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Bilateral Sterile Granulomatous Uveitis Caused by Intravitreal Injections of Faricimab

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Abstract

Purpose: To describe a case of severe bilateral granulomatous uveitis caused by treatment with faricimab. **Methods:** A single case was reviewed. **Results:** A 79-year-old woman with diabetic macular edema developed severe uveitis OU 16 days after bilateral intravitreal (IVT) injections of faricimab. The patient's visual acuity (VA) was hand motions OD and 20/400 OS. She refused IVT antibiotics at bedside but consented to an emergency pars plana vitrectomy (PPV) OU. The laboratory workup for infectious and autoimmune etiologies was unremarkable, as were bacterial and fungal cultures from the PPV. High-dose systemic steroids were initiated after surgery. The patient's VA recovered to 20/30 OD and 20/25 OS. **Conclusions:** Reports of severe uveitis resulting from injections of faricimab have been documented. We describe a unique case in which the patient with granulomatous uveitis OU experienced a significant decline in vision. With high-dose systemic steroid therapy and surgical intervention, her VA recovered to near baseline.

Keywords

faricimab, endophthalmitis, uveitis, inflammation, sterile, anti-VEGF, VEGF, angiopoietin

Introduction

Intravitreal (IVT) injections of antivascular endothelial growth factor (anti-VEGF) agents are the mainstay treatment for common retinal diseases such as diabetic macular edema (DME).[1,2] Uveitis caused by IVT injection is a feared complication that can be caused by acute infectious endophthalmitis or sterile intraocular inflammation (IOI).[3,4] IVT antibiotics should be administered whenever there is high clinical suspicion for infection.

Faricimab (Genentech) is a humanized bispecific immunoglobulin G antibody that neutralizes both VEGF type A and angiopoietin-2 signaling pathways. Its safety and efficacy have been shown in clinical trials; however, in the 2 years since commercial availability, there have been reports of severe sterile IOI. Notably, the characteristics of these cases have not been universal. In the largest case series to date, Ben-Ghezala et al[5] described 6 eyes with severe IOI, for an estimated incidence of 0.6% per injection. All eyes had normal intraocular pressure (IOP), had no hypopyon, and displayed varying degrees of vision loss. Conversely, Thangamathesvaran et al[6] reported 3 cases of sterile IOI, all characterized by profound vision loss, hypopyon, and normal IOP. Numerous other case reports found instances of uveitis characterized by ocular hypertension, keratic precipitates, and mild to no vision loss.[7,8] Treatment with steroids often led to an improvement in these clinical findings.

In this report, we present a unique case of severe bilateral sterile IOI in a patient who received an IVT injection of faricimab. Improvement of the inflammation was seen after surgical intervention and high-dose steroid therapy.

Case Report

A 79-year-old woman with DME presented for treatment that comprised bilateral IVT faricimab injections. Her medical history included type 2 diabetes mellitus, hypertension, hyperlipidemia, asthma, and spinal stenosis. Her ocular history included pseudophakia and moderate nonproliferative diabetic retinopathy (NPDR) in both eyes. She did not have a history of autoimmune or uveitis disease. Initial management of the patient's DME was aflibercept before switching to faricimab to extend treatment intervals. The patient previously received 2 bilateral faricimab injections over the course of 6 months, with a Snellen

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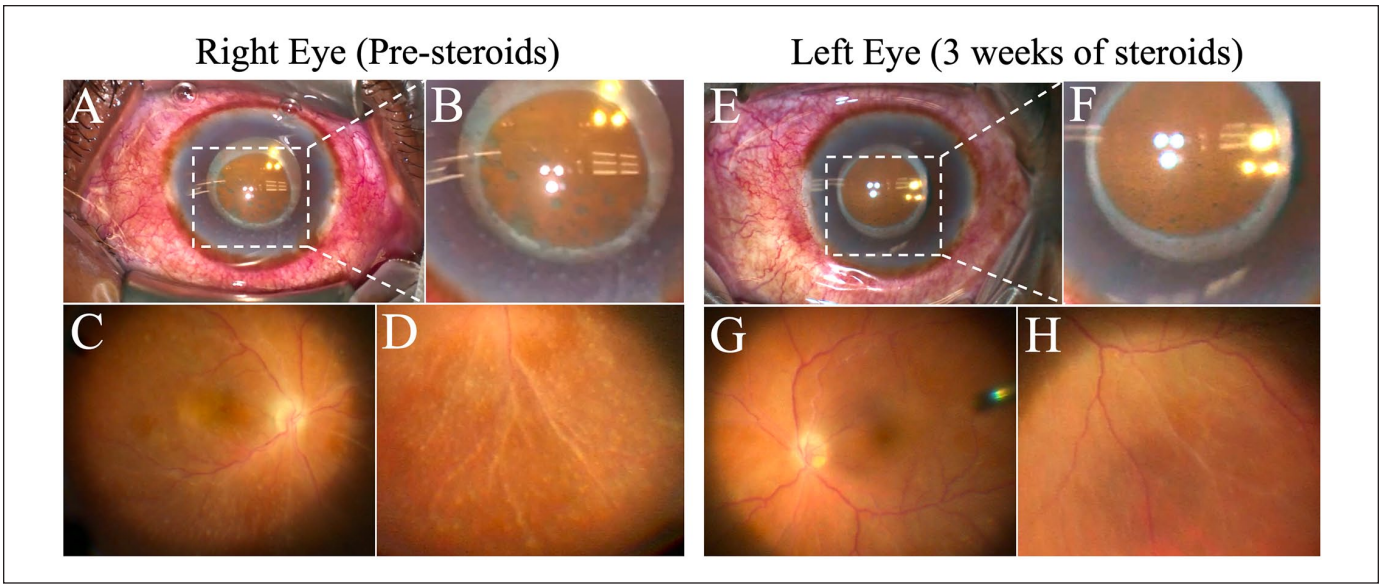

Figure 1. Improvement of granulomatous inflammation is seen after high-dose systemic steroid therapy. The patient had pars plana vitrectomy (PPV) in the right eye before initiation of high-dose systemic steroid therapy. (A) Keratic precipitates and (B) extensive vitritis are seen that, after its removal, show (C) sclerotic-appearing vasculature and (D) punctate intraretinal lesions throughout the periphery. After 3 weeks of high-dose steroid therapy, the patient had PPV in the left eye. An intraoperative evaluation shows (E) resolution of keratic precipitates and, (F) after removal of vitritis, (G) an improvement in retinal vascular attenuation and (H) punctate intraretinal lesions.

best-corrected visual acuity (BCVA) improving to 20/20 OU. After a delay in follow-up, she presented for her third faricimab treatment with a BCVA measuring 20/80 OD and 20/20 OS. Optical coherence tomography (OCT) imaging showed progression of the DME in both eyes. There were no other findings of concern at the time of the patient's presentation.

Per the injection protocol, the physician wears a face mask during the procedure. Topical anesthetic (0.5% proparacaine) followed by subconjunctival 2% lidocaine were used for anesthesia, and topical 5% povidone–iodine was used to prepare the ocular surface. Faricimab was injected through the pars plana using a 30-gauge short needle at the superior–temporal quadrant. Although an eyelid speculum was not used, the eyelashes were kept out of the surgical field, and no blink was allowed after placement of the last drop of povidone–iodine. The patient tolerated the treatment well.

Three days later, the patient left a voice message at our clinic stating decreased vision in both eyes. Multiple attempts, all unsuccessful, were made to reach the patient. Thirteen days later, she presented to the emergency department with a BCVA that had decreased to hand motions OD and 20/400 OS. The IOP measured using a Tonopen was elevated to 45 mm Hg OD and 41 mm Hg OS. Significant conjunctival injection along with moderate corneal edema, keratic precipitates, and inflammatory cells in the anterior chamber were seen in both eyes; however, there was no hypopyon (Figure 1A). An examination of the posterior segment showed dense bilateral vitritis obstructing a view of the fundus; thus, fluorescein angiography (FA) could not be performed for further evaluation. No findings of retinal detachment or a mass were found on a B-scan ultrasound. The patient denied eye pain during this time.

Given the concern for acute infectious endophthalmitis, the patient was offered bilateral IVT injections of broad-spectrum antibiotics and a bedside biopsy of the anterior chamber (AC) or vitreous fluid; however, all invasive ophthalmic interventions were declined. A comprehensive infectious and autoimmune laboratory evaluation included syphilis, tuberculosis, Lyme disease, sarcoidosis, HLA-B27, sedimentation rate, C-reactive protein, antinuclear antibody, rheumatoid factor, and cytoplasmic neutrophil antibodies, all of which were unremarkable. One dose of intravenous levofloxacin was given, and the patient was discharged on topical prednisolone acetate, ofloxacin, IOP-lowering drops, and oral valaciclovir. Her vision began to improve immediately. At the 3-day follow-up visit, the BCVA was 20/350 OD and 20/250 OS. The IOP measured by applanation was 15 mm Hg OD and 20 mm Hg OS. At this time, the patient consented to an AC fluid biopsy in the right eye, which was negative on polymerase chain reaction (PCR) testing for herpes virus; therefore, the oral valaciclovir therapy was discontinued.

The patient continued to refuse IVT antibiotics; thus, an emergency pars plana vitrectomy (PPV) was performed in the right eye because it had worse vision (Supplemental Video 1). A vitreous biopsy was performed, during which vascular attenuation with arteriolar sheathing and numerous punctate intraretinal whitening throughout the peripheral retina were noted (Figure 1, C and D). IVT injections of vancomycin (1.0 mg/0.1 mL), ceftazidime (2.25 mg/0.1 mL), and voriconazole

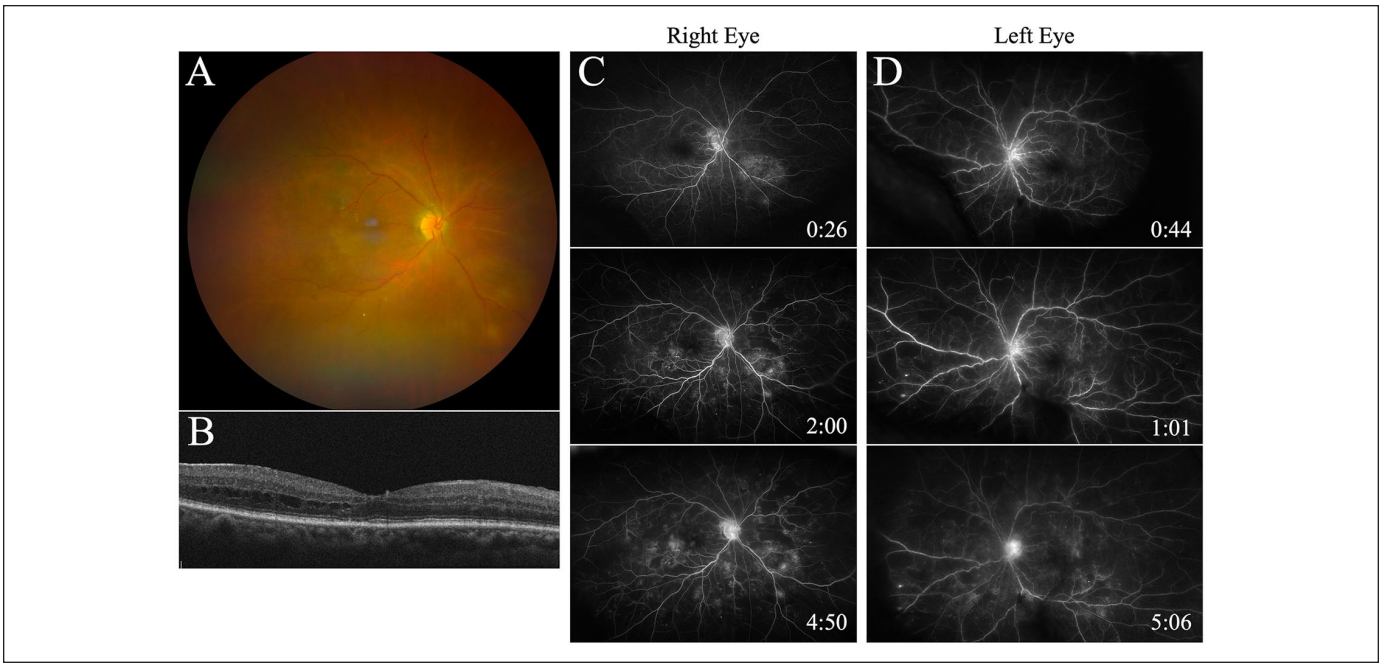

Figure 2. Perfusion of retinal vasculature is maintained during faricimab-associated granulomatous uveitis. After 1 week of systemic high-dose steroid therapy and after pars plana vitrectomy in the right eye, (A) vascular attenuation and sheathing as well as punctate inner retinal lesions in the right eye appear to be improving. (B) Optical coherence tomography imaging of the macula of the right eye shows trace intraretinal leakage temporal to the fovea likely representing persistent diabetic macular edema. Fluorescein angiography of (C) the right eye and (D) the left eye shows persistent retinal vascular perfusion with mild peripheral microaneurysms and generalized findings consistent with moderate nonproliferative diabetic retinopathy. There is also moderate late leakage of dye from the optic nerves in both eyes, indicating persistent low-grade inflammation.

(100 µg/0.1 mL) were administered as well as a sub-Tenon injection of triamcinolone (40 mg/1 mL) at the conclusion of surgery. Intraoperatively, the patient was also given 1 g of methylprednisolone. The postoperative regimen included 60 mg of daily oral prednisone.

Two weeks after PPV, the patient's BCVA improved to 20/40 OD and 20/70 OS; thus, the oral prednisone was tapered to 20 mg daily. Bacterial and fungal cultures from the surgical biopsy of the vitreous grew no organisms. The IOP measured by applanation was 20 mm Hg OD and 21 mm Hg OS. The keratic precipitates had resolved, and the AC was deep and quiet in both eyes (Figure 1E). The vitreous of in the right eye remained clear after PPV, while the vitritis in the left eye was slowly improving. The vascular attenuation with arteriolar sheathing and the punctate intraretinal lesions in the periphery were resolving in both eyes (Figure 2A). Normal transit and perfusion of the major retinal vessels with pinpoint leakage and microaneurysms consistent with moderate NPDR were seen on FA in both eyes; however, there was still mild late leakage from the optic disc in both eyes, suggesting continued mild inflammation (Figure 2, C and D). Because of a persistent visual decline in the left eye as a result of vitritis, the patient elected to have PPV with a sub-Tenon injection of triamcinolone (Supplemental Video 1). A surgical biopsy showed no growth on bacterial and fungal cultures. Intraoperatively, keratic precipitates and vascular attenuation with arteriolar sheathing were seen and the intraretinal lesions in the periphery were continuing to resolve (Figure 1, E–H). Two weeks after PPV in the left eye (6 weeks after beginning bilateral faricimab injections), the patient's BCVA improved to 20/30 OD and 20/25 OS.

Conclusions

Recent reports have documented numerous cases of sterile IOI resulting from IVT administration of faricimab.[5–8] Despite an apparent heterogeneity in its presentation, this form of inflammation appears to respond well to steroid therapy, as was seen in our patient. Preemptive additional counseling to recognize the signs and symptoms of sterile IOI may decrease the time to presentation and subsequent treatment. The onset of symptoms for our patient was most likely 3 days; however, she did not present until 16 days after the inciting event. In other reports, the onset of symptoms varied from 1 to 20 days after faricimab treatment in both treatment-naïve eyes and previously treated eyes. More studies are needed to evaluate the clinical characteristics indicative of a higher likelihood of sterile IOI because closer surveillance for these patients may be warranted.

Our case report is unique in that the patient experienced a significant decline in vision bilaterally caused by an injection of faricimab but presented with granulomatous uveitis without hypopyon, which we often associate with acute infectious endophthalmitis. Furthermore, her refusal of early antibiotic intervention before surgical biopsy, along with negative bacterial and fungal cultures and a negative herpes virus PCR significantly

decrease the probability of this case having an infectious etiology. The likelihood that our clinical findings are associated with an issue with the specific lot number of faricimab (ie, the patient received the same lot in both eyes) is highly unlikely because this lot was used to treat 32 eyes of 27 unique patients with no complications. Furthermore, we reported our findings along with the specific lot number to Genentech, which did not find similar reports of complications.

It is important to emphasize that our patient did not have an ocular or medical history of autoimmune disease. Whether this inflammation was associated with the unique dual pathway inhibition of VEGF and angiopoietin-2 by faricimab or with its specific formulation is beyond the scope of this report. The patient's BCVA and symptoms improved significantly after PPV and high-dose steroid therapy, which is in accordance with other reports that faricimab-associated sterile IOI responds well to steroids and does not cause retinal vascular occlusive disease. Our findings emphasize the importance of timely evaluation of patients after they receive IVT faricimab.

Ethical Approval

Ethical approval was not sought for the present study because of its retrospective nature and case report.

Statement of Informed Consent

The patient provided informed consent for publication of the case report and accompanying images.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material is available online with this article.

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