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Sterile Intraocular Inflammation in Patients Receiving Both Faricimab and High-Dose Aflibercept in Consecutive Order

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Abstract

Purpose: To describe 3 cases of intraocular inflammation (IOI) in patients who received faricimab and high-dose aflibercept in consecutive order. **Methods:** Retrospective case review. **Results:** Three patients, 2 with neovascular age-related macular degeneration (nAMD) and 1 with central retinal vein occlusion (CRVO), transitioned from 2 mg aflibercept to either faricimab (in cases 1 and 2) or high-dose aflibercept (in case 3) due to persistent disease activity. In all cases, contemporary medication provided minimal effect. Subsequently, patients in cases 1 and 2 were switched to high-dose aflibercept at their next visit, and the patient in case 3 was switched to faricimab. On follow-up, the disease worsened in all 3 cases. Each patient returned to their previous drug. Shortly after, each patient developed an episode of IOI. **Conclusions:** Patients receiving different high-dose or longer-acting agents in short order may be at risk for developing antidrug antibodies and IOI.

Keywords

anti-VEGF, intraocular inflammation, intravitreal injection

Introduction

Until recently, the availability of multiple antivascular endothelial growth factor (anti-VEGF) treatment options was limited. Most patients were treated with 2 mg aflibercept, which was approved for up to 8-week intervals.[1] In 2022, Genentech released faricimab, a dual-pathway molecule purported to hasten fluid resolution and prolong treatment duration in neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and central retinal vein occlusion (CRVO), when compared with 2 mg aflibercept dosing. In 2023, Regeneron received approval from the US Food and Drug Administration (FDA) for 8 mg aflibercept (high-dose aflibercept), adding another anti-VEGF treatment option. Similar to faricimab, high-dose aflibercept demonstrated noninferiority with prolonged treatment duration, up to 16 weeks between injections in select patients with nAMD and DME.[2]

Although the benefit of stronger, more durable medication options can be valuable for many treatment-resistant patients, there is limited experience switching between these newer agents. As more retina specialists consider these contemporary agents, sometimes in combination, physicians need to consider drug-to-drug interactions in their treatment calculations. This series highlights 3 cases of sterile intraocular inflammation (IOI) in patients receiving faricimab and high-dose aflibercept in consecutive order.

Results

Case 1

An 80-year-old man received treatment for choroidal neovascularization (CNV) of the left eye secondary to nAMD at a frequent interval of 4 to 4.5 weeks. He received 2 mg aflibercept at every visit for 8 years for persistent subretinal fluid (SRF). Visual acuity (VA) remained 20/40 with normal intraocular pressures. He presented with endophthalmitis 4 years prior, with early identification, treatment, and return to baseline. Endophthalmitis treatment included a tap and inject (T&I), followed by a vitrectomy 4 days later due to persistent vitreous debris. Other ocular history included a mild epiretinal membrane (ERM) in both eyes and mild age-related nuclear sclerosis. In 2022, the patient switched to monthly faricimab injections and showed a slightly improved response with persistent SRF.

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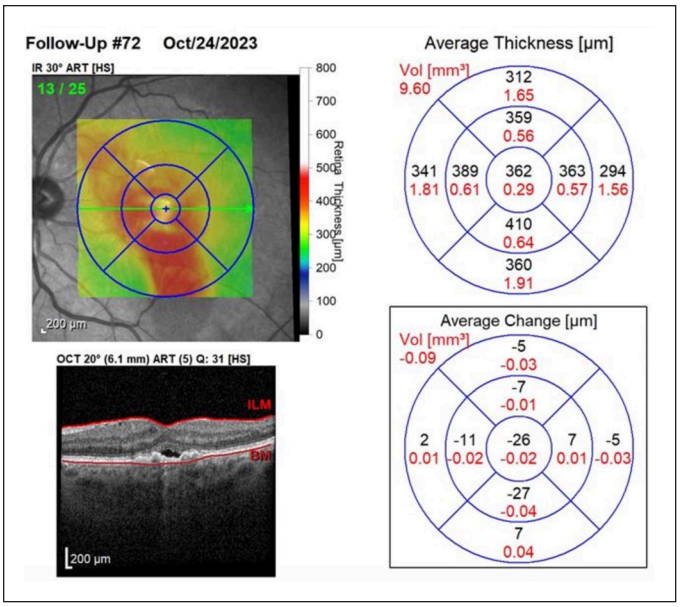

Figure 1. Optical coherence tomography image of case 1 after 17 consecutive faricimab injections. There was persistent subretinal fluid with increased central subfield thickness.

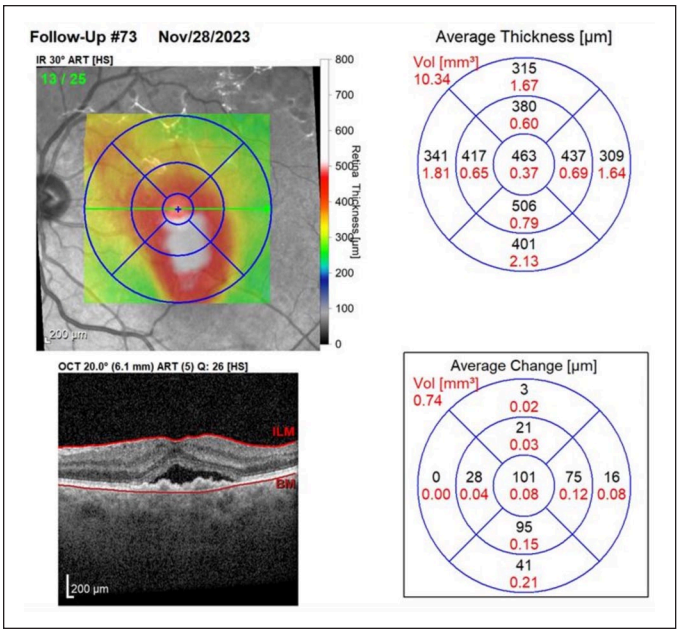

Figure 2. Optical coherence tomography image of case 1, 35 days after high-dose aflibercept injection, demonstrating significantly worsened subretinal fluid with an increased central subfield thickness of 101 µm.

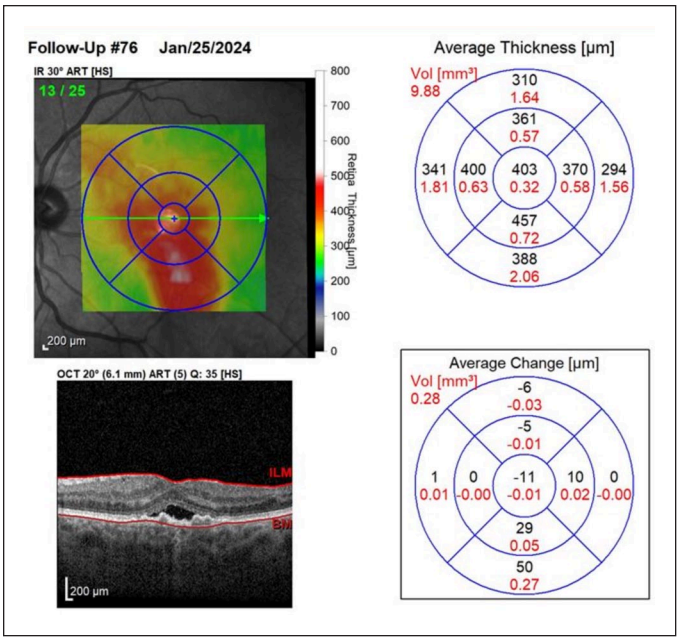

Figure 3. Optical coherence tomography image of case 1 after resolution of intraocular inflammation. There was persistent subfoveal fluid on monthly ranibizumab injections.

An anti-VEGF response was confirmed at the 2-week mark, with a reduction in SRF suggestive of a resistant disease process. He was intermittently treated with a sample of aflibercept at these 2-week intervals in addition to monthly faricimab. This was unsuccessful in reducing SRF and was abandoned for monthly faricimab alone. Prior to the switch, the patient had also received 2 treatments of photodynamic therapy, with no significant effect.

In October 2023, after 17 consecutive treatments with monthly faricimab, the decision was made to switch the patient to high-dose aflibercept (Figure 1). At follow-up 35 days later, he presented with worsened SRF (Figure 2). The patient returned to faricimab at this visit due to his suboptimal fluid response. After 1 day, he presented with an acute onset of foggy vision, normal intraocular pressure, and 20/100 VA. The examination demonstrated diffuse AC cells and dense vitritis. The eye was otherwise white and quiet with no pain, consistent with an acute inflammatory response. A T&I was performed (vancomycin and ceftazidime) out of caution.

No growth was observed on the cultures, and the patient returned to baseline after 28 days of using topical steroid therapy alone. SRF worsened in the interim. At this visit, the patient was switched to ranibizumab owing to presumed hypersensitivity to faricimab and/or high-dose aflibercept. The patient had no further inflammatory reactions on subsequent follow-up (Figure 3). He continued to demonstrate persistent SRF.

Case 2

A 76-year-old woman with CRVO and symptomatic macular edema (ME) received 2 mg aflibercept every 28 days (since 2018) in the left eye for persistent intraretinal fluid (IRF). Additional ocular history included pseudophakia in 2022 and an uncomplicated posterior vitreous detachment (PVD). She was treated with dexamethasone (Ozurdex, Allergan) in August 2023 and had a significant steroid response, negating further steroid use. After the cessation of steroid therapy, her intraocular pressure returned to

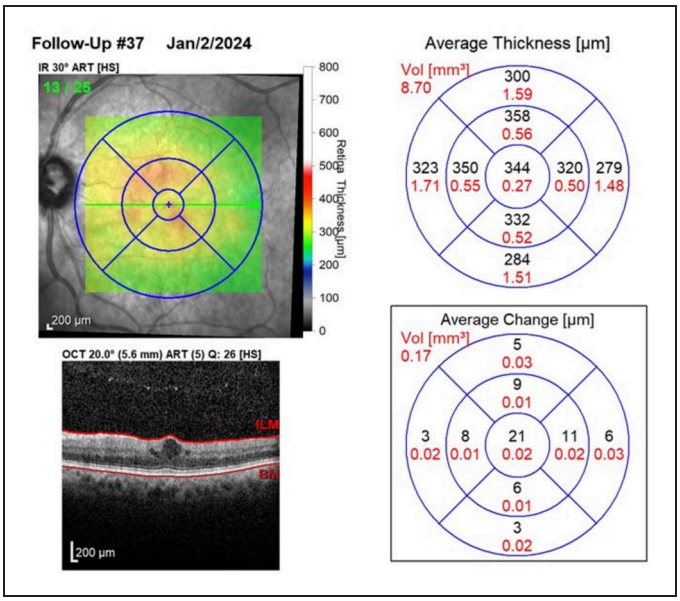

Figure 4. Optical coherence tomography of case 2 demonstrating persistent macular edema despite consecutive monthly faricimab injections.

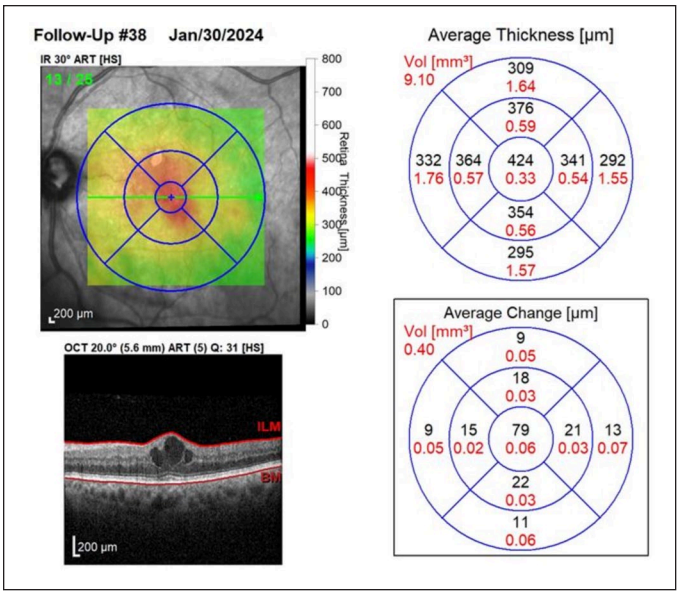

Figure 5. Optical coherence tomography of case 2 demonstrating increased macular edema 28 days after switching to high-dose aflibercept. There was a reduction in visual acuity from 20/20 to 20/30.

normal, and her central VA continued to fluctuate between 20/20 and 20/30 with monthly aflibercept injections.

In November 2023, the patient switched to faricimab and received 2 monthly faricimab injections with minimal added effect (Figure 4). She was given high-dose aflibercept, and after 28 days, she presented with a significant increase in IRF on optical coherence tomography (OCT), with a reduction in VA from 20/20 to 20/30 (Figure 5). The patient returned to faricimab at that visit. After 3 weeks, she reported an increasing haze and fogginess that presented several days after the injection. She did not report any pain. The examination showed 2+ anterior chamber cells with mild light sensitivity, consistent with a sterile IOI (20/40 VA). The patient received topical steroid treatment, and the uveitic episode resolved without complication. Subsequent use of intravitreal ranibizumab injections resulted in no recurrent episodes.

Case 3

An 89-year-old woman with a history of CNV in the left eye secondary to nAMD received 2 mg aflibercept injections every 10 to 11 weeks for 7 years without complication. The patient presented with persistent fluid throughout and tolerated SRF to reduce treatment burden. Her vision fluctuated from 20/30 to 20/80 throughout her treatment history.

In January 2024, the patient was switched to high-dose aflibercept. After 11 weeks, SRF remained or recurred (VA 20/40), and she was trialed on faricimab instead. After 10 weeks, the patient's vision worsened to 20/50 with increased SRF, consistent with a suboptimal response to faricimab when compared to aflibercept and high-dose aflibercept. She returned

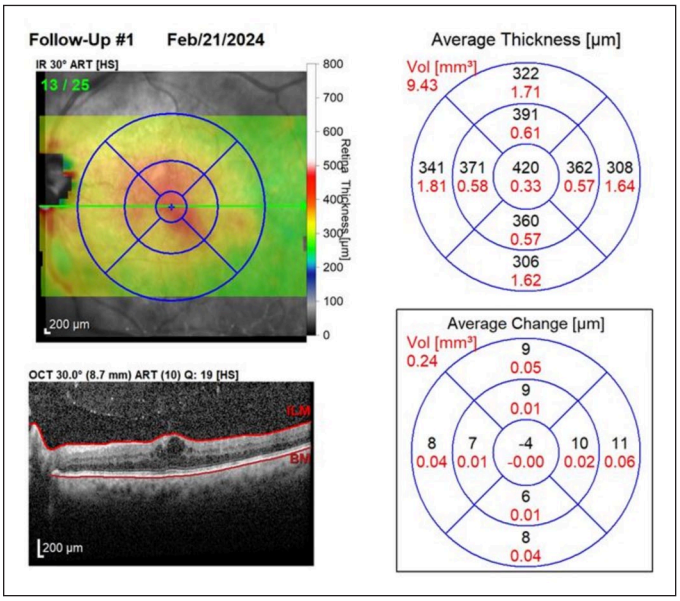

Figure 6. Optical coherence tomography of case 2 demonstrating persistent macular edema after resolution of the patient's inflammatory episode. She continued treatment with monthly ranibizumab.

to high-dose aflibercept at the subsequent visit. After 7 days, the patient re-presented with blurry vision (20/80 VA), floaters, and pain. The examination showed a mild anterior chamber reaction with 1+ vitritis. The patient received topical steroid treatment for 2 weeks, and the uveitic episode resolved without complication.

Conclusions

In phase 3 clinical trials, sterile IOI remained exceedingly rare (ranging from 1%-2%) when compared with 2 mg aflibercept for both faricimab and high-dose aflibercept.[3,4] Clinical trial participants were naïve to anti-VEGF therapy and included patients without other ocular pathology, such as a history of endophthalmitis, systemic history of autoimmune disease, or other potentially confounding factors.[3,4] These 3 cases highlight a possible hypersensitivity of the eye when switching between 2 high-dose intravitreal medications in a short period.

In all cases, the patients tolerated faricimab or high-dose aflibercept alone, including in case 1, when the patient received several treatments of faricimab and aflibercept just 2 weeks apart. None of the patients in these 3 cases received an injection from the same medication lot as per practice policy. Each case was injected by a different physician and occurred months apart. There were no deviations from standard protocols when performing the injections.

Sterile IOI following intravitreal injections may arise from different factors. These include patients' susceptibility to inflammation, how the biological agent was produced, or the pharmacologic properties of the agent itself. For example, the proinflammatory Fc portion on some anti-VEGF biologics can bind to intraretinal Fc receptors, leading to an inflammatory response. This likely explains the reduced inflammatory response by intravitreal injections, such as ranibizumab, which lack the Fc portion.[5,6] The low molecular weight of ranibizumab (48 kD) compared to aflibercept (115 kD) and faricimab (149 kD) might also contribute to the comparatively low immunologic response seen with ranibizumab.[7] Patients who receive different medications targeting the same receptors or with similar properties and/or mechanisms of action can also develop antidrug antibodies, induced and or amplified by these various treatments.[5] These antidrug antibodies increase sensitivity to subsequent inflammation.[5] Moreover, patients with a history of ocular inflammation, autoimmune disease, prostaglandin analog drops, or diseases and/or procedures that impair the blood-retinal barrier may also have increased susceptibility to inflammation.[6–8] For example, the patient in case 1 had a history of endophthalmitis and vitrectomy, which might have increased his susceptibility to varied medication use. Increased concentrations of a biological agent in a susceptible eye, such as high-dose aflibercept (8 mg) and faricimab (6 mg), may result in a greater risk of IOI.

The first 2 cases are different from the updated vasculitis risk reported by Genentech and the FDA regarding faricimab, as neither patient demonstrated any arterial or venous vascular inflammation.[9] In a recent case series, 1 institution reported 3 cases of significant IOI in patients receiving faricimab within a month, suggesting that rates of IOI with faricimab may be greater than those reported in the clinical trial data.[5] In our series, it remains unclear which medication (or both) may be the source of IOI in these patients. Additionally, the second case includes an off-label use of high-dose aflibercept at the time, though approval for patients with CRVO is generally expected.[10,11] The third case was the reverse order of the first 2 cases, with a return to high-dose aflibercept resulting in IOI. Cases 1 and 3 demonstrated a more acute infection mimicker, with a dramatic drop in vision within 2 to 7 days,[12] while Case 2 was more reminiscent of the delayed hypersensitivity reaction, usually 14 days after injection,[13] previously seen with brolucizumab.

High-dose aflibercept is estimated to reach unquantifiable concentrations after approximately 3.5 weeks. Faricimab has an estimated half-life of 7.5 days, resulting in a drug concentration of approximately 1.5% after 45 days, with sustained suppression of angiopoietin-2 reported at 16 weeks post-treatment.[14,15] Although inexact and patient-specific, this suggests an overlap in drug pharmacokinetics in the first 2 cases. As these longer-acting agents remain in the eye, including a wash-out period when switching agents may be prudent. The FDA includes guidance on wash-out periods in several crossover studies, recommending a wash-out period of at least 5 half-lives, though this guidance is not eye-specific.[16,17] Several clinical trial protocols looking at patients on prior anti-VEGF therapy have included a wash-out period of 4 weeks or more.[18,19] Although instituting a wash-out policy may be admirable moving forward, it is not all-encompassing. The third case, for example, involved injections at least 10 weeks apart ($>$ 5 half-lives). In addition to a wash-out period, retina specialists need to be more cognizant of other ocular factors that could sensitize an eye to these higher-dose agents, including endophthalmitis history, surgical history, and steroid use.

Further study of such rare events is challenging for many reasons. First, treatment-resistant patients tend to have complex ocular histories. Second, these patients comprise a tiny portion of the retina patient population. Third, IOI is rare and relies heavily on self-reporting. In all 3 cases, IOI was generally mild, as it was treatable with aggressive topical therapy and did not leave residual sequelae. Surveillance on the interaction between medications in switch patients is an important process for identifying patients at increased risk of IOI. Although these cases may be coincidental, our objective is to raise awareness, as such events may increase in frequency with expanded use.[5]

Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. Collecting and evaluating all protected patient health information was performed in a US Health Insurance Portability and Accountability Act–compliant manner.

Statement of Informed Consent

The consent to publish was not required from the institutional review board as the information included in these cases excludes any patient identifiers.

Declaration of Conflicting Interests

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