Review Article

Systemic and ocular complications related to intravitreal administration of anti-VEGF agents

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ABSTRACT

Background: Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the backbone of the treatment of neovascular retinal disorders and among the most frequently performed procedures in ophthalmic practice. This narrative review aims to summarize the current evidence on systemic and ocular adverse events associated with intravitreal anti-VEGF therapy and to reiterate their clinical implications in daily practice.

Methods: A structured PubMed/MEDLINE database search was conducted to identify relevant manuscripts published between 1 January 2004 and 31 March 2026. Search strategies included combinations of keywords and controlled vocabulary related to intravitreal anti-VEGF therapy and associated adverse events. Evidence from randomized trials, observational research, meta-analyses, experimental models, and case reports or series were included to provide a broad perspective.

Results: Systemic adverse events associated with intravitreal anti-VEGF therapy appear to be uncommon; however, potential cardiovascular events, blood pressure alterations, and renal effects have been reported, particularly in patients with preexisting vascular risk factors. Ocular complications represent the most frequently discussed as safety concerns. Sterile intraocular inflammation is among the most clinically relevant events and may range from mild self-limited reactions to severe inflammatory blinding conditions such as occlusive retinal vasculitis. Distinguishing sterile inflammation from infectious endophthalmitis is critical, as clinical management and prognosis differ substantially. Elevation of intraocular pressure is another frequently observed complication and may present either as a transient spike occurring immediately after the injection or as sustained ocular hypertension following repeated treatments. Additional ocular complications reported in the literature include rhegmatogenous retinal detachment, retinal tears, retinal vascular occlusions, cataract formation, and retinal pigment epithelium tears.

Conclusions: Although intravitreal anti-VEGF therapy is generally safe, a wide variety of ocular and systemic adverse events has been described. Timely recognition and individualized monitoring strategies are key to excel in treatment safety and achieve better visual outcomes.

KEYWORDS

adverse effects, aflibercept, anti-VEGF agents, bevacizumab, brolucizumab, endophthalmitis, faricimab, glaucoma, intraocular pressure, intravitreal injections, ranibizumab, rhegmatogenous retinal detachment, retinal pigment epithelium, vascular endothelial growth factor.

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INTRODUCTION

Since its introduction, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has become a key treatment alternative in the management of macular edema of various etiologies, improving both anatomical and functional outcomes [1, 2]. In 2004, pegaptanib was the first anti-VEGF agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of neovascular age-related macular degeneration, but was discontinued in 2019 [3]. Ranibizumab, bevacizumab (off-label), and aflibercept are widely used anti-VEGF agents with proven efficacy in suppressing pathological angiogenesis [2].

More recently, additional anti-VEGF agents have expanded the therapeutic options available. Brolucizumab was approved in 2019 for the treatment of neovascular age-related macular degeneration and subsequently in 2022 for diabetic macular edema [4, 5], although its clinical use has remained limited because of safety concerns. Faricimab was subsequently approved for neovascular age-related macular degeneration and diabetic macular edema in 2022, and later for retinal vein occlusion in 2024 [6–8]. Aflibercept 8 mg was also approved in 2024, further broadening the therapeutic options [3]. Abicipar pegol, another anti-VEGF therapy evaluated for neovascular age-related macular degeneration, did not receive FDA approval, largely owing to a higher incidence of intraocular inflammatory events observed in clinical studies [9, 10].

Because of its high efficacy, low risk, and ease of use, anti-VEGF therapy has become a preferred treatment modality. Despite these advantages, serious systemic and ocular adverse effects have been reported [11–13]. The aim of this narrative review is to provide an overview of the ocular and systemic complications associated with intravitreal anti-VEGF therapy and to discuss their clinical relevance.

METHODS

This narrative review was based on a structured search of the PubMed/MEDLINE database, without language restrictions, to identify articles published between 1 January 2004 and 31 March 2026. Search strategies incorporated combinations of free-text keywords and Medical Subject Headings (MeSH) related to intravitreal anti-VEGF therapy and its associated complications, including terms such as “intravitreal injections”, “vascular endothelial growth factor”, “anti-VEGF agents”, “endophthalmitis”, “intraocular pressure”, “glaucoma”, “retinal detachment”, and “adverse effects”. Emphasis was placed on clinically meaningful studies addressing systemic and ocular safety outcomes of intravitreal anti-VEGF therapy. Priority was given to randomized clinical trials, large observational studies, meta-analyses, and influential experimental investigations, while case reports and case series were also reviewed to provide additional insight into relatively rare complications. Studies were selected based on their clinical relevance, methodological rigor, and contribution to the understanding of safety outcomes.

RESULTS and DISCUSSION

1. Systemic Adverse Events

Intravitreal anti-VEGF agents can reach systemic circulation at detectable levels; intravitreal injection may lead to suppression of systemic VEGF activity, potentially facilitating systemic adverse events [14]. Consequently, even limited systemic exposure after intravitreal administration has raised systemic concerns [7]. Thromboembolic events, myocardial infarction, cerebrovascular events, hypertension, and renal dysfunction are among the main systemic complications attributed to intravitreal anti-VEGF therapy [14]; several rare systemic adverse events associated with the therapy are also reported in the literature (Table 1) [15–28].

Although controlled trials have not shown a clear increase in major systemic events, real-world data suggest that patients with significant vascular risk factors may warrant more careful monitoring [29]. The following sections primarily address cardiovascular and thromboembolic complications, blood pressure alterations and renal effects.

1.1. Cardiovascular Safety and Arterial Thromboembolic Risk

Available systematic reviews and meta-analyses indicate that intravitreal anti-VEGF agents, including bevacizumab, ranibizumab, and aflibercept, are not associated with an increased risk of major adverse cardiovascular events such as myocardial infarction, stroke, or cardiovascular death compared with controls [12, 30, 31].

A pharmacovigilance analysis based on the VigiBase database, including over 23 000 reported adverse drug reactions related to intravitreal anti-VEGF therapy, identified higher reported rates of cardiovascular and cerebrovascular events compared with the overall database. These events included myocardial infarction, angina, arrhythmias, hypertension, and hypertensive crisis. In comparative analyses, aflibercept showed lower reporting odds for myocardial infarction, atrial fibrillation, and cerebrovascular events than ranibizumab [32].

Table 1. Previously reported rare systemic complications associated with intravitreal injections of FDA-approved anti-VEGF agents

Author (Year)	Anti-VEGF Agent	Age / Sex	Indication	Complication	Key Clinical Features	Management & Outcome
Kasl et al. (2015) [15]	Ranibizumab	74 / F	CSCR	Pituitary apoplexy	Headache, ptosis, diplopia and vision loss 2 days after intravitreal injection; hemorrhage in a pituitary adenoma compressing the optic chiasm.	Urgent endoscopic transsphenoidal tumor resection with corticosteroid therapy; ophthalmoplegia resolved and vision significantly improved.
Cifuentes-Canorea et al. (2016) [16]	Ranibizumab	75 / F	nAMD	Charles Bonnet syndrome	Structured visual hallucinations starting 10 days after injection.	Spontaneous resolution.
Attal et al. (2018) [17]	Ranibizumab	83 / F	nAMD	Digital ischemia with distal phalangeal necrosis	Acute ischemia of the left hand with occlusion of radial and ulnar arteries one month after injection.	Endovascular revascularization and antithrombotic therapy; clinical improvement with auto-amputation of distal phalanx.
Emami et al. (2020) [18]	Ranibizumab	76 / F	nAMD	Dental implant failure	Failure of two immediately loaded mandibular implants within 6 weeks despite adequate primary stability 20 days after injection.	Conversion to single-implant overdenture; long-term stable outcome.
Gan et al. (2022) [19]	Ranibizumab	57 / M	CRVO	Membranoproliferative glomerulonephritis	Proteinuria, hematuria and renal failure 2 weeks after injection.	Discontinuation of injections; spontaneous recovery of renal function.
Li et al. (2023) [20]	Ranibizumab	53 / M	nAMD	Esophageal ulcer	Dysphagia and retrosternal pain 3 days after injection; endoscopic esophageal ulcer.	Discontinuation of ranibizumab and proton pump inhibitor therapy; complete healing without recurrence.
Rzayev et al. (2023) [21]	Ranibizumab	43 weeks / M	ROP	Intestinal perforation	Abdominal distension and free intraperitoneal air 12 hours after injection.	Surgical bowel resection and jejunostomy; stabilization.
Zhou et al. (2023) [22]	Ranibizumab	53 / F	BRVO	Guillain–Barre syndrome	Limb weakness progressing to respiratory paralysis after injection.	ICU care and IVIG therapy; gradual recovery without relapse.
Fuerte-Hortigon et al. (2023) [23]	Ranibizumab	50 / M	nAMD	Guillain-Barre syndrome	Paresthesia and gait instability with electrophysiologic evidence of demyelinating neuropathy.	IVIG therapy; complete recovery.
Morotti et al. (2024) [24]	Ranibizumab	27 weeks / M	ROP	Necrotizing enterocolitis	Large bowel necrotizing enterocolitis episode occurring within the first week after injection.	Neonatal ICU care.
Nagai et al. (2017) [25]	Aflibercept	60 / M	PCV	Systemic maculopapular rash	Generalized erythematous papular eruption with pruritus 10 hours after injection.	Oral prednisolone; rash resolved.
Batteux et al. (2019) [26]	Aflibercept	80 / F	nAMD	Ischemic colitis	Abdominal pain and rectal bleeding 3 days after injection.	Conservative treatment and drug discontinuation; symptoms resolved.
Ornek et al. (2021) [27]	Aflibercept	62 / M	DME	Sudden sensorineural hearing loss	Tinnitus and profound unilateral hearing loss 4 days after injection.	Otorhinolaryngology evaluation and treatment (not specified); no improvement after 10 days.
Hamadneh et al. (2021) [28]	Aflibercept	63 / F	DME	Transient ischemic attack with hypoventilation	Confusion, right-sided weakness and hypoventilation 12 hours after injection.	ICU supportive care; complete recovery within 24 hours.

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CSCR, central serous chorioretinopathy; DME, diabetic macular edema; F, female; FDA, Food and Drug Administration; ICU, intensive care unit; IVIG, intravenous immunoglobulin; M, male; nAMD, neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor

Differences between these findings may reflect methodological variation, as meta-analyses are based on controlled trial data, whereas pharmacovigilance studies rely on real-world reporting that may be influenced by bias and confounding. Nonetheless, the observed safety signals support careful monitoring, particularly in patients with existing cardiovascular or cerebrovascular disease [12].

1.2. Blood Pressure Alterations and Renal Implications

Beyond its angiogenic role, VEGF is integral to endothelial regulation through its effects on nitric oxide synthesis and vascular relaxation. Pharmacologic blockade of VEGF may disrupt this pathway, predisposing to vasoconstriction and hypertension [33]. Reduced VEGF activity can lead to diminished capillary perfusion, commonly termed microvascular rarefaction, potentially contributing to higher systemic blood pressure. Additional mechanisms may involve dysregulation of vasoactive mediators, resulting in endothelial dysfunction, as well as renal effects that promote sodium retention and volume expansion [7, 34, 35].

Despite these potential biological mechanisms, clinical evidence regarding the risk of hypertension following intravitreal anti-VEGF therapy remains inconsistent. Findings from a recent systematic review and meta-analysis indicated similar hypertension rates among ranibizumab, bevacizumab, aflibercept, brolucizumab, and faricimab, and did not demonstrate an increased risk when anti-VEGF therapy was compared with sham control [7].

Current literature suggests that intravitreal anti-VEGF therapy does not appear to cause significant short- to medium-term renal impairment, even in patients with diabetes or chronic kidney disease. However, careful monitoring is recommended, particularly in individuals with borderline or severely reduced baseline renal function [12, 36].

2. Local (Ocular) Adverse Events

Although intravitreal anti-VEGF injections are generally considered safe, a variety of ocular adverse events may occur, ranging from mild, transient reactions to rare but vision-threatening complications. The most notable ocular complications include sterile intraocular inflammation, endophthalmitis, transient or sustained elevation of intraocular pressure (IOP) that may contribute to glaucoma, retinal detachment, retinal tears, retinal vascular occlusions, and cataract formation [1, 37, 38]. In addition to these well-recognized complications, several rare ocular adverse events are also described in the literature, as summarized in Table 2 [39–77].

2.1. Inflammatory Complications

2.1.1. Sterile Intraocular Inflammation

Sterile intraocular inflammation, sometimes accompanied by occlusive retinal vasculitis, has been reported after intravitreal anti-VEGF injections [78–80]. This inflammation likely reflects a multifactorial process that remains incompletely understood [11]. Anderson et al. grouped the potential factors into three categories: patient-related, drug-related, and delivery system factors [81]. Patient-related factors reflect individual immune predisposition, including anti-drug antibody formation, disruption of the blood-retina barrier, and prior inflammatory eye disease. Drug-related factors arise from the immunogenic profile of the agent and may be influenced by impurities, endotoxins, formulation properties, and structural features such as the Fc domain. Delivery-related factors are linked to syringe components and handling conditions, including silicone oil contamination and mechanical stressors that can promote protein aggregation and inflammatory cascades [81–84].

The safety profile of anti-VEGF agents is also influenced by their immunogenic potential, which depends on molecular design, manufacturing processes, and host immune variability [84]. Immunogenicity differs among agents [1]. Faricimab's bispecific antibody structure is associated with measurable rates of both pre-existing and treatment-emergent anti-drug antibodies, which may contribute to inflammatory or occlusive retinal events. Its Fc region, however, has been engineered to reduce receptor binding and may help mitigate systemic and inflammatory effects. Aflibercept appears to have relatively lower immunogenicity, consistent with its VEGFR1/2-Fc fusion protein structure [85]. In contrast, brolucizumab has been associated with the highest rates of antibody formation, with pre-existing anti-drug antibodies reported in approximately 36–52% of clinical trial patients—a finding that may partly explain its heightened risk of intraocular inflammation and vascular complications [4, 86, 87]. Patient characteristics may also influence immunogenicity. Repeated intravitreal exposure has been proposed to promote the development of anti-drug antibodies, which may increase the likelihood of immune reactions with subsequent injections [81].

Table 2. Previously reported rare ocular complications associated with intravitreal injections of FDA-approved anti-VEGF agents.

Author (Year)	Anti-VEGF Agent	Age / Sex	Indication	Complication	Key Clinical Features	Management & Outcome
Querques et al. (2009) [39]	Ranibizumab	79 / F	nAMD	Macular hole	Stage 2 macular hole developed 1 month after injection	Persistence of macular hole
Georgalas et al. (2009) [40]	Ranibizumab	71 / M	nAMD	Filtering bleb leak with severe hypotony	Positive Seidel test, IOP 2 mmHg with corneal edema after injection	Surgical repair with pericardial graft; IOP normalized
Meyer et al. (2010) [41]	Ranibizumab	88 / F	nAMD	Choroidal detachment	Asymptomatic inferotemporal choroidal detachment detected 1 month after injection	Observation; spontaneous resolution
Grigoropoulos et al. (2010) [42]	Ranibizumab	67 / F	nAMD	Full-thickness macular hole	Full-thickness macular hole developed over retinal pigment epithelium tear 1 month after injection	Observation
Micieli et al. (2011) [43]	Ranibizumab	64 / M	nAMD	Third nerve palsy	Acute ptosis, impaired adduction and elevation 2 weeks after injection	Observation; complete spontaneous resolution within 7 weeks
Ranchod et al. (2011) [44]	Ranibizumab	81 / M	nAMD	Hyphema	Visual decline with red blood cells in the anterior chamber 1-7 days after injection	Topical atropine and steroid; resolution with return to baseline vision
Thoongsuwan et al. (2011) [45]	Ranibizumab	41 / M	MNV secondary to radiation retinopathy	Blebitis	Infected filtering bleb with mucopurulent discharge 3 days after injection	Intravitreal, subconjunctival, topical, and oral antibiotics
Shienbaum et al. (2012) [46]	Ranibizumab	73 / F	nAMD	Orbital hemorrhage	Bullous 360° subconjunctival hemorrhage extending into the orbit 1 day after injection	Observation; spontaneous resolution
Bastion et al. (2012) [47]	Ranibizumab	28 / F	PDR	Intraocular crystallization	Multicolored crystals in anterior chamber and subretinal space 1 day after injection	Vitrectomy with removal of crystals
Raiji et al. (2013) [48]	Ranibizumab	69 / F	nAMD	Full-thickness macular hole	Visual decline with full-thickness macular hole overlying retinal pigment epithelium detachment 1 month after injection	Vitrectomy with membrane peeling and gas tamponade; hole closure with visual improvement
Kon Graversen et al. (2013) [49]	Ranibizumab	77 / M 66 / M	nAMD BRVO	Hyphema	Anterior chamber bleeding immediately after injection with transient IOP rise	Observation; spontaneous resolution with recovery of vision
Aslan Bayhan et al. (2014) [50]	Ranibizumab	56 / M	DME	Marginal keratitis	Peripheral subepithelial corneal infiltrates with mild anterior chamber reaction	Topical steroid and antibiotic therapy; complete resolution
Al Bdour and Ali (2014) [51]	Ranibizumab	50 / M	DME	Intravitreal cotton fiber foreign body	Cotton fiber suspended in posterior vitreous causing floaters	Observation; no inflammation during follow-up
Caglar et al. (2016) [52]	Ranibizumab	55 / M	DME	Isolated sixth nerve palsy	Diplopia with abduction limitation 4 days after injection	Spontaneous resolution within 2 months
Sluch et al. (2016) [53]	Ranibizumab	54 / M	DME	Scleral abscess related to *Mycobacterium chelonae*	Injection-site pain and erythema starting 10 days after injection; progression to scleral abscess without intraocular inflammation	Incision and drainage alongside topical, subconjunctival, and systemic antibiotics; complete resolution by return to baseline vision
Kabanarou et al. (2017) [54]	Ranibizumab Ranibizumab Aflibercept Ranibizumab	66 / M 64 / F 67 / M 57 / F	nAMD	Full-thickness macular hole	Full-thickness macular hole 1-4 months after injection	Not specified

Onda et al. (2019) [55]	Ranibizumab	63 / M	BRVO	Corneal endothelitis and anterior uveitis related to *human herpes virus 6*	Corneal edema, keratic precipitates, IOP 45 mmHg 20 days after injection	Oral and topical antivirals; inflammation resolved and vision returned to baseline
Pan et al. (2021) [56]	Ranibizumab	67 / M	nAMD	Acute retinal necrosis related to *varicella zoster virus*	Visual decline and peripheral necrotizing retinitis with vitritis 3 days after injection	Systemic and intravitreal antiviral therapy and vitrectomy; severe residual visual loss
Ozturk et al. (2021) [57]	Ranibizumab	54 / M	DME	Herpetic keratouveitis	Corneal edema, dendritic ulcer and marked IOP rise 1 week after injection	Oral antiviral therapy alongside topical antiviral and steroid; complete resolution
Oshiro et al. 2021) [58]	Ranibizumab	66 / M	BRVO	Rapid macular pucker with partial traction retinal detachment	Rapid ERM proliferation causing retinal folds and traction	Vitrectomy with membrane removal and scleral buckle; retina attached with visual improvement
Goel (2022) [59]	Ranibizumab	67 / M	CRVO	Full-thickness macular hole	Full-thickness macular hole with hyperreflective material 1 month after injection	Observation; spontaneous closure with visual improvement
Lima-Fontes et al. (2022) [60]	Ranibizumab	52 / M	Angioid streaks-related MNV	Hypotony maculopathy	Vision loss, low IOP, and chorioretinal folds 2 days after injection; recurrence after second injection with scleral wound leak.	First episode treated with topical steroid and atropine; second episode required scleral suture plus topical therapy; resulted in IOP normalization and visual recovery
Kim (2024) [61]	Ranibizumab	78 / M	nAMD	Capsular block syndrome	Posterior capsular distension with fluid accumulation 1 week after injection	Nd:YAG capsulotomy; visual improvement
Liang et al. (2024) [62]	Ranibizumab	23 / F	Pachychoroid-related MNV	Hypotony maculopathy with multiple serous retinal detachments	Visual decline, hypotony, multiple serous retinal detachments, bacillary layer detachment and chorioretinal folds with marked choroidal thickening mimicking Vogt-Koyanagi-Harada disease one day after injection	Topical and systemic steroids; IOP normalized and serous retinal detachments resolved with visual recovery
Oshima et al. (2015) [63]	Aflibercept	94 / M	nAMD	Full-thickness macular hole	Visual decline with full-thickness macular hole after 3 loading injections	Observation; macular hole persisted at 1 year with stable poor vision
Kabanarou et al. (2017) [54]	Aflibercept	67 / M	nAMD	Full-thickness macular hole	Full-thickness macular hole 1 month after injection	Not specified
Hernandez-Pons et al. (2021) [64]	Aflibercept	98 / F	nAMD	Necrotizing scleritis related to *Aspergillus terreus*	Pain and injection-site scleral necrosis with purulent discharge 2 weeks after injection	Topical antifungal therapy and surgical debridement; infection resolved
Hebert et al. (2022) [65]	Aflibercept	51 / M	CRVO	Posterior scleritis	Severe ocular pain, photophobia, choroidal folds and scleral thickening 3 days after injection	Oral and topical steroids; posterior scleritis resolved with improvement of choroidal folds
Ali Said et al. (2022) [66]	Aflibercept	71 / F	nAMD	Full-thickness macular hole	Central scotoma with full-thickness macular hole 4 weeks after injection	Surgery recommended but declined

Drnovsek and Lumi (2022) [67]	Aflibercept	86 / M	nAMD	Intravitreal cotton fiber foreign body	White thread-like fiber in posterior vitreous after injection	Vitrectomy with removal of fiber; vision stabilized
Radwan et al. (2022) [68]	Aflibercept	48 / M	CRVO	Acute macular neuroretinopathy	Central scotoma with OPL/ONL hyperreflectivity on optical coherence tomography 5 days after injection	Partial resolution of scotoma with spontaneous improvement
Paxton et al. (2022) [69]	Aflibercept	82 / F	nAMD	Nonarteritic anterior ischemic optic neuropathy	Optic disc edema with inferior altitudinal visual field defect 1 day after injection	Temporary cessation of injections
Khoo et al. (2022) [70]	Aflibercept	84 / F 77 / F	nAMD	Submacular hemorrhage	Large subretinal macular hemorrhage with visual decline after injection	Vitrectomy with subretinal tPA; hemorrhage resolved but vision limited
Gopalakrishnan et al. (2024) [71]	Aflibercept	49 / F	Myopic MNV	Progression of myopic macular retinoschisis	Worsening retinoschisis with perifoveal retinal detachment after injection	Pars plana vitrectomy with ERM/ILM peeling; anatomical improvement with stable vision
Sim et al. (2022) [72]	Brolucizumab	71 / M	nAMD	Choroidal effusion	Serous choroidal effusion 3 days after injection	Observation; spontaneous resolution within 12 days
Schonbach et al. (2023) [73]	Faricimab	70 / F	nAMD	Suprachoroidal hemorrhage with choroidal detachment	Ocular pain, visual field defect and hypotony 1 day after injection	Conservative management; hemorrhage resolved in 2 months
Kitson et al. (2025) [74]	Faricimab	69 / F	DME	Hypertensive uveitis	Bilateral episodes with IOP 42 and 35 mmHg 4 weeks after injections	Steroid and antiglaucoma drops; complete resolution
Sano et al. (2025) [75]	Faricimab	72 / F	BRVO	Full-thickness macular hole	Developed 1 month after injection in eye with vitreomacular traction	Vitrectomy with ILM peeling; hole closure and visual recovery
Kaganovski et al. (2025) [76]	Faricimab	78 / M	nAMD	Submacular hemorrhage	Large submacular hemorrhage spanning vascular arcades with sudden vision loss	Vitrectomy with tPA deferred due to rebleeding risk; switched to aflibercept; long-term subretinal fibrosis with severe visual loss
Tabuenca Del Barrio et al. (2020) [77]	Not specified	57 / F	nAMD	Infectious scleritis related to *Mycobacterium chelonae*	Severe ocular pain and scleral abscess at injection site 1 week after injection	Topical and oral antibiotics; infection resolved with residual scleral thinning

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DME, diabetic macular edema; ERM, epiretinal membrane; F, female; ILM, internal limiting membrane; IOP, intraocular pressure; IV, intravenous; M, male; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; Nd:YAG, neodymium-doped yttrium aluminum garnet; ONL, outer nuclear layer; OPL, outer plexiform layer; PDR, proliferative diabetic retinopathy; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

Clinically, sterile intraocular inflammation after anti-VEGF therapy generally presents in two patterns: early-onset and delayed-onset inflammation. The acute form typically occurs within several days of injection and is characterized by ocular discomfort, reduced vision, and inflammatory cells in the anterior chamber and vitreous [88]. In contrast, delayed inflammation (reported with agents like brolucizumab and faricimab) usually develops around two weeks after treatment and may be associated with retinal vasculitis or occlusive vascular events [89]. Occlusive vasculitis is a severe, vision-threatening form of intraocular inflammation marked by inflammatory retinal vessel occlusion, which leads to capillary nonperfusion, retinal ischemia, and secondary neovascularization [29]. Acute inflammation is thought to involve IgE-mediated type I hypersensitivity reactions, whereas delayed presentations are more consistent with type IV hypersensitivity responses that may intensify with repeated exposure [78].

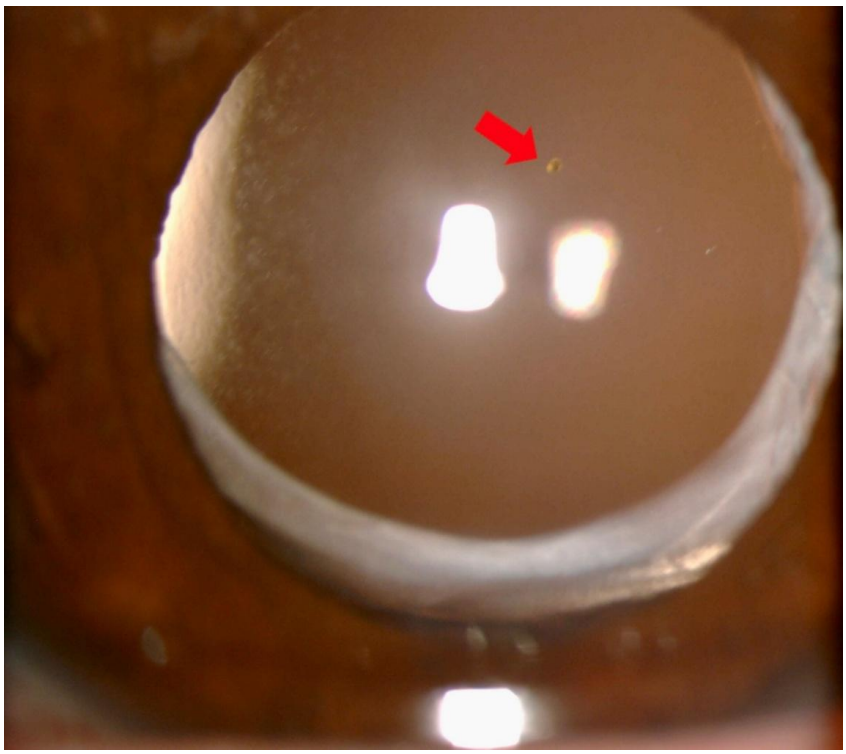

Figure 1. Silicone oil droplet detected following intravitreal ranibizumab (Lucentis®, Novartis, Basel, Switzerland) injection for branch retinal vein occlusion in the right eye of a 54-year-old male patient. Slit-lamp examination demonstrating a silicone oil droplet (red arrow), presumably originating from the injection syringe, located in the anterior vitreous cavity.

Hypersensitivity to pharmacological agents may develop through several immunologic pathways. Small molecules can act as haptens by binding to host proteins and forming neoantigens that are recognized by antigen-presenting cells. Alternatively, direct interactions with HLA complexes or T-cell receptors may trigger inappropriate T-cell activation [9].

The presence of silicone oil droplets in the vitreous cavity after repeated intravitreal injections was first documented by Freund et al. in 2006 [90]. Silicone oil microdroplets have been commonly observed in the anterior vitreous following intravitreal injections, with reported prevalence rates ranging from 68% to 78% (Figure 1)**.** Factors such as freeze-thaw cycles, mechanical agitation, spray-siliconized low-dead-space syringes, and improper plunger handling may contribute to the formation of either asymptomatic droplets or symptomatic floaters [91]. In certain cases, silicone oil droplets have also been proposed as a potential trigger of intraocular inflammatory responses [82, 92]. Mechanical processes during drug preparation, including syringe agitation and silicone oil contamination, may further promote protein or particulate aggregation capable of activating innate immune pathways, such as the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [83, 92, 93]. Wei et al. [82] also described the potential benefits of silicone-free prefilled syringes. Lower silicone oil exposure may reduce intraocular accumulation with repeated injections, a factor associated with increased IOP and occasional inflammatory reactions [82].

Post-marketing surveillance of faricimab identified cases of retinal vasculitis and retinal vascular occlusion, leading to a safety communication from Genentech in November 2023 [78, 94]. One proposed mechanism involves protein aggregation within faricimab preparations interacting with residual silicone oil from syringes, potentially triggering inflammatory responses. In addition, faricimab has been associated with a somewhat higher frequency of severe intraocular inflammation compared with earlier anti-VEGF agents, which may relate to differences in molecular structure or manufacturing processes [84].

A population-based observational pharmacovigilance analysis shows increased reporting of inflammatory adverse events with faricimab compared with aflibercept and ranibizumab. These events primarily involved intraocular inflammation affecting both anterior and posterior segment structures, including vascular inflammatory manifestations such as retinal vasculitis. Nevertheless, the overall incidence remained lower than that observed with brolucizumab, which has been associated with the highest risk of both inflammatory and occlusive complications [1]. Yavari et al. [78] reported bilateral hemorrhagic occlusive retinal vasculitis with panuveitis after intravitreal faricimab administration. Similarly, to

brolucizumab-related cases, vitreous analysis revealed a chronic lymphohistiocytic infiltrate, suggesting a possible delayed type III and IV hypersensitivity reaction [78]. Still, real-world evidence suggests that the overall incidence of such events remains low. In a large real-world study conducted at a tertiary referral center, intraocular inflammation associated with faricimab was reported in 0.19% of injections, with most cases presenting as mild anterior uveitis and showing favorable visual outcomes, further supporting its safety profile [95].

Additional pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) have identified safety signals for drug-related uveitis associated with several anti-VEGF agents, including aflibercept and faricimab; however, these data do not provide reliable information on administered doses, limiting dose-specific interpretation [96]. Notably, faricimab evidenced one of the strongest disproportionality signals among ophthalmic drugs in this database [96]. In contrast, retrospective multicenter real-world data from the FARTURK study reported only a single mild inflammatory case, suggesting that clinically significant inflammation remains uncommon in routine practice [6].

Inflammatory complications have also been described with other anti-VEGF agents. Acute sterile intraocular inflammation following intravitreal aflibercept, bevacizumab, or ranibizumab has been reported with rates ranging from 0.02% to 0.37% [97, 98]. Shortly after its approval in 2011, aflibercept (2 mg) was associated with reports of intraocular inflammation, with the American Society of Retina Specialists Research and Safety in Therapeutics Committee documenting 66 cases within the first two years [96].

Recently, concerns have been raised regarding a possible increase in intraocular inflammation and retinal vasculitis among patients receiving aflibercept 8 mg [99, 100]. Matsumoto et al. [100] suggested that the higher incidence of intraocular inflammation with aflibercept 8 mg may reflect its more pronounced VEGF-A inhibition relative to the 2-mg dose [100]. Excessive VEGF inhibition may impair endothelial stability, potentially increasing the risk of inflammatory complications [99]. A large pharmacovigilance analysis using FAERS data further reported that aflibercept 8 mg showed the strongest association with intraocular inflammatory events, including vitritis, retinal vasculitis, and sterile endophthalmitis, compared with aflibercept 2 mg and faricimab [92]. Real-world data suggest that sterile intraocular inflammation with aflibercept 8 mg may occur more frequently than in clinical trials, with significantly lower rates observed when prefilled syringes are used instead of vial preparations [101]. However, both faricimab and aflibercept 8 mg carry a low but clinically meaningful risk of immune-mediated intraocular inflammation, with no clear difference between them [92].

Transient dense vitreous opacity has been reported after combined injection of pegcetacoplan and faricimab. Experimental findings suggest that this phenomenon may result from reversible formulation incompatibility, most likely related to faricimab, with spontaneous resolution as the material disperses within the vitreous cavity [102]. Similar vitreous opacity is observed with brolucizumab injections alone, without concurrent intravitreal therapy [103]. The relatively high rate of treatment-emergent antidrug antibodies observed with brolucizumab has been attributed to its unique structural properties, including its low molecular weight, single-chain antibody fragment design, and high molar concentration [104].

2.1.2. Infectious Endophthalmitis

Post-injection endophthalmitis represents a rare yet clinically devastating complication with an incidence rate of 0.056% (Figure 2) [105]. In some studies, the reported incidence of endophthalmitis reached 0.3% [106, 107]. Both the pattern and severity of clinical findings play a key role in assessing post-injection inflammation. The key clinical features distinguishing sterile intraocular inflammation from infectious endophthalmitis are summarized in Table 3 [108]. Severe pain, hypopyon, and rapid visual decline tend to indicate an infectious origin, while mild, transient inflammatory changes typically reflect a sterile reaction [108]. Post-injection endophthalmitis is typically related to contamination from the patient's skin or conjunctival flora, most commonly involving coagulase-negative staphylococci and streptococcal species [107, 109].

Table 3. Comparative clinical features of sterile intraocular inflammation and infectious endophthalmitis following intravitreal anti-VEGF injections [108]

Feature	Sterile Intraocular Inflammation	Endophthalmitis
Onset	1-7 days (or delayed ~2 weeks)	2-5 days
Pain	Mild or absent	Severe
Vision loss	Mild to moderate	Severe and rapid
Hypopyon	Rare	Common
Redness	Mild	Marked conjunctival injection
Anterior chamber/vitreous reaction	Variable, usually mild to moderate	Severe and diffuse
Management	Steroids, observation	Urgent intravitreal antibiotics ± pars plana vitrectomy
Prognosis	Generally favorable	Variable, often poor

Abbreviations; VEGF, vascular endothelial growth factor.

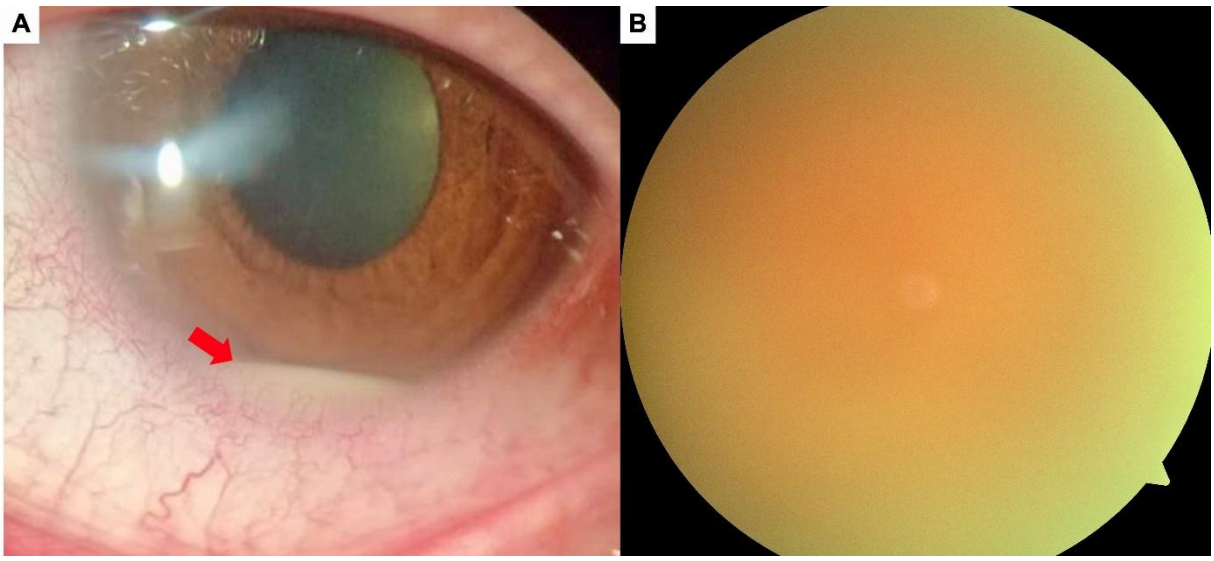

Figure 2. Endophthalmitis occurring after intravitreal bevacizumab (Avastin®, F. Hoffmann-La Roche AG, Basel, Switzerland) injection for neovascular age-related macular degeneration in the left eye of a 55-year-old female patient. (A) Slit-lamp examination displaying marked conjunctival hyperemia accompanied by hypopyon (red arrow). (B) Color fundus photograph (VISUCAM 500®, Carl Zeiss Meditec, Jena, Germany) showing severely impaired visualization of the posterior segment secondary to dense vitritis.

In a multicenter study comparing dexamethasone implant and anti-VEGF injections over a 5-year period in U.S. outpatient centers, dexamethasone implants were associated with a significantly higher incidence of endophthalmitis [107]. A French nationwide cohort of more than 3.5 million injections also reported a higher endophthalmitis rate with corticosteroids (0.067%) than with anti-VEGF agents (0.020%) [110].

A large retrospective cohort study including 43 393 eyes and 652 421 intravitreal anti-VEGF injections (ranibizumab, aflibercept, and bevacizumab) reported an overall endophthalmitis incidence of 0.035% per injection (approximately 1 in 2857 injections). The authors observed that the cumulative risk of endophthalmitis increased with the number of injections, with a steeper rise during earlier injections and a more gradual increase later in the treatment course. However, subsequent correspondence suggests that alternative statistical approaches incorporating censoring (e.g., Kaplan-Meier analysis) might yield different estimates of cumulative incidence [111].

Findings from the IRIS® Registry suggest that endophthalmitis following the first anti-VEGF injection most often develops within the first week, typically between days 3 and 8. The likelihood of occurrence seems to vary depending on patient-related factors, particularly prior intravitreal corticosteroid exposure and underlying clinical or demographic characteristics, while non-smoking status may be protective. Earlier symptom onset has been observed in older individuals, as well as in those with diabetic retinopathy or a history of corticosteroid treatment [112].

In a retrospective cohort analysis, Patel et al. [113] assessed whether systemic immunosuppressive therapy influences the risk of endophthalmitis after intravitreal anti-VEGF injections. The study included over 270 000 injections and demonstrated that patients receiving systemic immunosuppressive medications had a markedly higher likelihood of developing post-injection endophthalmitis compared with non-immunosuppressed individuals. Furthermore, the onset of symptoms occurred earlier in this group. Still, despite the increased risk of infection, visual acuity outcomes at six months were similar between the two groups [113].

No significant differences in endophthalmitis incidence have been observed among anti-VEGF agents [114]. The risk of endophthalmitis appears to be greater in patients receiving treatment for diabetic retinopathy or age-related macular degeneration compared with those treated for branch or central retinal vein occlusion. Reduced immune competence in diabetic and elderly patients may partly explain this finding [115].

Povidone-iodine antisepsis remains the most effective measure to reduce bacterial load during intravitreal injections. Additional precautions may further reduce risk, whereas routine prophylactic topical antibiotics are not recommended due to lack of efficacy and potential for antimicrobial resistance [116, 117]. According to a recent systematic review and meta-analysis, topical antibiotic prophylaxis is not associated with a reduced risk of endophthalmitis and may even increase the risk in patients receiving intravitreal anti-VEGF injections [118]. Eyelids, eyelashes, and the associated glands may act as potential reservoirs of infection. An eyelid speculum may help minimize contamination during needle insertion [114].

Recent evidence suggests that injection technique and drug preparation methods may also influence the risk of endophthalmitis. A large meta-analysis showed that the use of prefilled syringes was associated with a 47–48% reduction in endophthalmitis risk compared with glass vial preparations, highlighting the importance of procedural factors in improving injection safety [119]. This reduction likely reflects the elimination of manual preparation steps, thereby minimizing contamination risk and particulate exposure during drug handling [120]. In addition, the use of prefilled syringes has been linked to lower rates of culture-positive endophthalmitis [121]. Consistently with these observations, good manufacturing practice (GMP)-grade prefilling, involving preparation under controlled conditions by specialized pharmacies, is also shown to reduce endophthalmitis risk [122].

2.2. Pressure-Related Complications

2.2.1. Acute IOP Elevation

Several factors have been associated with severity of acute IOP elevation following intravitreal injection, including absence of subconjunctival reflux, smaller needle size, tunneled injection techniques, phakic lens status, corneal biomechanical properties, and a history of glaucoma [123]. Among these, the lack of subconjunctival reflux appears to be the most important risk factor [124]. Previous studies suggest that eyes without subconjunctival vitreous reflux are more likely to experience IOP elevations above 25 mmHg within 30 minutes of injection [125, 126]. Both injection technique and needle size play a role in the development of reflux. Needles with a larger bore create a wider scleral entry tract, which raises the likelihood of reflux [127].

Another important risk factor for severe acute ocular hypertension and delayed recovery after intravitreal injection is a prior history of glaucoma [128]. Although glaucoma is associated with impaired aqueous humor drainage, evidence linking a diagnosis of glaucoma to post-injection IOP elevation remains inconsistent [124].

Lens status appears to influence early IOP fluctuations after intravitreal injection. Pseudophakic eyes, characterized by a deeper anterior chamber and wider angle after cataract surgery, may exhibit less pronounced pressure elevations than phakic eyes. However, existing evidence on this topic is conflicting [126, 129, 130]. Eyes with shorter axial length and smaller vitreous volume have also been identified as a potential risk factor for immediate IOP elevation following intravitreal injection [126, 129].

Currently available anti-VEGF therapies are generally administered at an intravitreal volume of 0.05 mL. However, aflibercept 8 mg is delivered at a volume of 0.07 mL, which has raised concerns regarding the potential risk of IOP elevation [3, 131]. Paris et al. [132] evaluated IOP 30 seconds after intravitreal injection and observed a smaller pressure spike with faricimab than with aflibercept, while the 2-mg and 8-mg aflibercept doses showed no significant difference [132].

Prefilled syringes have become the preferred method for administering contemporary anti-VEGF therapy. Their advantages include simpler handling, shorter injection time, reduced risk of infectious endophthalmitis, and improved dosing accuracy. Aflibercept 2 mg, brolucizumab, and ranibizumab biosimilars are available in this format. However, compared with vial formulations of aflibercept 2 mg, prefilled syringes are associated with more frequent immediate IOP spikes and an approximately fivefold higher risk of transient visual acuity reduction [3]. The larger barrel diameter of prefilled syringes may increase dosing alignment errors, while the lower injection force may promote more rapid delivery of the injected solution [133].

A retrospective cohort study evaluated whether the use of filtered anti-VEGF agents administered with silicone-free syringes influences the incidence of ocular hypertension following intravitreal injections. Compared with conventional insulin syringes containing non-filtered medication, the use of filtered anti-VEGF in silicone-free syringes was associated with significantly lower rates of IOP elevation. Notably, no cases of severe IOP increase or need for pressure-lowering therapy were observed in the silicone-free syringe group. These findings suggest that filtration of anti-VEGF agents and the use of silicone-free syringes may help reduce the risk of post-injection ocular hypertension [134].

2.2.2. Sustained IOP Elevation and Glaucoma

Repeated intravitreal anti-VEGF injections have been linked to chronic ocular hypertension in some patients, which is distinct from the transient IOP elevation observed immediately after each injection [124]. In an analysis of the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trials, Bakri et al. [135] reported higher rates of IOP elevation in patients treated with ranibizumab compared with control groups. These findings suggest that repeated anti-VEGF therapy may lead to sustained ocular hypertension in a subset of patients and may also indicate a possible dose-related effect [135]. Moreover, a population-based study from Canada reported that patients receiving seven or more

injections per year were more likely to undergo glaucoma drainage surgery [136].

Several mechanisms have been suggested to explain sustained IOP elevation after repeated anti-VEGF injections, including possible obstruction of the trabecular meshwork by microparticles such as silicone oil droplets or protein aggregates [137]. It has also been suggested that intravitreal anti-VEGF agents may directly affect trabecular meshwork cells [124]. Protein aggregates or other high-molecular-weight molecules may induce inflammation in the trabecular meshwork, leading to trabeculitis and decreased aqueous outflow [138, 139].

Anti-VEGF agents may also affect aqueous outflow directly, as VEGF receptors are expressed in the trabecular meshwork and Schlemm's canal endothelial cells [140]. VEGF signaling promotes endocytosis of vascular endothelial cadherin, whereas its inhibition may disrupt endothelial barrier function and reduce cellular permeability [141]. In addition, anti-VEGF therapy may lower nitric oxide bioavailability through inhibition of nitric oxide synthase, which can alter potassium and calcium ion dynamics in trabecular meshwork cells and affect their contractile properties [142]. Together with stabilization of endothelial junctions, decreased endothelial fenestrations, and reduced nitric oxide production, these mechanisms may contribute to impaired aqueous humor outflow and sustained IOP elevation during anti-VEGF therapy [124].

Wen et al. [143] proposed a potential "2-hit" hypothesis, suggesting that eyes with underlying outflow dysfunction may be more susceptible to sustained ocular hypertension following repeated anti-VEGF injections [143]. This hypothesis may partly explain why sustained ocular hypertension occurs only in a minority of patients [124].

2.3. Structural Complications

2.3.1. Cataract Formation

Cataract formation reported during anti-VEGF therapy is generally attributed to the injection procedure rather than to a direct pharmacological effect of the agents [1]. Most cases arise from inadvertent lens injury during injection, an uncommon complication with an estimated incidence of approximately 0.006%, and appear to occur more frequently in hyperopic eyes [144]. In these cases, traumatic cataracts typically develop following accidental contact between the injection needle or intravitreal implant and the crystalline lens during the procedure [145]. Quiescent posterior capsular injuries have also been documented after intravitreal injections (Figure 3) [146, 147].

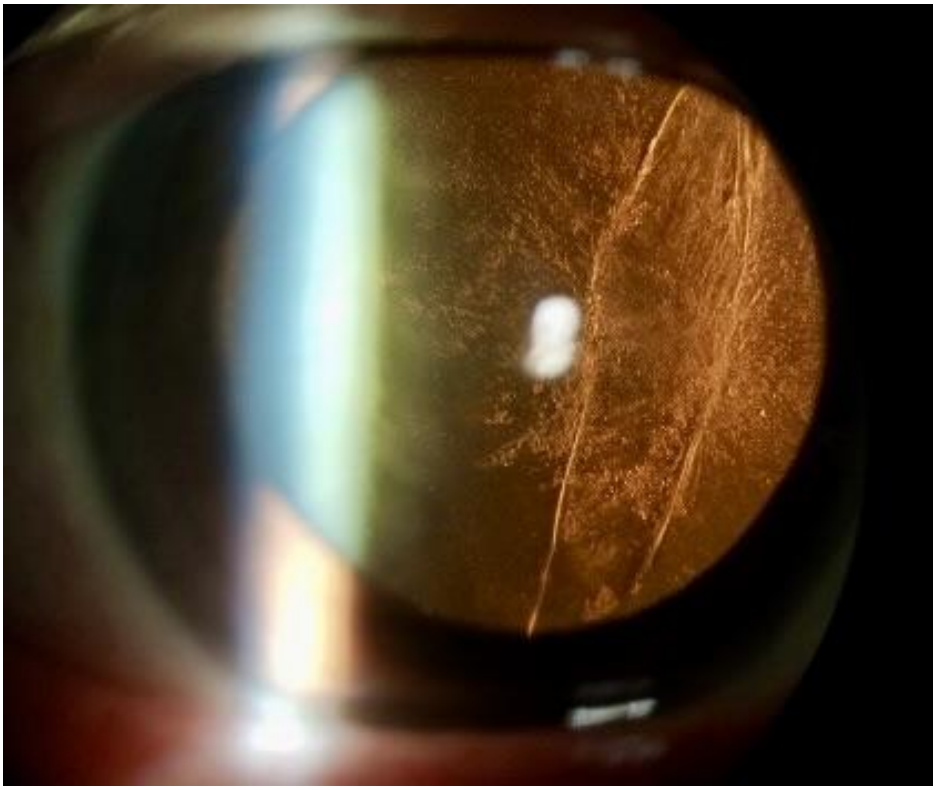

Figure 3. Posterior capsule injury following the fifth intravitreal bevacizumab (Avastin®, F. Hoffmann-La Roche AG, Basel, Switzerland) injection for neovascular age-related macular degeneration in the left eye of a female patient. Slit-lamp examination showing a focal posterior capsular defect consistent with needle-related injury.

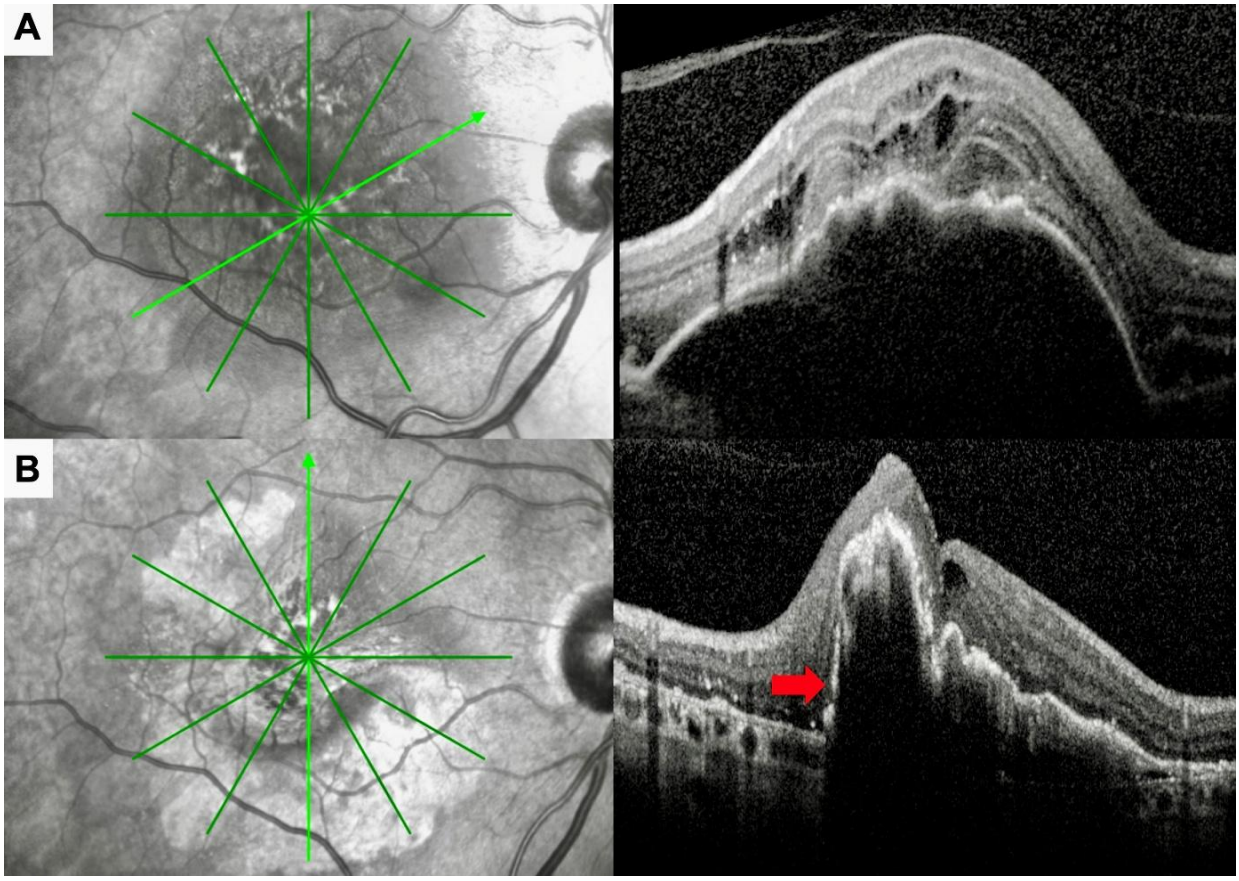

Figure 4. Retinal pigment epithelium (RPE) tear occurring one month after the second intravitreal ranibizumab (Lucentis®, Novartis, Basel, Switzerland) injection for neovascular age-related macular degeneration in the right eye of a 70-year-old female patient. (A) Pre-injection transfoveal spectral-domain optical coherence tomography (OCT, Heidelberg Spectralis®, Heidelberg Engineering, Heidelberg, Germany) demonstrating a large RPE detachment accompanied by intraretinal hyperreflective foci, as well as intraretinal and subretinal fluid. (B) Post-injection transfoveal spectral-domain OCT revealing a marked reduction in intraretinal and subretinal fluid, along with the development of an RPE tear (red arrow).

A recent retrospective study reported that long-term intravitreal anti-VEGF therapy was associated with a higher risk of cataract surgery. The 10-year cumulative incidence of cataract surgery was 40.7% in injected eyes compared with 7.2% in fellow untreated eyes, with injected eyes showing an approximately eightfold increased risk [148].

2.3.2. Retinal Pigment Epithelium Tears

Retinal pigment epithelium tears are identified by distinct, sharply bordered areas of exposed choroid alongside retracted retinal pigment epithelium. On optical coherence tomography, they appear as a discontinuity in the hyperreflective retinal pigment epithelium layer, accompanied by elevation of the torn flap and increased choroidal signal beneath the defect (Figure 4) [149]. The risk of early retinal pigment epithelium tears may increase after anti-VEGF injections, particularly at higher doses [150]. Real-world studies on neovascular age-related macular degeneration report an incidence of 5.3–7.9%, with most cases occurring within the first year of anti-VEGF therapy [151, 152].

Several structural features have been associated with an increased risk of retinal pigment epithelium tear formation, including the presence and increased height of pigment epithelial detachment, particularly when exceeding 400 micrometers, as well as a larger pigment epithelial detachment diameter [153]. Spectral-domain optical coherence tomography has shown that, preceding a retinal pigment epithelium tear, eyes frequently display a vascularized pigment epithelial detachment, with choroidal neovascularization attached to the undersurface of the retinal pigment epithelium producing contractile folds [154]. During anti-VEGF treatment, contraction of the choroidal neovascular membrane can generate mechanical stress on the retinal pigment epithelium, thereby predisposing to tear development and potentially resulting in sudden and severe vision loss [155].

Given that aflibercept targets VEGF-A, VEGF-B, and placental growth factor, it may theoretically induce stronger contraction of choroidal neovascularization, which could predispose to retinal pigment epithelium tears. However, in the absence of randomized controlled trials comparing anti-VEGF agents, the role of drug type remains unclear [156].

In a recent meta-analysis, Shi et al. [157] evaluated the incidence of retinal pigment epithelium tears associated with anti-VEGF therapy in patients with neovascular age-related macular degeneration. Based on 24 studies involving 17 354 patients, the pooled incidence of retinal pigment epithelium tears was estimated at 1.9%. The authors reported that most retinal pigment epithelium tear cases developed shortly after treatment initiation, particularly within the first month or after the first intravitreal injection. Although continued anti-VEGF therapy did not result in statistically significant visual improvement, it was associated with stabilization of visual acuity [157].

Current clinical recommendations support ongoing anti-VEGF therapy following RPE tear when signs of active disease persist and functional stabilization is anticipated [152]. A recent meta-analysis evaluating eyes with retinal pigment epithelium tears found no significant visual improvement after continued intravitreal anti-VEGF therapy over 12 months, regardless of injection frequency. Although a slight decline in visual acuity was observed over longer follow-up, continued treatment appeared to help maintain overall visual stability [158].

2.3.3. Rhegmatogenous Retinal Detachment

Proper localization of the injection site is essential for intravitreal injections. Entry is generally recommended at about 3.5–4 mm posterior to the limbus, since more posterior penetration beyond 4.5 mm may lead to damage to the anterior vitreous base and the ora serrata [159]. Improper needle angulation or overly posterior placement may lead to transretinal penetration, whereas an oblique approach helps reduce vitreous incarceration and subsequent rhegmatogenous retinal detachment [38].

In retrospective studies, the incidence of rhegmatogenous retinal detachment following intravitreal injections is reported to range from 0% to 9.5%, though most of these studies included fewer than 10 000 injections [37, 160, 161]. In another study evaluating over 35 000 intravitreal injections performed with 30-gauge needles, retinal detachment occurred in one out of 7188 injections (0.013%) [162].

Experimental studies show that a 31-gauge needle may require almost twice the penetration force compared with 27- or 30-gauge needles, which could influence vitreous traction or accuracy of scleral needle entry [163, 164]. On the other hand, smaller-gauge needles create smaller puncture wounds, potentially reducing the risk of retinal tears or vitreous prolapse (Figure 5) [37]. In a large single-center retrospective analysis of over 180 000 intravitreal anti-VEGF injections, the incidence of rhegmatogenous retinal detachment was approximately 0.013% (1 in 7500 injections; 1 in 530 patients), with no significant association observed between rhegmatogenous retinal detachment risk and injection number, needle gauge, or injection site [37].

The occurrence of posterior vitreous detachment after intravitreal injections has been documented [165, 166]. This finding may partly account for the observed temporal association between the injection procedure and the development of rhegmatogenous retinal detachment [13].

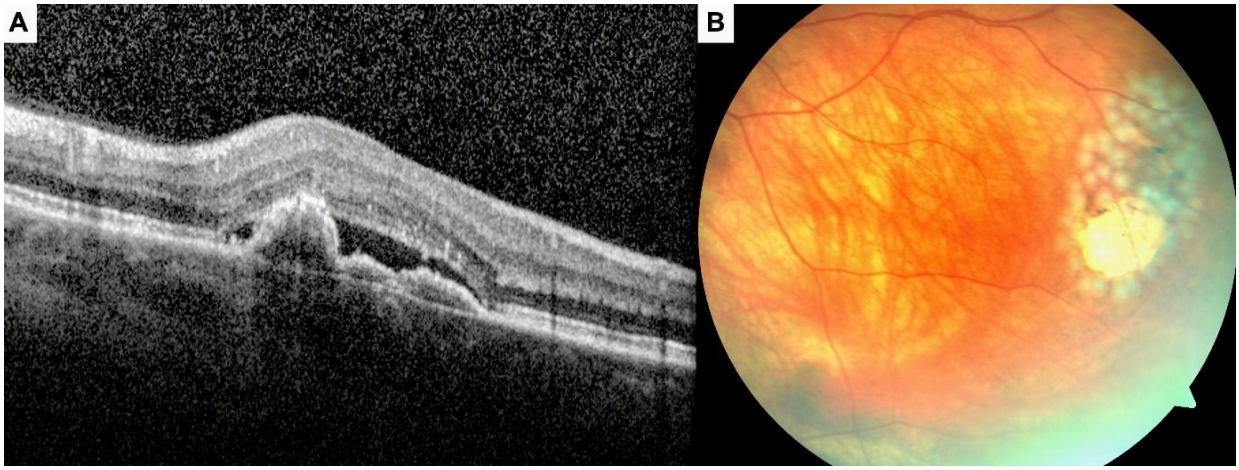

Figure 5. Retinal tear identified seven weeks after the eighth intravitreal ranibizumab (Lucentis®, Novartis, Basel, Switzerland) injection administered for exudative age-related macular degeneration in the left eye of a 57-year-old female patient. (A) Transfoveal spectral-domain optical coherence tomography (Heidelberg Spectralis®, Heidelberg Engineering, Heidelberg, Germany) obtained prior to the injection, showing retinal pigment epithelium detachment accompanied by subretinal fluid. (B) Post-injection color fundus photograph (VISUCAM 500®, Carl Zeiss Meditec, Jena, Germany) revealing a retinal tear adjacent to a hyperpigmented area in the temporal peripheral retina, with surrounding laser photocoagulation scars.

Gabrielle et al. [167] analyzed data from the Fight Retinal Blindness! registry to investigate the incidence, risk factors, and outcomes of rhegmatogenous retinal detachment following intravitreal anti-VEGF injections in routine clinical practice. Among 16 915 treated eyes receiving more than 265 000 injections, only 36 cases of rhegmatogenous retinal detachment were reported, corresponding to an estimated incidence of 0.77 cases per 1000 patients per year (1.36 per 10 000 injections). Importantly, the probability of rhegmatogenous retinal detachment did not significantly increase with successive injections. Older age was identified as a risk factor, whereas better baseline visual acuity was associated with a lower risk. Despite its low incidence, rhegmatogenous retinal detachment was associated with unfavorable visual outcomes, with an average loss of approximately three lines of vision at one year [167].

In proliferative diabetic retinopathy, anti-VEGF therapy may rarely precipitate "crunch syndrome", characterized by rapid contraction of fibrovascular tissue that can increase retinal traction and lead to tractional retinal detachment. Therefore, intravitreal injections should be used cautiously in eyes with advanced fibrovascular proliferation [168].

2.4. *Non-inflammatory Retinal Vascular Occlusions*

VEGF plays a central role in pathways maintaining microvascular integrity and regulating the coagulation cascade [169]. Vascular endothelial growth factor stimulates endothelial nitric oxide production, a key mediator of vasodilation. Hence inhibition of VEGF signaling may decrease nitric oxide availability, potentially resulting in vasoconstriction and increased peripheral vascular resistance [170]. Intravitreal anti-VEGF therapy has been associated with a potential risk of arterial or venous occlusive events, particularly in patients with preexisting vascular risk factors [171].

Rare cases of central retinal vein occlusion without associated inflammation or vasculitis have been reported following intravitreal injections [172]. Retinal artery occlusion has also been reported after intravitreal anti-VEGF therapy [173]. Given the small number of documented cases, the underlying mechanism remains uncertain; however, a prior study indicates that bevacizumab may reduce retinal vessel caliber [174]. Sustained VEGF inhibition could theoretically promote endothelial impairment and thrombotic events [173].

Analysis of recent pharmacovigilance data suggests that brolucizumab is associated with the highest reporting odds of retinal artery and vein occlusions [1]. Ranibizumab, in contrast, has been more specifically linked to retinal artery embolism. Although faricimab and aflibercept display a greater propensity for retinal artery occlusion compared with ranibizumab, their overall vascular risk profile appears less pronounced than that observed with brolucizumab [1].

Table 4. Ocular adverse events and clinical features of intravitreal anti-VEGF injections.

Complication	Incidence	Risk Factors	Clinical Importance
Sterile inflammation [97, 98]	0.02 – 0.37%	Drug immunogenicity, repeated exposure, protein aggregates, silicone oil exposure, and injection-related factors	Usually, self-limited
Endophthalmitis [105]	~0.02 – 0.05%	Poor aseptic technique, contamination, immunosuppression	Vision-threatening
Acute IOP elevation [126]	Common	Absence of subconjunctival reflux, injection technique and needle size, silicone oil exposure, syringe characteristics, history of glaucoma, small ocular volume, lens status, and injection volume	Transient
Sustained IOP elevation [143]	Variable	Repeated injections, cumulative dose, impaired aqueous outflow, silicone oil/protein aggregates, and history of glaucoma	Chronic ocular hypertension and progressive glaucomatous optic nerve damage
Cataract formation [144]	~ 0.006%	Accidental lens injury during injection, hyperopic eyes, and cumulative exposure to intravitreal therapy	May require cataract surgery
RPE tear [151, 152]	~1.9 – 7%	PED height and size, vascularized PED, contraction of choroidal neovascularization following anti-VEGF therapy	Often associated with poor visual prognosis
Retinal detachment [162]	~0.01%	Injection technique, vitreous traction/posterior vitreous detachment, and older age	Vision-threatening
Retinal vascular occlusion [171]	Rare	Pre-existing vascular risk factors, drug-related effects	Potentially severe vision loss

Abbreviations: IOP, intraocular pressure; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

3. Clinical Implications and Risk-Based Practical Approach

The expanding use of intravitreal anti-VEGF agents across a wide range of retinal disorders underscores the need to consider not only their therapeutic efficacy but also their safety profiles in routine clinical practice, with the aim of preventing or minimizing potential adverse events. In this context, a structured, risk-based, and individualized approach is essential to minimize adverse events and optimize treatment outcomes. The key ocular complications associated with intravitreal anti-VEGF therapy, together with their incidence, risk factors, and clinical relevance, are summarized in Table 4 [97, 98, 105, 126, 143, 144, 151, 152, 162, 171].

3.1. Risk Stratification

Before initiating therapy, a comprehensive pre-injection evaluation is essential to identify patients at increased risk for ocular or systemic adverse events associated with anti-VEGF treatment. Particular attention should be paid to individuals with pre-existing glaucoma or ocular hypertension, as repeated intravitreal injections have been linked to both transient and sustained elevations in IOP [134]. Likewise, a history of intraocular inflammation may predispose patients to post-injection inflammatory responses [80].

Beyond ocular factors, systemic conditions such as uncontrolled hypertension, diabetes mellitus, and a history of thromboembolic events—especially stroke and myocardial infarction—should also be carefully evaluated, as these may influence both treatment selection and the overall safety profile of anti-VEGF therapy [12]. Integrating both ocular and systemic risk factors into the pre-treatment assessment is therefore essential for individualized and safe treatment planning.

3.2. Drug Selection

Treatment selection should be based on the individual risk profile. As currently available anti-VEGF agents demonstrate broadly comparable efficacy across a range of retinal pathologies, differences in their molecular structure and pharmacodynamic profiles may result in subtle yet clinically relevant variations in safety [97]. Accordingly, treatment selection should be individualized rather than applied uniformly across all patients.

Emerging evidence indicates variability among agents with respect to immunogenicity and incidence of intraocular inflammation, which may have direct implications for clinical decision-making. Notably, reports of occlusive retinal vasculitis and intraocular inflammation associated with certain newer agents like brolucizumab have reinforced the need for careful patient selection and thorough risk assessment [79]. Hence in patients with a known history of intraocular inflammation, agents with a well-established safety record and lower reported rates of inflammatory adverse events may be preferred [108]. Conversely, in individuals for whom treatment adherence is a concern, longer-acting agents that permit extended dosing intervals may provide practical advantages by reducing treatment burden [2]. Treatment decisions should balance disease characteristics, patient risk factors, and evolving evidence from clinical trials and real-world data.

A comparative overview of currently available anti-VEGF agents, including their molecular characteristics, therapeutic targets, advantages, and key safety considerations, is summarized in Table 5 [2].

Table 5. Comparative characteristics, therapeutic targets, and safety profiles of currently available anti-VEGF agents [2]

Agent	Structure	Target	Key Advantage	Main Safety Concern
Bevacizumab	Humanized monoclonal IgG1 antibody	VEGF-A	Cost-effective (off-label)	Compounding/repackaging-related contamination risk
Ranibizumab	Fab fragment of humanized IgG1 antibody	VEGF-A	Well-established efficacy and safety	Favorable safety profile; requires more frequent dosing
Aflibercept (2 mg)	Fusion protein (VEGFR1/2 extracellular domains fused to human IgG1 Fc)	VEGF-A VEGF-B PlGF	High binding affinity with good durability	Favorable safety profile with low rates of intraocular inflammation
Aflibercept (8 mg)	Fusion protein (VEGFR1/2 extracellular domains fused to human IgG1 Fc)	VEGF-A VEGF-B PlGF	Extended durability with longer dosing intervals	Intraocular pressure spikes (higher injection volume), intraocular inflammation/retinal vasculitis
Brolucizumab	Single-chain antibody fragment	VEGF-A	High molar concentration and tissue penetration (small molecular size)	Intraocular inflammation, retinal vasculitis, and vascular occlusion
Faricimab	Bispecific monoclonal antibody	VEGF-A Ang-2	Dual pathway inhibition	Intraocular inflammation and retinal vascular events

Abbreviations: Ang-2, angiopoietin 2; PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

3.3. Monitoring and Follow-up

Careful, structured follow-up after injection is essential to ensure safe and effective anti-VEGF therapy. Although follow-up intervals are generally individualized based on the underlying disease and preferred treatment regimen, particular attention should be directed to the early post-injection period. While routine examination the day after injection is not universally necessary, patients should be properly instructed about warning symptoms and encouraged to seek prompt evaluation in the presence of ocular pain, decreased vision, or increasing redness. Serious complications, such as endophthalmitis, have been reported to occur most frequently within the first few days after injection, particularly during the first week [105].

Clinical assessment should include measurement of best-corrected visual acuity, IOP measurement, and a thorough fundus examination. Transient increases in IOP typically tend to return to baseline levels within a relatively brief period in most patients. However, in susceptible individuals such as those with pre-existing glaucoma or ocular hypertension, closer monitoring may be warranted, as repeated injections and cumulative treatment burden have been associated with sustained IOP elevation [126]. Accordingly, individualized follow-up strategies should take into account both baseline risk factors and the potential for pressure-related complications. A balanced approach combining patient education, timely access to care, and risk-based follow-up is essential for the early detection and management of post-injection complications [1].

3.4. Management of Post-injection Complications

Complications following intravitreal anti-VEGF injections require prompt recognition and appropriate management. Mild sterile inflammatory reactions can often be managed conservatively with topical corticosteroids and close observation. However, distinguishing these from infectious endophthalmitis is of critical importance, as the latter represents a vision-threatening condition that necessitates urgent intervention, including intravitreal and systemic antibiotic administration, and in selected cases vitreous sampling and pars plana vitrectomy [29].

Even though acute post-injection increases in IOP typically return to baseline within a short period, significant or persistent elevations may necessitate medical antiglaucoma therapy, laser treatment, or surgical intervention [124]. In addition, procedure-related complications such as crystalline lens injury, retinal tears, or retinal detachment may require timely surgical management depending on severity and clinical presentation [13, 148].

3.5. Preventive Strategies

Preventive measures are fundamental to minimizing complications associated with intravitreal anti-VEGF injections. Current evidence consistently supports the use of povidone-iodine as the most effective antiseptic agent for reducing ocular surface bacterial load and lowering the risk of endophthalmitis, although alternative agents like chlorhexidine have also been explored [175, 176]. Notably, routine use of prophylactic topical antibiotics, both before and after injection, has been increasingly questioned, with accumulating evidence indicating limited clinical benefit [177, 178].

Beyond antisepsis, adherence to strict aseptic technique and meticulous procedural execution are essential. This includes appropriate selection of the injection site, typically 3.5 mm posterior to the limbus in pseudophakic eyes and 4.0 mm in phakic eyes, to reduce the risk of crystalline lens injury and retinal tears [159]. Furthermore, patient education on expected post-injection symptoms and clear instructions to seek prompt evaluation in the presence of pain or visual changes remain critical components of an effective preventive strategy.

Artificial intelligence (AI) is increasingly being integrated into ophthalmology [179, 180] and is poised to optimize anti-VEGF therapy across multiple aspects of retinal care [181]. By incorporating OCT-derived biomarkers with clinical data, AI can improve prediction of treatment response, stratify patients according to risk of ocular and systemic adverse events, and personalize retreatment intervals. In addition, automated retinal image analysis enables efficient detection and longitudinal monitoring of DME, AMD, and other retinal diseases, while AI-assisted decision support may further optimize therapeutic selection and injection scheduling [182–184]. Although anti-VEGF therapy remains highly effective and generally safe, its use is not without potential ocular and systemic complications [12]. The integration of AI into anti-VEGF management therefore holds substantial promise for enhancing precision, safety, and individualized patient care [185]. Continued investigation into AI-driven applications in this domain is warranted and may meaningfully advance the future of retinal therapeutics.

Future Directions

The field of intravitreal anti-VEGF treatment continues to advance rapidly, driven by efforts to enhance therapeutic efficacy, reduce treatment burden, and optimize safety while minimizing potential complications. In this context, the development of novel long-acting agents and sustained-release delivery systems aims to lower injection frequency and improve patient adherence [186]. Nevertheless, the long-term safety profiles of these approaches remain to be fully clarified.

Emerging therapeutic strategies that extend beyond VEGF inhibition, including dual-pathway targeting and combination regimens, are expected to broaden the current therapeutic landscape for various retinal disorders [187]. These modalities offer the potential for improved durability and superior functional outcomes. However, they may also introduce distinct safety concerns, underscoring the need for rigorous evaluation in both controlled clinical trials and real-world clinical settings.

Personalized treatment strategies are likely to gain importance, with management methods tailored to individual patient characteristics and disease profiles. Accordingly, advances in artificial intelligence and multimodal retinal imaging are anticipated to facilitate earlier detection of complications, enhance the prediction of therapeutic response, and support more precise, individualized follow-up strategies. Moreover, real-world evidence and large-scale pharmacovigilance studies will remain critical for identifying rare, delayed, or previously unrecognized adverse events, thereby contributing to a more comprehensive understanding of the long-term safety of both established and emerging anti-VEGF agents.

Strengths and Limitations

A major strength of the present review lies in its comprehensive and up-to-date synthesis of both systemic and ocular adverse events associated with intravitreal anti-VEGF therapy. By integrating evidence from pharmacovigilance data, randomized controlled trials, real-world studies, and rare case reports, the review provides a broad and clinically relevant perspective. The inclusion of recently approved agents and emerging safety concerns enhances its relevance to current clinical practice.

Certain limitations should be acknowledged. As a narrative review, it may be subject to selection bias. In addition, heterogeneity among the included studies in terms of methodology, patient selection, and outcome definitions limits the ability to provide definitive conclusions regarding causality and incidence rates. Despite these limitations, this review provides a comprehensive overview of the potential complications associated with anti-VEGF therapy, which may aid in risk assessment and patient management in daily practice.

CONCLUSIONS

Although intravitreal anti-VEGF therapy is generally well tolerated, a wide spectrum of ocular and systemic adverse events may occur. Accordingly, a structured and individualized approach based on patient risk is essential to optimize safety and visual outcomes in routine clinical practice.

ETHICAL DECLARATIONS

Ethical approval: This narrative review did not require formal ethical committee approval, as it was a review study. All figures presented were obtained from the patient documentation archives of our unit, and informed consent was obtained from each patient prior to inclusion in the review.

Conflict of interest: None.

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