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Editorial

Distinguishing Between Infectious Endophthalmitis and Noninfectious Inflammation Associated With Newer Agents to Treat Age-Related Macular Degeneration

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Intravitreal medications, including anti-vascular endothelial growth factor (anti-VEGF) agents and complement inhibitors, comprise standard treatment of patients with advanced age-related macular degeneration (AMD). Distinguishing infectious endophthalmitis from noninfectious intraocular inflammation remains one of the most challenging clinical dilemmas for retina specialists [1].

Since 2019, several new medications have been approved for advanced AMD in the United States. Three new anti-VEGF agents have been approved for the treatment of neovascular AMD: brolucizumab (Beovu, Novartis, Basel), faricimab (Vabysmo, Genentech, South San Francisco, CA), and high-dose aflibercept (Eylea HD, Regeneron, Tarrytown, NY). In addition, several biosimilars referencing ranibizumab and aflibercept have been approved. Two new complement inhibitors have also been approved for the treatment of geographic atrophy: pegcetacoplan (Syfovre, Apellis, Waltham, MA) and avacincaptad pegol (Izervay, Astellas, Tokyo).

Reported rates of infectious endophthalmitis after intravitreal injection range from 0.016% to 0.07% per injection, with coagulase-negative Staphylococcus (38–67%) and Streptococcus species (10–29%) being the common causative organisms [2,3,4].

Reported rates of noninfectious inflammation vary considerably but are likely comparable to those of infectious endophthalmitis [5]. Brolucizumab has a reported intraocular inflammation incidence of 3.47%–4.60%, and is associated with an approximately 11-fold higher hazard compared with ranibizumab; it also has a higher reported incidence of intraocular inflammation than aflibercept and can be associated with occlusive retinal vasculitis [6,7]. Events typically occur at a median of 28 days after treatment initiation, with approximately 50% occurring after a single injection and 87.5% within 30 days of the most recent injection [8].

Rates of noninfectious inflammation associated with high-dose aflibercept (8 mg) and faricimab range from approximately 0.6% to 2.2% [9]. For faricimab, reported rates of retinal vasculitis are low (0.06–0.17 per 10,000 injections) [9], and at least three cases of retinal vasculitis following high-dose aflibercept have been reported to date [10].

Complement inhibitors also carry a risk of intraocular inflammation. Pegcetacoplan, a complement component 3 (C3) inhibitor used for geographic atrophy, has reported intraocular inflammation rates of 0.22%–0.24% per injection, with most events described as mild to moderate [11]. However, a 2025 pharmacovigilance study analyzing the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System reported that pegcetacoplan was associated with hemorrhagic occlusive retinal vasculitis (reporting odds ratio [ROR] 4606, 95% confidence interval [CI] 2000–10,611) and retinal occlusive vasculitis (ROR 2352, 95% CI 1313–4212) [12]. At least 14 cases were identified in the American Society of Retina Specialists Research and Safety in Therapeutics (ReST) report from the initial post-marketing period (2023), with a median onset of 10.5 days (range, 8–23 days) after injection [13].

Avacincaptad pegol, a complement component 5 (C5) inhibitor, appears to have a more favorable inflammatory profile, with no reported cases of intraocular inflammation, endophthalmitis, or occlusive vasculitis in clinical trials or large real-world cohorts [12]. However, it has recently been associated with the development of noninfectious vitritis (reporting odds ratio [ROR] 782, 95% CI 316–1936) [12].

Proposed mechanisms of noninfectious intraocular inflammation include treatment-induced antidrug antibodies (ADA) and manufacturing-related factors, such as protein aggregates or silicone oil microdroplets in syringes that may also contribute to inflammatory responses [5].

How can clinicians differentiate infectious endophthalmitis from noninfectious inflammation after intravitreal injection with these newer agents? There are important differences in presentation patterns, but unfortunately there is no clear “litmus test” and the treating physician must use his or her best judgment.

Infectious endophthalmitis typically presents earlier (mean 3 days, range 1–9 days) following injection, whereas noninfectious intraocular inflammation tends to present later (mean 8 days, median 10.5 days, range 1–23 days) [5,13].

Clinical features also differ (Table 1). Infectious endophthalmitis most commonly presents with rapidly worsening decreased vision, ocular pain, and conjunctival injection [2]. In contrast, noninfectious intraocular inflam-

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Table 1. Distinguishing infectious endophthalmitis from noninfectious inflammation following newer agents to treat age-related macular degeneration.

Features	Infectious endophthalmitis	Noninfectious inflammation
Presentation	Earlier: mean 3 days (range 1–9 days)	Later: mean 8 days, median 10.5 days (range 1–23 days)
Symptoms	Rapidly worsening decreased vision; ocular pain (85%)	Gradual, painless visual decline; floaters
Anterior chamber	Severe reaction with fibrin; hypopyon in ~62.5%	Mild cell and flare
Vitreous	Moderate to severe cell	Mild to moderate cell
Initial management	Vitreous cultures + intravitreal antibiotics	Topical/subconjunctival corticosteroids
Prognosis	Variable depending on organism and timing	Generally good

Note: substantial overlap exists in the first week after injection; timing alone cannot always distinguish the two entities.

mation more often presents with gradual, painless visual decline or floaters. Infectious cases typically demonstrate a severe anterior chamber reaction (fibrin) with hypopyon in approximately 62.5% of patients, diffuse intraocular inflammation, and dense vitreous opacification [2,3]. Noninfectious intraocular inflammation generally presents with anterior chamber and vitreous cells without a severe fibrinous reaction or hypopyon. Brolucizumab-associated inflammation has distinctive features, including retinal arterial sheathing, cotton-wool spots, Kyrieleis plaques, and vascular occlusion, findings that are highly suggestive of drug-related inflammation [14].

When infectious endophthalmitis cannot be excluded, prompt vitreous cultures and treatment with intravitreal antibiotics (vancomycin 1.0 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL) should be considered [15]. The diagnosis is primarily clinical, as culture results may require several days and up to 30% of infectious cases are culture negative [2]. Emerging polymerase chain reaction assays may allow faster pathogen identification in culture-negative cases, although this is not available in most practice settings [3].

For suspected noninfectious intraocular inflammation, conservative management with topical or subconjunctival corticosteroids is appropriate, with a low threshold for initiating intravitreal antibiotic therapy if no improvement occurs within 24–48 hours [2]. Most cases demonstrate meaningful visual recovery over 6–8 weeks (mean improvement from 35 to 49 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) [5]. In brolucizumab-associated retinal vasculitis, corticosteroid treatment has been attempted, though visual recovery is often limited [14].

When evaluating post-injection inflammation, clinicians should consider: (1) timing of onset (earlier onset favors infection); (2) severity of pain; (3) rate of progression; and (4) severity of anterior chamber reaction and presence of hypopyon.

Key Points

• In patients treated with newer anti-vascular endothelial growth factor (anti-VEGF) injections, distinguishing infectious endophthalmitis from noninfectious inflammation remains an important clinical challenge.

• Although there is no clear “litmus test” in distinguishing between these two entities, infectious endophthalmitis typically is associated with earlier onset, more severe pain, faster progression, and a more severe anterior chamber reaction, including hypopyon.

• If infectious endophthalmitis cannot be excluded, then prompt vitreous cultures and treatment with intravitreal antibiotics (vancomycin 1.0 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL) should be considered.

• For suspected noninfectious intraocular inflammation, topical or subconjunctival corticosteroids may be considered, provided that the infection is carefully assessed and the patient is closely monitored.

Availability of Data and Materials

Not applicable.

Author Contributions

FP, SGS, and HWF contributed to conceptualisation. FP wrote the initial draft. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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