RNFL thickness is observed in the treated eyes, accompanied by an increase in RPC-VD at 3 months (155), 4 months (154) and 6 months (156). The initial thickening of the p-RNFL before treatment, followed by thinning post-anti-VEGF injections, is attributed to the regression of edema. Regarding the fellow eyes, Liu *et al* (154) reported no significant differences in p-RNFL thickness and RPC-VD before and after treatment. Similarly, Nicolai *et al* (157) found that RPC-VD in the fellow eyes was not statistically significant, while post-injection RPC-VD was markedly elevated in the affected eyes with central RVO; however, the RPC-VD of the affected eye remained lower than that of the fellow eyes. The authors attributed the gradual increase following anti-VEGF therapy to a sudden reduction in RPC-VD after an RVO event (157). The absence of changes in the fellow eyes indicates that there is no potential systemic effect of anti-VEGF on the untreated fellow eye.

In a study examining branch RVO with macular edema, changes in the vessel MBR were investigated. The findings indicated that the MBR values at 1, 3 and 6 months were 38.3 ± 7.3 , 37.4 ± 9.4 and $41.2 \pm 7.3\%$, respectively (158). When compared with the baseline level of $40.2 \pm 8.5\%$, the slight increase observed at 6 months in the treated eyes was comparable to that in the unaffected fellow eyes, which was $41.0 \pm 8.3\%$ (158). By contrast, Nagasato *et al* (159) reported a slight decrease in MBR in eyes affected by central RVO, with values of $34.8 \pm 11.2\%$ at baseline, $32.0 \pm 10.3\%$ at 1 month, $31.6 \pm 10.9\%$ at 3 months and $32.9 \pm 12.2\%$ at 6 months, although these changes did not reach statistical significance. The discrepancies between the two studies may be attributed to measurement errors caused by the dilation or blood stasis of papillary capillary vessels, which obscure the boundary between the vessel and tissue in LSFG images. Furthermore, Nagasato *et al* (159) also observed that best-corrected visual acuity and retinal sensitivity at 1, 3 and 6 months were markedly improved compared with baseline. Similarly, another study indicated that visual acuity markedly improved and macular thickness markedly decreased during a 2-month follow-up, with a notable reduction in MBR and RFV following anti-VEGF treatment in branch RVO eyes (160). These findings suggest that anti-VEGF treatment induces transient vasoconstriction of the papillary/peripapillary vessels, leading to a reduction in blood flow and velocity. The alterations in papillary/peripapillary microcirculation may not affect vision and retinal sensitivity.

13. Effects of anti-VEGF on papillary/peripapillary blood circulation in DME

In patients with DME, the MBR in the papillary and peripapillary retinal vessels markedly decreases at 1 week (12), 2 weeks (161) and 1 month (162) post-injection. This reduction is associated with a decrease in macular edema and an

improvement in best-corrected visual acuity. No significant differences in MBR reduction were observed between different types of anti-VEGF agents, such as aflibercept and faricimab (162). During anti-VEGF treatment, there is a notable reduction in vascular calibers, an indicator of vascular integrity, in the retina of DME patients and macular edema is markedly reduced (163). It is established that VEGF induces vasodilation of retinal vessels, increasing retinal blood flow and velocity, likely due to elevated nitric oxide levels (161,164). Anti-VEGF agents are effective not only in resolving macular edema but also in inducing vasoconstriction (12). Furthermore, post-injection regression of macular edema was not correlated with a reduction in vascular caliber in the retinal vessels of patients with DME (163). This suggests that anti-VEGF therapy reduces macular edema and improves vision, potentially, also diminishing papillary and peripapillary microcirculation and disrupting vascular integrity due to vasoconstriction.

A meta-analysis of 21 randomized clinical trials involving 9,557 patients with DME reported that the frequency of systemic side effects following anti-VEGF treatment was not high in patients with retinal diseases (165). In a study by Fung *et al* (166), which was similar to the aforementioned meta-analysis, an internet-based survey of 5,228 patients with retinopathies was conducted to evaluate systemic complications from anti-VEGF therapy, concluding that none of the adverse event rates exceeded 0.21%. Another review of 10 trials, encompassing >4,000 patients with DME, suggested that the rates of ocular and systemic adverse events following anti-VEGF injections were comparable to those of the controls (167). Thus, there remains controversy regarding the systemic circulation of anti-VEGF agents. Sugimoto *et al* (12) evaluated the effects of anti-VEGF therapy on the papillary circulation of the fellow eyes in patients with DME and found that, unlike the treated eyes, significant changes in MBR were not observed in the untreated fellow eyes. This suggests that anti-VEGF agents may not enter the systemic circulation at concentrations sufficient to affect the circulation of the fellow eyes. However, the precise mechanisms causing systemic complications in patients with retinopathies treated with anti-VEGF agents remain unclear, necessitating further research. Additionally, no significant short-term changes are observed in RPC-VD, IOP and p-RNFL thickness in DME eyes treated with anti-VEGF agents (114). This indicates no short-term effects of anti-VEGF therapy on peripapillary microcirculation; however, further prospective studies with longer follow-up periods are required to confirm these findings.

14. Discussions on effects of anti-VEGF on p-RNFL in retinopathies

Thinning p-RNFL in the affected eyes. In examining the long-term effects (≥ 12 months), a significant thinning of the p-RNFL was observed in patients with w-AMD from 12 months to 8 years post-injection (61,63,68,86,92-94) and in patients with DR after 24 months (119). Regarding short-term effects (<12 months), significant p-RNFL thinning was noted in patients with w-AMD from 2 min to 4 months post-injection (60,75,76,81,108,109,168), in patients with DR from 1-6 months post-injection (110,112) and in RVO patients from 3-9 months post-injection (127,154-156).

Thickening p-RNFL in the affected eyes. Significant p-RNFL thickening was observed in patients with w-AMD from 3-47.9 months post-injection (58,102,111). A slight increase in p-RNFL thickness post-injection was found in patients with w-AMD (74) or non-proliferative DR concomitant with DME (114), although this increase did not reach statistical significance.

No changes in p-RNFL thickness in the affected eyes. No changes in p-RNFL thickness have been reported in several studies, indicating no significant alterations in p-RNFL thickness in patients with w-AMD during a follow-up period of 1-96 months post-injection (6,69,70-73,77,80). Of note, repeated anti-VEGF injections appeared to have no detrimental effects on p-RNFL.

Factors contributing to discrepancies in p-RNFL thickness. Contradictory results have been described in the effects of anti-VEGF on p-RNFL in retinopathies, such as p-RNFL thinning, p-RNFL thickening and no change. The present study systematically categorize factors contributing to discrepancies as IOP, edema, normal course of retinopathies, aging and co-morbidities. For p-RNFL thinning, studies are divided into long-term and short-term based on study duration.

Role of IOP spikes. For long-term p-RNFL thinning, data are mixed regarding the relationship between post-injection IOP increase and p-RNFL thinning. Certain studies suggest that p-RNFL thickness loss could be attributed to IOP spikes rather than age, with repeated anti-VEGF injections potentially leading to changes in optic nerve head structures (92-94). However, other findings indicate no changes in IOP accompanying p-RNFL thinning (63,68). Thus, the involvement of post-injection IOP elevation in long-term p-RNFL thinning remains contested, necessitating further investigation. For short-term p-RNFL thinning, the relationship between elevated IOP and p-RNFL thinning is also debated. A significant negative correlation between increased IOP and p-RNFL thinning, with IOP spikes immediately after anti-VEGF injection potentially affecting p-RNFL integrity, has been observed (71,75). Conversely, several studies have reported that short-term increased IOP may not be severe enough to cause p-RNFL damage (76,108). In cases where no changes in p-RNFL thickness were observed, sustained IOP was not detected (6,71-73,77).

Effect of edema. The long-term thinning of the p-RNFL is probably attributable to the anatomical improvement of macular lesions. By contrast, the short-term thinning of p-RNFL may be explained by the regression of retinal/macular edema following anti-VEGF injections (119,156). Another potential explanation is that in patients newly diagnosed with w-AMD, baseline p-RNFL values may have been elevated due to edema spreading from the macula, rather than actual thinning of the p-RNFL (111). Regarding the thickening of p-RNFL, there are two perspectives on the effect of edema. One view suggests that anti-VEGF injections may transiently affect relatively normal retinal vessels, leading to decreased blood flow and subsequent nerve fiber edema (102). Alternatively, the thickened p-RNFL may result from fluid spreading from the thickened central retina in patients with w-AMD (111). In studies reporting no changes in p-RNFL thickness, there is no mention of changes in patient edema (6,71-73,77).

Normal course of retinopathies. The normal progression of retinopathies may also contribute to the long-term thinning of p-RNFL, as observed in diabetic retinas (119), suggesting that the thinning could be a natural course rather than an effect of anti-VEGF treatment.

Aging. Aging is another factor, with p-RNFL thickness declining by $0.21 \mu\text{m}$ per year (65). Advanced age in patients with w-AMD is markedly associated with reduced p-RNFL thickness (66) and higher stages of w-AMD are associated with a thinner p-RNFL (67). Additionally, in patients with unilateral w-AMD, the fellow eyes exhibited thinner p-RNFL over a 12-month study period (42), indicating that aging may be linked to thinning.

Co-morbidities. Co-morbidities also play a role in the long-term thinning of p-RNFL. Hypertensive retinopathy, for example, involves high blood pressure damaging both retinal microcirculation and RNFL (169). Diabetes mellitus is another example, with a thinner p-RNFL observed in patients without diabetic retinopathy (170). Abnormalities in blood vessels by diabetes mellitus and hypertension (systemic diseases) give rise to RVO and glaucomatous optic neuropathy (125). Glaucoma is more prevalent in patients with RVO compared with healthy individuals (126). In patients with glaucoma, RNFL declines by $0.76 \pm 0.85 \mu\text{m}$ per year during 3.7 ± 1.5 years (171). Visual field damage in glaucoma, corresponding with RNFL thinning, is observed in the fellow eyes of certain patients with unilateral RVO (172). These findings suggest that RVO and glaucoma may share systemic risk factors, reflecting a common pathogenic mechanism (172). Consequently, the long-term thinning of p-RNFL in patients with retinopathy may be attributed to coexisting glaucoma.

Effects of anti-VEGF on the unaffected fellow eyes. No changes in the p-RNFL thickness have been observed in the fellow eyes, accompanying the post-injection thinning in the affected eyes after 1 year, indicating no effects via the systemic route (68). However, significant thinning was detected in both the fellow and affected eyes in an 8-year follow-up (63). The effect should have been cumulative over aging, although the systemic route was not excluded.

Correlation between the number of anti-VEGF injections and p-RNFL thickness in the affected eyes. Studies have reported that there are no associations between the number of injections (from 3-50 injections) and the p-RNFL thickness (64,66,68-70,85). However, other studies have suggested that there were associations and the injection number ranged from 11.27 ± 9.31 (58), 19.29 ± 6.92 (94) and ≥ 30 (86). Additionally, no associations have been reported between the types of anti-VEGF treatments and the p-RNFL thickness (132).

15. Discussions on effects of anti-VEGF on papillary/peripapillary blood circulation in retinopathies

Improvements in blood circulation in the affected eyes. An increase in VD was observed in patients with branch RVO (154-156), central RVO (157) and DR (147) following anti-VEGF treatment. There are three potential explanations for the observed improvement in blood circulation: i) The

anti-VEGF treatment reduces inflammatory features in macular edema (156,173-175); ii) the treatment enhances the compression of blood vessels and re-perfuses occluded capillaries (154); or iii) there may be an overestimation of blood circulation parameter values. Prior to anti-VEGF injection, these values might be underestimated due to macular edema, which causes a masking effect or retinal vessel displacement (157) and the movement rate of red blood cells may fall below the detection limit of OCTA due to increased blood viscosity and a decreased blood flow velocity in patients with retinopathies (154). Consequently, post-injection values may be overestimated, suggesting that a statistically significant increase after anti-VEGF injections may not reflect a genuine statistical gain.

Inhibited blood circulation in the affected eyes. Inhibited blood circulation has been observed in the affected eyes. Post-injection decreases in MBR were observed in patients with w-AMD within 30 min-3 months (102,132-134). A slight reduction in MBR post-injection was also noted in patients with central RVO (159) and branch RVO (160). Several studies have reported a decrease in post-injection MBR in patients with DME within 1-4 weeks (12,161,162). Additionally, post-injection decreases in VD (102), flux index (85), arterial diameter (131), perfusion density (140), vascular caliber (163) and CV (142) have been documented.

Potential reasons for the inhibited blood circulation due to anti-VEGF treatments are: i) Vasoconstriction, a possible pharmacological effect of anti-VEGF treatments accompanied by regression of macular edema and improvement in visual acuity (12,161,162) and retinal sensitivity (159); ii) increased IOP; certain studies have suggested a significant post-injection increase in IOP, accompanied by a significant reduction in blood circulation parameters (140). However, other findings indicate no correlation between post-injection changes in IOP and blood circulation parameters (85,102,132). Thus, the involvement of acute increased IOP after anti-VEGF injections in the reduction of peripapillary perfusion remains contested; iii) upregulation of pro-inflammatory cytokines in patients with w-AMD due to anti-VEGF treatments. In certain patients, IP-10 and IL-6 levels increased following anti-VEGF injections (26). The up-regulation of adhesion molecule levels during inflammation caused leukocyte arrest, potentially leading to capillary lumen obstruction (156); iv) measurement error due to obscuring the border between tissue and vessel on LSF images, caused by blood stasis or capillary vessel dilation (159).

Lack of changes in blood circulation in the affected eyes. Several short-term studies have reported no significant alterations in blood circulation parameters following an anti-VEGF injection (7,114). While these findings suggest an absence of short-term effects, further research employing prospective designs and extended follow-up periods are necessary to validate these results.

Potential mechanistic discussions of the effects of anti-VEGF on the papillary/peripapillary microcirculation in retinopathies. The potential mechanisms underlying the effects of anti-VEGF on papillary and peripapillary microcirculation

in retinopathies warrant discussion. VEGF-induced vasodilation may enhance blood flow to neuronal tissues, potentially contributing to neuroprotection in the retina, thereby indicating the neuroprotective role of VEGF (176). Ischemia is one of the important causes of retinopathy. The pathological mechanisms of retinal ischemia-reperfusion injury are complex, involving oxidative stress (OS), inflammation and neuronal apoptosis (177). OS-induced inflammatory cytokines, such as intercellular adhesion molecule-1, are implicated in VEGF transcription, with increased VEGF expression further exacerbating inflammation (178).

The results suggest that anti-VEGF injections mitigate certain types of damage induced by ischemia-reperfusion injury, such as increased VD in patients with branch RVO post-anti-VEGF injections (154-156), potentially due to reduced expression of inflammatory factors (156), decreased retinal cell apoptosis with significant downregulation of cleaved caspase-3 (177) and inhibition of oxidative stress via activation of the Akt/Nrf2 pathway by the anti-VEGF treatment and N-Acetylserotonin (177). However, potential reasons for reduced blood circulation by anti-VEGF treatments include vasoconstriction (161), upregulation of IL-6, a pro-inflammatory cytokine (26) and increased IOP (140). Although vasoconstriction may reduce edema (162), decreased volumetric blood flow to neuronal tissues could adversely affect the optic nerve. IL-6 induces phosphorylation (S47) of Sirtuin 1 through activation of PI3K/AKT/mTOR signaling, thereby inhibiting Sirtuin 1 activity and increasing acetylation of E2F transcription factor 1, consequently elevating apoptosis in RPE cells under OS (27). Additionally, elevated adhesion molecule levels during inflammation can cause leukocyte arrest, potentially obstructing the capillary lumen (156) and resulting in decreased blood flow to neuronal tissue. The volume of anti-VEGF injections could induce ischemia mediated by elevated IOP, possibly leading to decreased blood flow to neuronal tissue (8). However, the increase in IOP due to the volume of anti-VEGF injections typically returns to baseline over time. Therefore, further investigation is required to determine whether anti-VEGF affects the optic nerve due to decreased volumetric blood flow to neuronal tissues caused by increased IOP and if so, whether retinal neuronal cell damage is related to recurrent vascular defects, or whether retinal blood vessels become more susceptible to damage from repeated elevated IOP in patients with retinopathy undergoing multiple anti-VEGF injections remains to be determined, particularly in those with pre-existing vasculopathy or glaucoma.

Effects of anti-VEGF on the unaffected fellow eyes. In patients with retinopathies post-injection, no statistically significant changes in the blood circulation parameters were observed in the fellow eye, accompanying the changes in the affected eyes (12,133,134,154,157). It is possible that anti-VEGF treatments do not enter the systemic circulation in a concentration at a high enough level to affect the circulation of the fellow eyes.

Correlations between the number of anti-VEGF injections and blood circulation in the affected eyes. No correlations have been observed between blood circulation parameters and the different types of anti-VEGF treatments (132,162) or the number of anti-VEGF injections (85).

16. Conclusions

Present data are mixed on the effects of anti-VEGF on p-RNFL in patients with retinopathies. Researchers commonly attribute the p-RNFL thinning to edema regression, ageing and the physiological course of retinopathies. It is still contested whether the p-RNFL thinning is due to an elevated IOP. The effects of anti-VEGF on papillary/peripapillary blood circulation in retinopathies have been evaluated in numerous studies; however, the results remain inconclusive. Researchers commonly attribute the reduced blood circulation to vasoconstriction, upregulated pro-inflammatory cytokines and measurement errors following anti-VEGF injections. It is still contested whether the reduced blood circulation is due to an elevated IOP.

In summary, these discrepancies across studies indicate the complex responses to anti-VEGF treatments on p-RNFL and papillary/peripapillary blood circulation in patients with retinopathies. No direct evidence of optic nerve damage associated with anti-VEGF treatment has been reported. Studies with large cohorts and long follow-up times are required to explore whether anti-VEGF treatment has adverse effects on p-RNFL and papillary/peripapillary blood circulation, which subsequently leads to damage of the optic nerve in patients with retinopathies.

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Authors' contributions

HW conceived and designed the entire review and wrote the manuscript and created the images. RD and WJ collected the literature. SL, YW, JM and YC proofread the manuscript. PS and MS were fully responsible for drafting and finalizing the review. All authors contributed to the article. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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