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Sterile endophthalmitis following same-day intravitreal aflibercept 8 mg injections: a single-center observational study

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Abstract

Background

Aflibercept 8 mg was developed to extend treatment intervals in neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). Although pivotal trials reported low rates of intraocular inflammation (IOI), post-marketing sterile inflammatory events have been described. We report a same-day cluster of sterile endophthalmitis after vial-drawn intravitreal aflibercept 8 mg at a tertiary center.

Methods

This retrospective single-center study included all six consecutive patients who received vial-drawn intravitreal aflibercept 8 mg on one treatment day in May 2024. Serial examinations included best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy, and optical coherence tomography. Fluorescein angiography and vitreous microbiological testing were performed where indicated. Descriptive statistics were used.

Results

Five of six patients (83%) developed sterile endophthalmitis within 2–4 days (mean 3.0 ± 0.7 days), with blurred vision, floaters, anterior chamber cells, and vitritis; one patient developed hypopyon. Mean BCVA worsened from 0.44 ± 0.20 logMAR at baseline to 1.29 ± 0.88 logMAR at diagnosis. All affected patients received topical anti-inflammatory treatment with antibiotic coverage and cycloplegia; systemic corticosteroids were administered in four patients. The patient with hypopyon additionally underwent pars plana vitrectomy, anterior chamber washout, vitreous sampling, and intravitreal antibiotics. Vitreous cultures obtained from the patient who underwent pars plana vitrectomy were negative for bacterial and fungal pathogens, and fluorescein angiography in four patients showed no retinitis or vasculitis. At approximately 1 year, mean BCVA was 0.41 ± 0.20 logMAR; four eyes matched or exceeded baseline, while one showed a minor decline attributable to recurrent exudative activity. Same-day injections of other anti-VEGF agents in the same operating theatre were uneventful.

Conclusions

This same-day cluster supports sterile endophthalmitis as a clinically relevant post-marketing event after aflibercept 8 mg. The absence of comparable events after other same-day anti-VEGF injections argues against a general aseptic-procedure problem and suggests a product-, vial-, handling-, or batch-related factor. Prompt recognition, exclusion of infection when appropriate, anti-inflammatory treatment, and pharmacovigilance reporting are important.

Background

Intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors is the standard of care for neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) [1, 2]. Aflibercept 2 mg has been used since 2012 and is associated with a well-established safety profile [3, 4].

A higher-dose 8 mg formulation of aflibercept was developed to extend the dosing interval and reduce treatment burden. Non-inferior efficacy and a comparable safety profile to aflibercept 2 mg were demonstrated at 48 weeks in the phase 2 CANDELA, phase 3 PULSAR (nAMD), and phase 2/3 PHOTON (DME) trials [5–7]. Pooled analyses through 96 weeks subsequently reported comparably low rates of IOI-related adverse events with aflibercept 8 mg and 2 mg [8].

Following broader clinical introduction, however, several real-world reports have described clusters of sterile IOI after intravitreal aflibercept 8 mg, in some instances with severe presentations including retinal vasculitis and vascular occlusion [9–15]. A pharmacovigilance signal for an increased risk of retinal vasculitis with aflibercept 8 mg compared with aflibercept 2 mg has also been identified in an analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS) [16]. Recent multicenter real-world data have reported per-injection IOI rates of 1.4–1.84% with vial-drawn aflibercept 8 mg and a numerically lower rate with pre-filled syringe (PFS) administration [11, 12].

We report a temporally clustered series of five patients with sterile endophthalmitis after intravitreal aflibercept 8 mg at a single tertiary center. All five affected patients and one unaffected patient received injections on the same day from sealed single-use vials, whereas same-day injections of other anti-VEGF agents under identical procedural conditions remained uneventful. Available departmental documentation indicated that the aflibercept 8 mg vials originated from the same commercial batch, although the exact batch identifier was not retained. This pattern provides additional support for a possible product-, vial-, handling-, or batch-related factor.

Patients and methods

Study design and setting

This retrospective, single-center observational study included all six consecutive patients who received intravitreal aflibercept 8 mg (Eylea, 114.3 mg/mL solution for injection; Bayer AG, Leverkusen, Germany) on a single treatment day in May 2024 at Jena University Hospital. The Ethics Committee of Friedrich Schiller University Jena / University Hospital Jena raised no ethical or legal objections (protocol no. AFL8-SE-2026-01; reference no. 2026-4247-BO-D; vote dated 26 May 2026). The study adhered to the Declaration of Helsinki.

Injection technique

All intravitreal injections were performed in a dedicated ophthalmic operating theatre under standardized aseptic conditions. The drug was withdrawn from sealed single-use vials using a single-use withdrawal needle (Sterican, 18 G × 1½ inch, 1.20 × 40 mm; REF 4665120B; LOT 2412043; manufactured by BERPU Medical Technology Co., Ltd., Wenzhou, Zhejiang, China; distributed under the B. Braun label, with EU authorized representative Shanghai International Holding Corp. GmbH [Europe], Hamburg, Germany). The vial rubber stopper was disinfected with alcohol and allowed to dry before withdrawal. The injection field was prepared with povidone-iodine 5%, sterile drapes and a lid speculum were placed, and the injection was administered 3.5 mm posterior to the limbus through the inferotemporal pars plana. Departmental records indicated that all six vials originated from the same commercial batch; however, the exact batch identifier was not retained beyond the discard cycle and is no longer available. The injections were performed by the same surgeon under the operating-theatre protocol used routinely in our department for intravitreal anti-VEGF therapy.

Additional intravitreal injections of other anti-VEGF agents (aflibercept 2 mg, faricimab, and ranibizumab) were performed on the same treatment day, in the same operating theatre, by the same personnel, using the same antisepsis protocol and withdrawal-syringe technique. None of these same-day injections was followed by an inflammatory event.

Outcomes and follow-up

Patients underwent complete ophthalmic examination at every visit, including BCVA, intraocular pressure (IOP) by Goldmann applanation tonometry, slit-lamp biomicroscopy of the anterior and posterior segments, and spectral-domain macular optical coherence tomography (OCT). Fluorescein angiography (FA) was performed during the inpatient course in four of the five affected patients. Vitreous sampling for bacterial and fungal culture was performed in the patient who underwent pars plana vitrectomy; anterior chamber paracentesis and polymerase chain reaction testing for ocular pathogens were not performed in the remaining patients. BCVA was recorded in decimal notation and converted to logMAR for analysis. Central retinal thickness (CRT) was extracted from OCT reports. Outcomes were assessed at presentation, at the 2-week follow-up after discharge, and at approximately 1 year.

The diagnosis of presumed sterile endophthalmitis was based on the acute onset of intraocular inflammation after intravitreal injection, the absence of progressive clinical deterioration, and the favorable response to anti-inflammatory treatment. In the patient who underwent pars plana vitrectomy, bacterial and fungal cultures of the vitreous sample remained negative.

Statistics

Given the small sample size, descriptive statistics were used. Continuous variables are reported as mean ± standard deviation (SD), and categorical variables as counts. No formal hypothesis testing was performed.

Use of generative AI and AI-assisted technologies

During preparation of this manuscript, the authors used ChatGPT (OpenAI) and Claude (Anthropic) solely for language editing, improvement of clarity and readability, and assistance with manuscript structuring. All AI-assisted output was critically reviewed, edited, and verified by the authors. No generative AI tool was used for data collection, data analysis, interpretation of clinical findings, image generation, or reference verification. The authors take full responsibility for the content of the manuscript.

Results

Cluster and attack rate

Five of the six aflibercept 8 mg-treated patients (83%) developed sterile endophthalmitis. The unaffected sixth patient, an 85-year-old woman with nAMD and three prior ranibizumab injections, remained free of intraocular inflammation at scheduled follow-up. Whether her vial belonged to the same sub-lot as the vials used for the affected patients could not be reconstructed.

Baseline characteristics

Demographic and baseline characteristics of the five affected patients are summarized in Table 1. The median age at the event was 79 years (range 74-90), with three women and two men. Three patients had treatment-experienced nAMD and two had treatment-experienced DME. All patients had previously received multiple intravitreal anti-VEGF injections (median 47, range 18-78) without prior inflammatory events, including patient 1, who had tolerated 13 prior brolucizumab injections without IOI.

Table 1. Clinical characteristics of the five affected patients

Pt.	Sex	Age	Eye / indication	Prior anti-VEGF (n)	Time to onset (days)	Anterior segment / vitreous findings	Stay (days)
1	M	78	RE / nAMD (occult type I CNV)	71 (43 AFL, 13 BRO, 13 RAN, 2 FAR)	4	AC cells +, vitreous cells +, faint Tyndall; no hypopyon	7
2	M	90	LE / nAMD	47 (42 AFL, 5 RAN)	3	AC cells +, vitreous cells +; no hypopyon	8
3	F	88	LE / nAMD with occult CNV + PED (DD PCV)	78 (66 AFL, 12 RAN)	3	AC cells +++, vitreous cells ++, vitritis; no hypopyon	8
4	F	79	RE / DME (mild NPDR)	28 (23 AFL, 5 RAN)	2	AC cells ++, vitreous cells +++; no hypopyon	8
5	F	74	LE / DME	18 (5 AFL, 13 RAN)	3	AC cells +++, vitreous cells ++, hypopyon	9

Abbreviations: AC, anterior chamber; AFL, aflibercept 2 mg; AFL-8 mg, aflibercept 8 mg; BRO, brolucizumab; CNV, choroidal neovascularization; DME, diabetic macular edema; FAR, faricimab; nAMD, neovascular age-related macular degeneration; NPDR, non-proliferative diabetic retinopathy; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RAN, ranibizumab; RE, right eye; LE, left eye. DD indicates differential diagnosis.

Clinical presentation

Symptoms began 2-4 days after injection (mean 3.0 ± 0.7 days). All patients reported visual deterioration and floaters; two patients had hand-motion vision at the peak of inflammation. Slit-lamp examination showed anterior chamber cells and vitritis in all cases, with additional hypopyon in patient 5 (Figure 1A). IOP remained within the normal range (9-18 mmHg), and no retinal infiltrates, vasculitis, or vascular occlusion were seen clinically.

Multimodal imaging

The fundus photograph at presentation showed reduced fundus clarity consistent with vitritis (Figure 1B). OCT showed reduced intra- and subretinal fluid after injection, with mean CRT decreasing from 267 ± 55 µm before injection to 205 ± 36 µm at the IOI-related visit or first follow-up (Figure 1D, panels a-c). FA in four patients showed no retinitis, vasculitis, vascular occlusion, or late optic-disc leakage (Figure 1C).

Microbiology

In patient 5, who underwent pars plana vitrectomy, direct microscopy of the vitreous sample showed no bacteria. Aerobic, anaerobic, and fungal cultures remained negative throughout the incubation period. Broad-range bacterial 16S rRNA and panfungal polymerase chain reaction testing were not performed.

Treatment

All five patients were admitted as inpatients and received a combination of topical and systemic anti-inflammatory and antibiotic therapy, including topical prednisolone acetate (Inflanefran forte), topical cycloplegia (cyclopentolate), topical moxifloxacin (Vigamox), intravenous cefuroxime 1500 mg three times daily, and weight-adapted oral prednisolone in four patients. In the most severely affected patient (patient 5), immediate diagnostic and therapeutic pars plana vitrectomy with anterior chamber washout, vitreous sampling, and intravitreal vancomycin and gentamicin was performed, combined with intravenous ceftazidime 2 g three times daily and hourly topical fortified antibiotics and corticosteroids. Mean inpatient stay was 8 days (range 7-9 days).

Visual and anatomical outcomes

BCVA development is summarized in Table 2. Mean BCVA declined from 0.44 ± 0.20 logMAR (approximately Snellen 20/55) before injection to 1.29 ± 0.88 logMAR at diagnosis, driven predominantly by two patients with hand-motion vision at the peak of inflammation. BCVA recovered to 0.54 ± 0.24 logMAR at the 2-week follow-up after discharge and stabilized at 0.41 ± 0.20 logMAR at approximately 1 year. Four of five eyes returned to a BCVA equal to or better than the pre-injection baseline. Patient 1 showed a modest decline from 0.3 logMAR at baseline to 0.4 logMAR at 1 year, most plausibly explained by ongoing exudative disease activity rather than inflammation-related structural damage, because OCT showed recurrent subretinal fluid and increased CRT (252 µm at 1 year versus 242 µm at the 2-week post-event examination). Patient 5, who developed hypopyon and required pars plana vitrectomy, recovered to her pre-injection BCVA of 0.7 logMAR at 1 year despite recurrent DME.

Table 2. Visual acuity and retinal thickness over time

Pt.	BCVA pre-injection (logMAR)	BCVA at IOI diagnosis (logMAR)	BCVA 2 weeks post-event (logMAR)	BCVA ~1 year post-event (logMAR)	CRT pre / post (µm)
1	0.3	0.6	0.2	0.4	355 / 242
2	0.6	1.0	0.7	0.5	204 / 184
3	0.2	0.4	0.4	0.2	251 / 205
4	0.4	2.3 (hand motion)	0.6	0.2	261 / 156
5	0.7	2.3 (hand motion)	0.8	0.7	266 / 237
Mean ± SD	0.44 ± 0.20	1.29 ± 0.88	0.54 ± 0.24	0.41 ± 0.20	267 ± 55 / 205 ± 36

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; IOI, intraocular inflammation; SD, standard deviation. Pre indicates before the index aflibercept 8 mg injection; post indicates the first follow-up examination after the inflammatory event.

Subsequent anti-VEGF management

At 5-7 days after discharge, only mild residual intraocular irritation was present, and no recurrent active inflammation occurred. No patient was rechallenged with aflibercept 8 mg. Four patients continued or switched to aflibercept 2 mg, one later switched to faricimab, and one required no further injections.

Discussion

This series describes a tightly clustered sterile endophthalmitis event after aflibercept 8 mg. The uniform 2-4-day latency, predominant anterior and vitreous inflammation, normal IOP, absence of retinitis or vasculitis, negative vitreous culture in the sampled case, and favorable response to anti-inflammatory therapy support a sterile rather than infectious etiology [9,11,12,17].

Comparison with the existing post-marketing literature

Although the pivotal CANDELA, PULSAR, and PHOTON trials reported low rates of IOI with aflibercept 8 mg, comparable to aflibercept 2 mg [5-8], post-marketing experience has consistently described a higher real-world incidence of sterile IOI. Hoffmann and colleagues described a multicenter cluster of eight patients with sterile IOI within 2-17 days after aflibercept 8 mg injection at three centers [9]. Binder and colleagues reported that 5 of 41 patients (136 injections) developed mild non-infectious IOI after

intravitreal aflibercept 8 mg, corresponding to a per-injection incidence of 3.7% [10]. A real-world multicenter analysis from three centers documented a cluster of 12 eyes between July 2024 and June 2025 with a per-injection IOI rate of 1.4% [12], and a 1.5-year multicenter analysis of 2631 injections by the Vista Augenklinik group reported an overall per-injection IOI rate of 1.56%, with a numerically lower rate when aflibercept 8 mg was administered from a PFS rather than withdrawn from a vial [11]. Several individual reports and small series have described severe events including retinal vasculitis [13,14] and occlusive retinal vasculitis [15]. A FAERS pharmacovigilance analysis also identified a signal for an increased risk of retinal vasculitis with aflibercept 8 mg compared with aflibercept 2 mg [16]. The short incubation, absence of vasculitis, and generally favorable visual outcome in our series fall within the milder end of this reported spectrum.

What is unusual about this series

The most informative feature is the same-day clustering pattern. Five of six aflibercept 8 mg-treated patients were affected, whereas other anti-VEGF agents injected in the same operating theatre by the same team remained uneventful. This argues against a general aseptic-procedure failure and points instead toward a factor related to the aflibercept 8 mg product, vial, handling process, or commercial batch. Because the exact batch identifier and sub-lot information were unavailable, the study cannot establish a batch-specific causal association.

Putative mechanisms

Plausible mechanisms include silicone oil droplets from siliconized syringes, protein aggregation at air-liquid or silicone-liquid interfaces, product-specific immunogenicity, and batch-level quality variation [18-20]. The higher protein concentration of aflibercept 8 mg may increase susceptibility to aggregation, and real-world data suggesting lower IOI rates with PFS administration support the importance of reducing vial-withdrawal handling steps [11]. In our series, the absence of the exact lot identifier and incomplete reconstruction of the syringe body preclude definitive proof of the mechanism.

Clinical implications

Patients receiving aflibercept 8 mg should be advised to seek prompt review for new floaters, blurred vision, or photophobia during the first 1-2 weeks after injection. Clustered or severe events should be reported to pharmacovigilance authorities and the manufacturer. Until further data are available, meticulous vial preparation, avoidance of agitation, and consideration of PFS presentations where available appear prudent.

Limitations

The main limitations are the small sample size, retrospective single-center design, incomplete lot and sub-lot traceability, inability to reconstruct the exact syringe body, and limited microbiological testing beyond culture of the single vitrectomized case. These limitations prevent definitive causal proof, although the temporal pattern, negative culture, and absence of same-day events with other anti-VEGF agents strongly support a sterile clustered event.

Conclusion

Sterile endophthalmitis after aflibercept 8 mg is uncommon but clinically important. This same-day cluster, together with uneventful same-day injections of other anti-VEGF agents, argues against a general aseptic-procedure problem and suggests a product-, vial-, handling-, or batch-related factor. Prompt recognition, empiric exclusion of infection when indicated, anti-inflammatory treatment, and close follow-up were associated with favorable visual recovery. Careful preparation of vial-drawn aflibercept 8 mg, pharmacovigilance reporting of clustered events, and consideration of PFS presentations may help reduce risk during routine use.

Abbreviations

AC: anterior chamber; AFL: aflibercept 2 mg; AFL-8 mg: aflibercept 8 mg; BCVA: best-corrected visual acuity; BRO: brolucizumab; CNV: choroidal neovascularization; CRT: central retinal thickness; DME: diabetic macular edema; FA: fluorescein angiography; FAERS: US Food and Drug Administration Adverse Event Reporting System; FAR: faricimab; IOI: intraocular inflammation; IOP: intraocular pressure; IVI: intravitreal injection; nAMD: neovascular age-related macular degeneration; NPDR: non-proliferative diabetic retinopathy; OCT: optical coherence tomography; PCV: polypoidal choroidal vasculopathy; PED: pigment epithelial detachment; PFS: pre-filled syringe; RAN: ranibizumab; SD: standard deviation; VEGF: vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Friedrich Schiller University Jena / University Hospital Jena reviewed the study and raised no ethical or legal objections to the conduct of this retrospective observational study (protocol no. AFL8-SE-2026-01; reference no. 2026-4247-BO-D; vote dated 26 May 2026). The study was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study, the requirement for written informed consent to participate was waived by the Ethics Committee; all procedures formed part of routine clinical care.

Consent for publication

Written informed consent for publication of de-identified clinical data and ophthalmic images was obtained from all participants. No directly identifying information is included.

Availability of data and materials

The de-identified datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

MP has received speaker honoraria from Bayer, Roche, AbbVie, and Santen; support for attending educational meetings, including registration fees, travel, and accommodation, from Bayer, Roche, AbbVie, and Alimera Sciences; and a registration fee from Oertli. FP has received support for attending an educational meeting, including registration fees, travel, and accommodation, from Bayer. CP has received speaker honoraria from AbbVie; support for attending educational meetings, including registration fees, travel, and accommodation, from Bayer and AbbVie; and a registration fee from Oertli. VC has no relevant financial or non-financial interests to disclose. DM has received speaker honoraria from Théa Pharma and Santen and support for attending an educational meeting, including accommodation, from Bayer. All activities were unrelated to the submitted work. The authors have no other relevant financial or non-financial interests to disclose.

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Authors' contributions

MP contributed to conceptualization, methodology, investigation, project administration, data interpretation, and drafting and revision of the manuscript. FP contributed to investigation, data curation, literature review, and manuscript drafting. CP contributed to investigation, data curation, validation, and critical revision of the manuscript. VC contributed to data curation, validation, and critical revision of the manuscript. DM supervised the study, provided resources, contributed to data interpretation, and critically revised the manuscript. All authors read and approved the final manuscript.

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Prior presentation

Part of this work was presented orally at the Annual Meeting of the German Ophthalmological Society (DOG), Berlin, Germany, September 2025.

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Figures

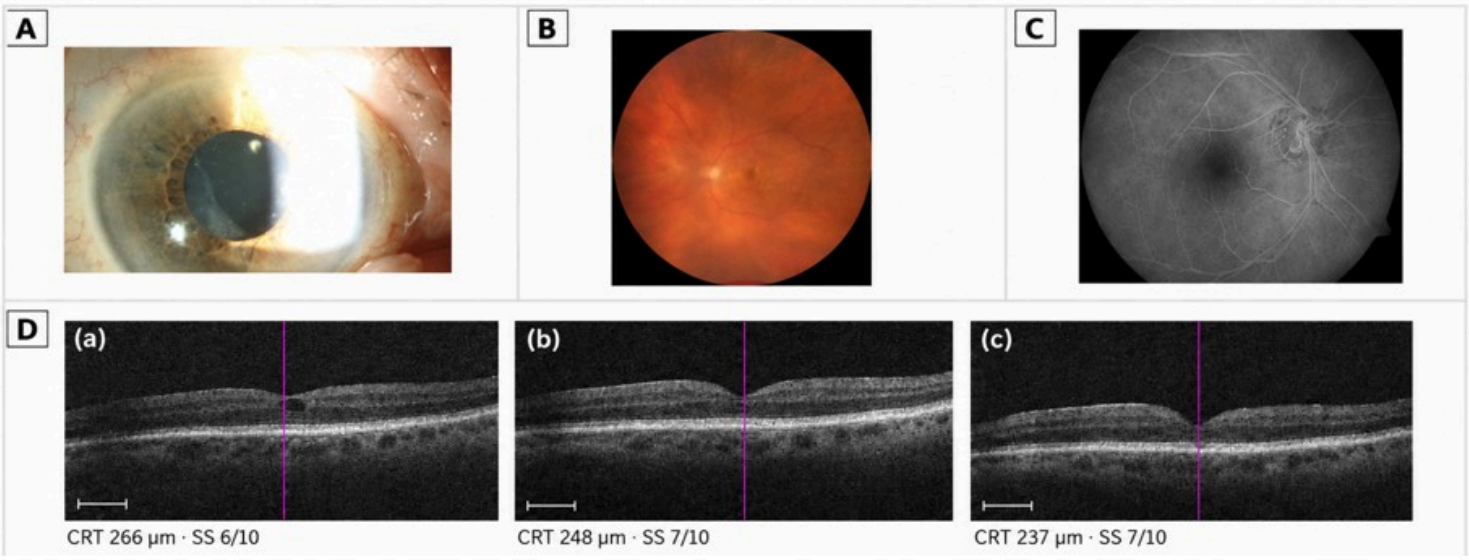


Figure 1

Multimodal imaging after sterile endophthalmitis following intravitreal aflibercept 8 mg. (A) Slit-lamp photograph showing anterior chamber inflammation. (B) Fundus photograph at presentation showing reduced fundus clarity consistent with vitritis. (C) Fluorescein angiography without evidence of retinitis, vasculitis, vascular occlusion, or late optic-disc leakage. (D) Macular OCT images of an affected eye: (a) baseline OCT before clinical inflammation with a central retinal thickness of 266 µm; (b) OCT during the acute inflammatory phase with a central retinal thickness of 248 µm; and (c) follow-up OCT showing a dry macula with a central retinal thickness of 237 µm after severe intraocular inflammation with hypopyon and subsequent pars plana vitrectomy.