Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Recurrent Intraocular Inflammation after Faricimab and Aflibercept 8 mg despite Intervening Tolerance of Aflibercept 2 mg: A Case Report and Literature Review

Da Eun Yoo
Gyeongsang National University, Gyeongsang National University Hospital
Jin-Seok Seo
Gyeongsang National University, Gyeongsang National University Hospital
Yong Wun Cho
Gyeongsang National University, Gyeongsang National University Hospital
Inyoung Chung
Gyeongsang National University, Gyeongsang National University Hospital
Woong-Sun Yoo
wsyoo@gnu.ac.kr

Gyeongsang National University, Gyeongsang National University Hospital

Short Report

Keywords: neovascular age-related macular degeneration, faricimab, aflibercept 8 mg, intraocular inflammation, case report

Posted Date: September 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11045661/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of Ophthalmic Inflammation and Infection on October 22nd, 2026. See the published version at https://doi.org/10.1186/s12348-026-00658-y.

Abstract

Background

Intraocular inflammation (IOI) has been reported after both faricimab and aflibercept 8 mg. How to maintain anti-vascular endothelial growth factor (VEGF) treatment after an inflammatory event is difficult when a standard-dose alternative is tolerated but provides insufficient efficacy or durability. We report recurrent presumed noninfectious IOI after faricimab and later aflibercept 8 mg, with intervening tolerance of aflibercept 2 mg and of the first two aflibercept 8 mg injections.

Case presentation

A patient with neovascular age-related macular degeneration in the left eye had received nine bevacizumab injections without documented inflammation. Approximately 3 days after the third faricimab injection, visual acuity declined from 20/125 to counting fingers, with anterior vitreous cells and grade 1–2 vitreous opacity despite a quiet anterior chamber. Systemic and topical corticosteroids were followed by visual recovery to 20/50. Faricimab was discontinued and aflibercept 2 mg was tolerated without recurrent IOI, but subretinal fluid persisted and the desired treatment interval could not be maintained. Treatment was therefore escalated to aflibercept 8 mg. The first two 8-mg injections were tolerated. Approximately 2 days after the third 8-mg injection, profound visual deterioration developed; 4 days after injection, the anterior chamber remained quiet but grade 2–3 vitreous opacity was present. Visual acuity recovered to 20/50 after systemic and topical corticosteroid therapy.

Conclusions

This sequence differs from previously reported immediate recurrence after direct faricimab-to-aflibercept 8 mg switching. Intervening tolerance of aflibercept 2 mg and earlier aflibercept 8 mg doses did not preclude later inflammation. Continued counseling and surveillance after every injection may be warranted when aflibercept 8 mg is required in an eye with previous anti-VEGF-associated IOI.

Clinical trial number

Not applicable. This manuscript describes a single-patient case report and does not report a clinical trial.

Background

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is the standard treatment for neovascular age-related macular degeneration (nAMD). Faricimab, which inhibits VEGF-A and angiopoietin-2, and aflibercept 8 mg were developed to improve anatomic control and treatment durability. Published phase 3 data from TENAYA (NCT03823287) and LUCERNE (NCT03823300) demonstrated noninferior visual outcomes with faricimab administered at intervals of up to 16 weeks in selected patients, while PULSAR (NCT04423718) similarly supported extended dosing with aflibercept 8 mg [1, 2].

Postmarketing and real-world reports have established a spectrum of noninfectious intraocular inflammation (IOI) after faricimab, including anterior uveitis, vitritis, posterior involvement, and retinal vasculitis [3–6]. Aflibercept 8 mg has also been associated with IOI in real-world cohorts, with events occurring after both initial and repeated exposure [7–10]. These safety observations create a practical dilemma when continued anti-VEGF suppression is required after an inflammatory event.

Two publications are particularly relevant to sequential exposure. Sato et al. reported recurrent mild anterior inflammation 2 days after the first aflibercept 8 mg injection following faricimab-associated anterior IOI and a direct switch between the agents [11]. Dwomoh et al. described three patients who received faricimab and high-dose aflibercept in close sequence and developed IOI after returning to a previously used agent, raising an immune-sensitization hypothesis [12]. The present case adds a different temporal pattern: faricimab-associated, vitreous-predominant IOI was followed by inflammatory tolerance but insufficient efficacy/durability with aflibercept 2 mg; aflibercept 8 mg was then tolerated twice before a second, vitreous-predominant inflammatory event after the third dose.

Case presentation

A 62-year-old woman with hyperlipidemia was referred for management of neovascular age-related macular degeneration (nAMD) in her left eye. She reported a 2-year history of decreased vision, floaters, and metamorphopsia and had received nine intravitreal bevacizumab injections at an outside clinic, most recently approximately 4 weeks before referral. No injection-associated intraocular inflammation (IOI) had occurred. At presentation, best-corrected visual acuity (BCVA) was 20/32 in the right eye and 20/125 in the left eye, with intraocular pressures (IOP) of 13 and 15 mmHg, respectively. Both anterior segments were quiet. Optical coherence tomography (OCT) of the left eye showed subretinal fluid (SRF) and pigment epithelial detachment (PED), and OCT angiography demonstrated choroidal neovascularization.

The left eye received three intravitreal faricimab injections over the subsequent 3 months. Immediately before the third injection, left-eye BCVA was 20/125 and IOP was 11 mmHg. Marked visual blurring developed approximately 3 days later. At examination 4 days after the injection, visual acuity had declined to counting fingers (CF). The cornea remained clear and the anterior chamber was quiet, but anterior vitreous cells and grade 2 vitreous opacity were present. OCT showed resolution of SRF with persistent PED, making worsening macular exudation an unlikely cause of the abrupt visual decline. Presumed faricimab-associated noninfectious IOI was diagnosed (Fig. 1). Oral prednisolone 30 mg and intensive topical corticosteroid therapy were initiated and subsequently tapered. Within 3 days, BCVA improved to 20/200 and vitreous opacity decreased to grade 1; approximately 1 month later, BCVA had recovered to 20/50.

Faricimab was discontinued because of concern for recurrent inflammation. After the IOI had resolved, a single aflibercept 2 mg injection was administered approximately 11 weeks later and was tolerated without recurrent inflammation. Although SRF decreased, it remained present at the 6-week follow-up,

indicating insufficient anatomic efficacy and durability for the intended treatment strategy. Treatment was therefore escalated to aflibercept 8 mg.

The first two aflibercept 8 mg injections were tolerated without inflammation. During this period, BCVA remained 20/50 and the anterior segment remained quiet. After third injection, profound visual deterioration developed approximately 2 days later. At examination 4 days after the injection, left-eye BCVA had decreased to CF and IOP was 15 mmHg. The cornea was clear, and no anterior chamber cell was detected; however, grade 2–3 vitreous opacity was present. OCT demonstrated decreased SRF and PED, while OCT angiography continued to show choroidal neovascularization. The abrupt postinjection visual decline with increased vitreous opacity despite improving macular exudation was considered consistent with recurrent presumed noninfectious IOI (Fig. 2).

Oral prednisolone 30 mg and topical corticosteroid therapy were initiated. BCVA improved to 20/100 after 1 week, 20/63 after 3 weeks, and 20/50 after 7 weeks during corticosteroid tapering. The detailed clinical chronology is summarized in Table 1.

Table 1
Clinical timeline of anti-VEGF treatment and intraocular inflammation

Therapy/event	**Key finding**
Bevacizumab x9, OS	No documented injection-associated IOI
Faricimab x3, OS	Preinjection VA 20/125
First IOI	VA CF; AC quiet; vitreous opacity G2
Systemic + topical corticosteroids	VA recovered to 20/50
Aflibercept 2 mg x1, OS	Tolerated without IOI
Aflibercept 2 mg follow-up	SRF decreased but persisted; efficacy/durability insufficient
Aflibercept 8 mg x3, OS	Preinjection VA 20/50
Second IOI	VA CF; AC quiet; vitreous opacity G2-3
Systemic + topical corticosteroids	VA recovered to 20/50

AC, anterior chamber; CF, counting fingers; G, grade; IOI, intraocular inflammation; OS, left eye; SRF, subretinal fluid; VA, visual acuity.

Discussion and Conclusions

This case illustrates a clinically relevant sequence of recurrent, temporally separated IOI after two newer anti-VEGF agents. Its principal distinction is not simply recurrence after faricimab followed by aflibercept 8 mg, which has already been reported [11]. Rather, after faricimab-associated IOI, aflibercept 2 mg was tolerated but did not provide sufficient efficacy or durability; the subsequent escalation to aflibercept 8 mg was initially tolerated for two injections, and IOI occurred only after the third 8-mg dose. The two

inflammatory events were more than 1 year apart and were both characterized predominantly by vitreous opacity with a quiet anterior chamber.

The first event is compatible with the recognized spectrum of faricimab-associated inflammation. Published series have described onset within days to weeks and phenotypes ranging from anterior/intermediate uveitis and vitritis to retinal vasculitis [3–6]. The current patient developed symptoms after the third faricimab dose, with anterior vitreous cells and vitreous opacity but no anterior chamber reaction. This vitreous-predominant presentation is therefore clinically plausible, although the absence of microbiologic sampling prevents definitive exclusion of infection.

Real-world data also show that aflibercept 8 mg-associated IOI can occur after repeated exposure. Hoffmann et al. initially reported eight cases with onset 2–17 days after injection [7]. Binder et al. reported five IOI events among 136 injections (3.7% per injection), and only one event occurred after the first aflibercept 8 mg exposure [8]. In a subsequent multicenter series, IOI occurred in 12 eyes after a mean of 2.3 aflibercept 8 mg injections; 66.7% of affected eyes had previously received aflibercept 2 mg without IOI [9]. A larger 2026 multicenter cohort reported 41 affected eyes among 2631 aflibercept 8 mg injections, with a mean of 4.7 injections before IOI and a lower per-injection rate with prefilled syringes than with vial preparation [10]. These observations reinforce that tolerance of initial aflibercept 8 mg doses does not eliminate later inflammatory risk.

The most directly comparable published reports are summarized in Table 2. Sato et al. described an 83-year-old man in whom mild anterior IOI occurred 13 days after the ninth faricimab injection; recurrent mild anterior inflammation developed 2 days after the first aflibercept 8 mg injection following a direct switch 13 weeks later [11]. By contrast, the current patient had an intervening aflibercept 2 mg exposure, two tolerated aflibercept 8 mg injections, and vitreous-predominant recurrence after the third 8-mg dose. Dwomoh et al. reported three cases involving faricimab and high-dose aflibercept in close sequence and proposed antidrug antibody formation or hypersensitivity as a possible mechanism [12]. The long interval and intervening treatment tolerance in the current case suggest that short-interval sequential exposure is not necessary for recurrent IOI, although an immune mechanism remains hypothetical.

Table 2
Reports most relevant to sequential anti-VEGF-associated intraocular inflammation

Report	Treatment sequence	Inflammatory phenotype	Relevance to present case
Sato et al., 2025 [11]	Faricimab IOI after dose #9 ◊ direct switch ◊ A8 IOI after dose #1	Mild anterior inflammation; no vitritis reported	Closest prior recurrence report; no intervening A2 and no tolerated A8 doses
Dwomoh et al., 2025 [12]	Three cases exposed to faricimab and A8 in close sequence; IOI after return to prior agent	Variable; authors emphasized short-order sequential exposure	Supports immune-sensitization hypothesis but differs in timing
Hashiya et al., 2025 [13]	Faricimab ◊ brolucizumab IOI ◊ A2 tolerated/inadequate ◊ A8 IOI	A8 event included retinal vasculitis/vascular occlusion	Shows A2 tolerance before A8 IOI, but prior IOI was brolucizumab-associated
Present case	Faricimab #3 IOI ◊ A2 tolerated/inadequate ◊ A8 #1/#2 tolerated ◊ A8 #3 IOI	Both events vitreous-predominant with quiet AC	Adds delayed recurrence after two tolerated A8 doses and > 1-year separation

A2, aflibercept 2 mg; A8, aflibercept 8 mg; AC, anterior chamber; IOI, intraocular inflammation.

Hashiya et al. reported a related but mechanistically different case in which brolucizumab-associated IOI preceded tolerance of aflibercept 2 mg and severe IOI with retinal vasculitis after aflibercept 8 mg [13]. This comparison is important because tolerance of the same active aflibercept molecule at 2 mg does not necessarily guarantee tolerance at 8 mg. However, the present case included only one aflibercept 2 mg injection, so a dose-response relationship cannot be inferred. Possible contributors include greater protein exposure, formulation or preparation factors, and patient-specific immune susceptibility. The 2026 observation of different IOI rates between aflibercept 8 mg vial and prefilled-syringe administration makes the unavailable formulation information in the present case particularly relevant [10].

A 2026 pharmacovigilance analysis also identified disproportionality signals for inflammatory ocular adverse events with both aflibercept 8 mg and faricimab [14]. Such reporting analyses cannot estimate incidence or prove causality, but they support continued postmarketing attention to IOI with these agents. The current case should likewise be interpreted as a temporal clinical association rather than proof of cross-reactive immunogenicity.

Several limitations must be acknowledged. This is a single case and cannot quantify risk or establish causality. Microbiologic sampling was not documented, so presumed noninfectious IOI is the most appropriate terminology. Fluorescein angiography during the acute episodes was not available in the source record, preventing formal assessment of retinal vasculitis. And aflibercept 8 mg lot numbers and vial versus prefilled-syringe preparation were not available.

In conclusion, recurrent IOI may occur after aflibercept 8 mg in an eye with previous faricimab-associated IOI despite intervening tolerance of aflibercept 2 mg and prior tolerance of aflibercept 8 mg itself. In this patient, escalation to aflibercept 8 mg was driven by insufficient efficacy and durability of tolerated standard-dose aflibercept rather than by a direct switch from faricimab. For patients with a history of anti-VEGF-associated IOI who still require durable VEGF suppression, counseling and surveillance should continue after every injection, even when early doses of the subsequent agent have been well tolerated.

Abbreviations

AC
anterior chamber
CF
counting fingers
IOI
intraocular inflammation
IOP
intraocular pressure
nAMD
neovascular age-related macular degeneration
OCT
optical coherence tomography
PED
pigment epithelial detachment
SRF
subretinal fluid
VA
visual acuity
VEGF
vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate

This case report was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Review Board of Gyeongsang National University Hospital reviewed the case report and determined that it was exempt from formal ethics approval. Written informed consent to participate was obtained from the patient.

Consent for publication

Written consent was taken from the individual for publication of personal data.

Availability of data and materials

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

None

Authors' contributions

Conception (DEY); Design (DEY, WSY); Data acquisition (DEY, JSS); Analysis (DEY, YWC, WSY); Interpretation (IYC, WSY); Writing (DEY, WSY); Review (All authors); Final approval of the article (All authors)

Acknowledgements

None

References

1. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022;399(10326):729-740. doi:10.1016/S0140-6736(22)00010-1.
2. Lanzetta P, Korobelnik JF, Heier JS, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority phase 3 trial. Lancet. 2024;403(10432):1141-1152. doi:10.1016/S0140-6736(24)00063-1.
3. Thangamathesvaran L, Kong J, Bressler SB, et al. Severe intraocular inflammation following intravitreal faricimab. JAMA Ophthalmol. 2024;142(4):365-370. doi:10.1001/jamaophthalmol.2024.0530.
4. Cozzi M, Ziegler A, Fasler K, Muth DR, Blaser F, Zweifel SA. Sterile intraocular inflammation associated with faricimab. JAMA Ophthalmol. 2024;142(11):1028-1036. doi:10.1001/jamaophthalmol.2024.3828.
5. Ben Ghezala I, Gabrielle PH, Sibert M, et al. Severe intraocular inflammation after intravitreal injection of faricimab: a single-site case series of six patients. Am J Ophthalmol. 2025;269:11-19.

doi:10.1016/j.ajo.2024.08.008.

6. Lischke R, Krause SM, Rauchegger T, et al. Intraocular inflammation after intravitreal injection of faricimab: a case series including one case of bilateral choroidal involvement. Int J Ophthalmol. 2026;19(1):185-192. doi:10.18240/ijo.2026.01.23.
7. Hoffmann L, Michels S, Eandi C, Karam MA, de Oliveira Figueiredo EC, Hatz K. Aflibercept high-dose (8 mg) related intraocular inflammation (IOI): a case series. BMC Ophthalmol. 2024;24(1):520. doi:10.1186/s12886-024-03788-w.
8. Binder KE, Bleidissel N, Charbel Issa P, Maier M, Coulibaly LM. Noninfectious intraocular inflammation after intravitreal aflibercept. JAMA Ophthalmol. 2025;143(6):499-506. doi:10.1001/jamaophthalmol.2025.0969.
9. Stoehr LN, Wakili P, Darwisch W, et al. Intraocular inflammation following aflibercept 8 mg: real-world data from a multicentre retrospective observational study. Int J Retina Vitreous. 2026;12:6. doi:10.1186/s40942-025-00768-0.
10. Hoffmann L, Hatz K. Lower rates of intraocular inflammation with aflibercept 8 mg delivered via pre-filled syringe versus vial. Ophthalmol Ther. 2026;15(4):1499-1508. doi:10.1007/s40123-026-01349-6.
11. Sato S, Sakurada Y, Fukuda Y, Kotoda Y, Kashiwagi K. Recurrence of intraocular inflammation following an aflibercept 8-mg injection in eyes with a history of intraocular inflammation from faricimab: a case report. Cureus. 2025;17(6):e86113. doi:10.7759/cureus.86113.
12. Dwomoh EA, Prasad A, Nanda T. Sterile intraocular inflammation in patients receiving both faricimab and high-dose aflibercept in consecutive order. J Vitreoretin Dis. 2025;9(6):871-875. doi:10.1177/24741264251365391.
13. Hashiya N, Maruko I, Miyaguchi Y, Maruko R, Hasegawa T, Iida T. Intraocular inflammation after intravitreal injection of aflibercept 8 mg for treatment-refractory neovascular age-related macular degeneration: a case report. BMC Ophthalmol. 2025;25(1):42. doi:10.1186/s12886-024-03827-6.
14. Lakhani M, Popovic MM, Al-Ani A, et al. Comparative analysis of ocular adverse events between aflibercept 8 mg and faricimab. Ophthalmol Retina. 2026;10(4):373-384. doi:10.1016/j.oret.2025.10.019.

Figures

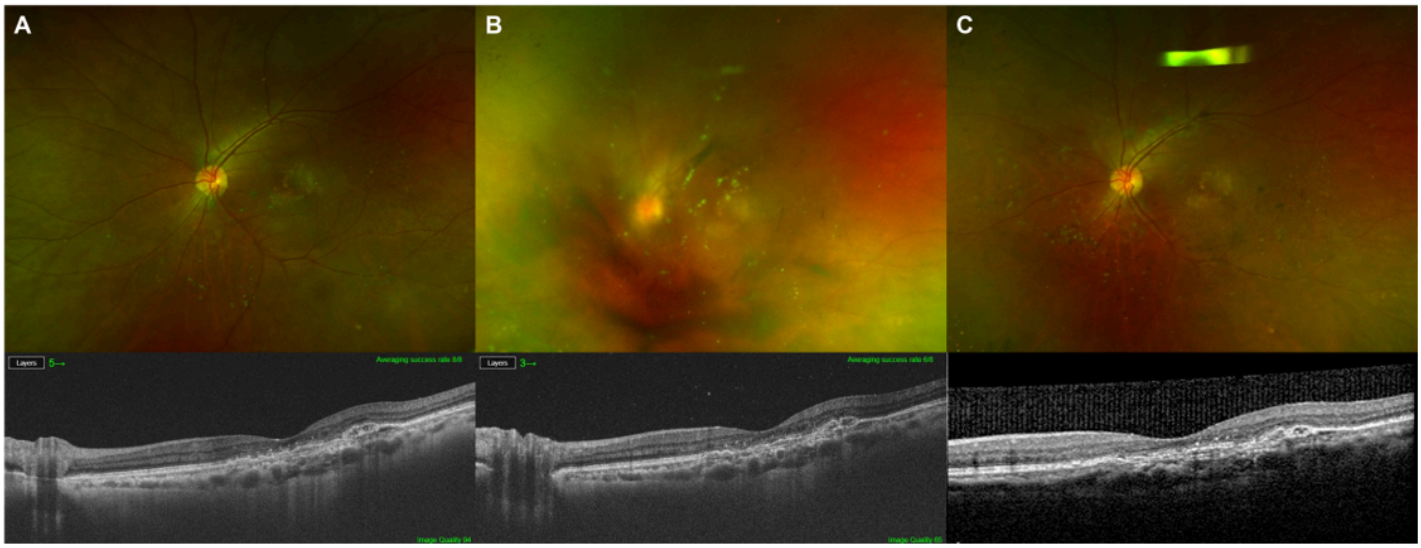


Figure 1

Faricimab-associated intraocular inflammation and recovery.

Color fundus photographs (top) and optical coherence tomography (OCT) images (bottom) of the affected eye. (A) Before the third intravitreal faricimab injection, the vitreous was clear, and OCT documented the choroidal neovascular membrane and pigment epithelial detachment (PED). (B) Four days after the injection, fundus photograph showed vitreous haziness, while OCT demonstrated resolution of subretinal fluid with persistent PED. (C) Following treatment with oral prednisone and topical corticosteroids, vitreous haziness improved with no recurrent subretinal fluid on OCT.

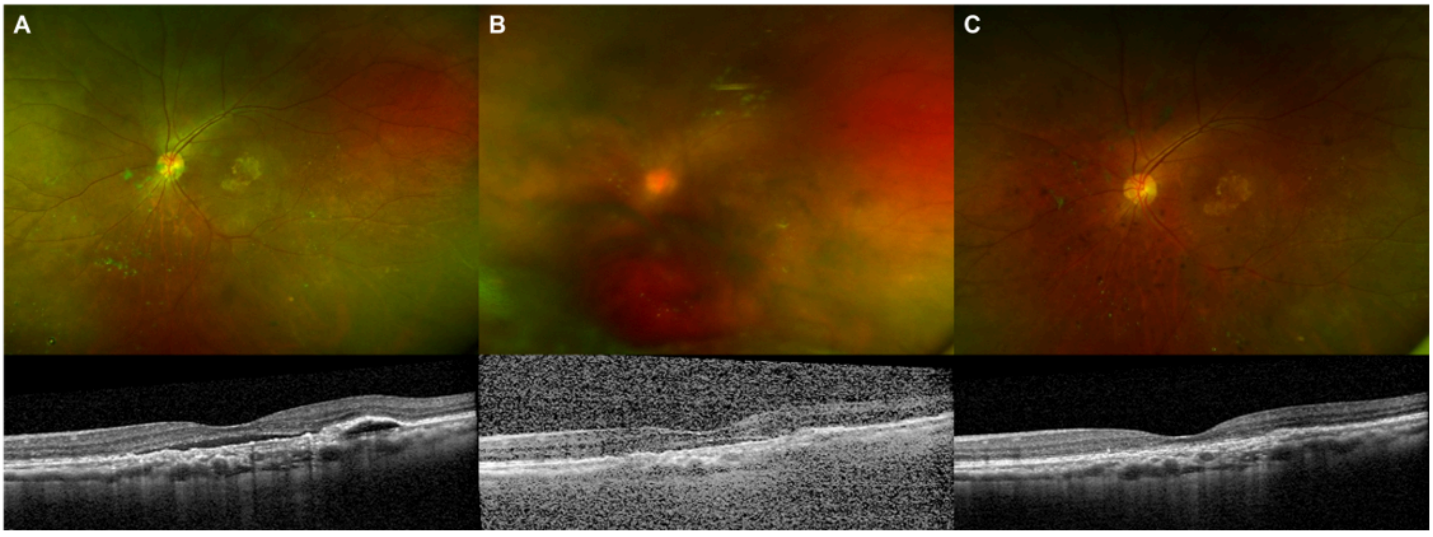


Figure 2

Aflibercept 8 mg-associated recurrent intraocular inflammation and recovery.

Color fundus photographs (top) and optical coherence tomography images (bottom) of the affected left eye. (A) Before the third intravitreal aflibercept 8 mg injection, the vitreous was clear, and OCT showed residual subretinal fluid (SRF) associated with pigment epithelial detachment (PED). (B) Four days after the third injection, fundus photograph demonstrated grade 2–3 vitreous haziness, while OCT showed decreased SRF and PED. (C) Following systemic and topical corticosteroid treatment, vitreous haziness was decreased with resolution of SRF and PED on OCT.