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Intraocular Inflammation Following Intravitreal Faricimab: Insights from Five Bilateral Cases

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Abstract

Purpose: To evaluate the incidence of intraocular inflammation (IOI) after intravitreal (IVT) faricimab injection. **Methods:** A retrospective observational study was performed of all patients who received IVT faricimab injections at NHS Highland between January 2023 and June 2024 and subsequently developed IOI. **Results:** IOI was seen in 11 eyes of 6 patients after faricimab injection. All aqueous and vitreous cultures were negative. Among patients who received bilateral faricimab injections, the incidence of IOI was 8.5% (5/59). Four eyes experienced a vision loss of 11.5 ± 8.6 Early Treatment Diabetic Retinopathy Study letters. Cases were characterized by a delayed onset of subacute symptoms after injection, keratic precipitates, and elevated intraocular pressure. **Conclusions:** Although the overall incidence of faricimab-related IOI is low, our findings highlight the need for increased vigilance in patients receiving bilateral faricimab injections.

Keywords

faricimab, intraocular inflammation, injection-related inflammation

Introduction

Faricimab (Vabysmo, Genentech) is a novel dual monoclonal antibody that targets and inhibits both vascular endothelial growth factor (VEGF) A and angiopoietin 2 (Ang2). After 2 parallel phase 3 preclinical trials found a safety profile comparable to aflibercept, faricimab was approved by the National Institute for Health and Care Excellence in June 2022 for the treatment of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME).[1,2] This was a significant turning point after reports of an increased incidence of vision-threatening intraocular inflammation (IOI) and vasculitis were seen with brolicizumab, an anti-VEGF agent marketed for its extended durability.[3–5] Agents such as faricimab and high-dose aflibercept[6] therefore present appealing options for both patients and clinicians.

Compared with aflibercept, faricimab offers favorable efficacy, durability, and safety. However, after its integration into clinical practice, case reports drew attention to its safety profile,[7–13] including IOI and associated vasculitis, leading to vision loss.

Here, we describe our experience with severe IOI after IVT faricimab injections, including 5 cases of bilateral involvement. These cases presented similarly, characterized by a delayed onset of subacute symptoms after injection, increased intraocular pressure (IOP), and completion of at least 3 loading injections.

Methods

This retrospective case review included all patients who had IVT injections across 3 NHS Highland sites between January 2023 and June 2024 and subsequently developed severe IOI. Patients were followed for a minimum of 3 months. All medical retina injection events were documented using the MediSight electronic patient record system, and records within the specified period were reviewed. All patient details were anonymized.

This study complied with the Declaration of Helsinki and the UK's Data Protection Act. Ethical permission was not required because it was viewed and registered as an audit and approved by the North of Scotland Ethics Committee. Informed consent was obtained from all patients. No experimentation was performed in this study.

Before initiation of treatment, all patients underwent a dilated slitlamp examination. Subsequent injections are managed within a virtual medical retina service, where patients receive assessments of visual acuity (VA) and IOP before each injection. When clinically indicated, macular optical coherence tomography (OCT) imaging is performed, such as for patients on a treat-and-extend regimen or in cases of decreased vision. A dilated examination by an ophthalmologist is conducted only when clinically indicated, such as in cases of VA deterioration, elevated IOP, or if the patient reports any red-flag symptoms, including pain, reduced vision, or new floaters.

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Table 1. Distribution of Anti-VEGF Injection Agents Administered from January 2023 to June 2024.

Anti-VEGF agent	Patients, n	Eyes, n	Injections, n
Bevacizumab	78	84	319
Lucentis	276	316	990
Ongavia	330	365	1721
Aflibercept	643	791	4312
Brolucizumab	9	12	59
Faricimab	208	267	2034
Total	1544	1835	9435

Abbreviation: VEGF, vascular endothelial growth factor.

All IVT procedures were administered in a dedicated injection suite under aseptic conditions by trained advanced nurse practitioners following standardized protocols. For bilateral injections, each eye was treated as a separate procedure, with a vial from a separate lot number used for the second injection.

Results

During the study period, a total of 9435 IVT anti-VEGF injections were administered. Table 1 describes the distribution of injections. Among the 208 patients treated with faricimab, 59 received bilateral injections, 10 had bilateral injections that comprised faricimab administered in 1 eye and another medicine in the fellow eye, and 139 had unilateral injections of faricimab. The indications for faricimab use included nAMD, DME, myopic choroidal neovascularization, and retinal vein occlusion. No patient had any history of IOI or elevated IOP before initiating treatment, and none had viral or autoimmune conditions that could increase the risk of IOI. Before initiating treatment, patients had received a median of 5 faricimab injections (interquartile range [IQR], 4-6; range, 4-6).

Upon presentation to the emergency eye service, patients had a median VA of 55 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (IQR, 0-67; range, 0-80). Before beginning treatment with faricimab, affected eyes had a median VA of 65 ETDRS letters (IQR, 48-79; range, 0-80).

Of the total number of injections administered, 13 eyes of 8 patients developed IOI, 1 case associated with aflibercept and another with ranibizumab. The remaining cases were attributed to treatment with faricimab (Table 2). Four cases of injection-related endophthalmitis were observed, all of which were related to aflibercept. Severe IOI was seen in 11 eyes of 6 patients after IVT faricimab injections, with a cumulative incidence of 3% (6/208) per patient over the course of 18 months, or a risk of 4.1% (11/267) per eye. Among patients who received bilateral faricimab, the incidence of IOI was 8.5% (5/59).

Symptoms including ocular pain, reduced vision, or floaters typically started at a median of 10 days (IQR, 9-21; range, 9-49) after injection. Clinical findings at presentation comprised elevated IOP, diffuse keratic precipitates, and anterior chamber inflammation in the affected eyes (Figures 1 and 2). The mean IOP at presentation was 33 mm Hg ± 13 (range, 14-51). One case of vasculitis with occlusion was documented.

Given the clinical examination findings and temporal relationship with recent faricimab injections, most cases were initially managed as suspected infectious endophthalmitis. Aqueous and vitreous samples were obtained for culture, and IVT antibiotics, oral and topical corticosteroids, and IOP-lowering medications were administered. All microbiological cultures, including 16S polymerase chain reaction, were negative. A systemic uveitis screen was not performed because the temporal relationship with faricimab injection, the absence of relevant inflammatory history, and the resolution of inflammation after discontinuing faricimab suggested a drug-related sterile uveitis as the most likely etiology.

Faricimab was discontinued in all cases, with patients switching to alternative anti-VEGF agents. Visual outcomes were variable; 4 eyes from 4 patients failed to recover their baseline vision, with a mean vision loss of 11.5 ± 8.6 ETDRS letters (range, 5-24).

Conclusions

Our real-world experience suggests that the risk of vision-threatening IOI associated with faricimab may be greater than reported in preclinical trials. In our case series the observed incidence of faricimab-related IOI per eye was 4.1% (11/267); and among patients who received bilateral faricimab, the incidence was 8.5% (5/59). In the TENAYA and LUCERNE trials, the incidence of IOI was 2% compared with 1.2% with aflibercept.[2] Similarly, the YOSEMITE and RHINE trials reported an incidence of 1.3% compared with 0.6% with aflibercept.[1] These data mirror the findings that brolucizumab caused IOI and vasculitis at significantly higher rates (4.6%[14]) compared with alternative anti-VEGF medications.[4,15–17]

The incidence of faricimab-related IOI reported by Ben Ghezala et al[7] was 0.62%, with patients presenting with vitritis, granulomatous keratic precipitates, and reduced VA. Thangamathesvaran et al[8] reported cases of severe vision loss 3 to 4 days after injection, with anterior hypopyon uveitis, intermediate uveitis, and normal IOP. In the current study, symptoms began more than a week after injection, and patients had already received 4 to 6 previous faricimab injections. Elevated IOP and keratic precipitates affected more than half the cases, and 4 of 11 eyes did not recover baseline VA.

Elevated IOP was not significantly reported in the preclinical trials, with only 2 patients affected across the TENAYA, LUCERNE, YOSEMITE, and RHINE trials. However, in our cohort, 7 of 11 eyes (64%) exhibited elevated IOP; 3 of those were asymptomatic, underscoring the importance of IOP measurements before each injection. The rapid resolution of both IOP elevation and anterior chamber inflammation suggests trabeculitis may be a possible cause, and other case reports support this finding. Kitson and McAllister[9] and Palmieri et al[10] found cases of hypertensive uveitis with fine keratic precipitates and stable VA.

We also observed 1 case of vasculitis with occlusion in the current study. Postmarket data reported the risk of faricimab-related vasculitis to be 0.17/10 000.[18] In a patient with nonocclusive vasculitis, Siddiqui et al[11] advocated the use of intravenous steroids to

Table 2. Patient Characteristics.

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6
Variable	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	One eye affected
Indication for injections	DMO	DMO	AMD	AMD	AMD	AMD	AMD	AMD	AMD	AMD	AMD
Symptoms first started after injection (d)	10	10	49	n/a	9	9	18	n/a	n/a	n/a	21
Symptoms	None	Reduced vision and pain	Blurred vision and floaters	None	Blurred vision and pain	Blurred vision and pain	Floaters	None	None	None	Blurred vision
Duration from last injection to hospital presentation (d)	14	14	53	54	12	12	25	25	47	47	37
Previous faricimab injections (n)	6	6	4	5	4	4	4	4	6	6	5
Other previous injections (n)	32 Eylea	32 Eylea	16 Eylea	13 Eylea	3 Ongavia	3 Ongavia	3 Eylea; 55 Lucentis	4 Eylea; 56 Lucentis	21 Eylea	26 Eylea	18 Eylea
Vision before injection (ETDRS letters)	65	43	68	80	48	64	80	67	79	CF	61
Vision at presentation (ETDRS letters)	58	47	CF	57	CF	55	67	70	80	CF	50
Change in vision from last injection	−7	4	−68	−23	−48	−9	−13	3	1	0	−11
IOP (mm Hg)	32	40	17	14	47	48	20	22	34	40	51
Red eye	No	Yes	yes	No	yes	yes	No	No	No	No	yes
Keratic precipitates	yes	yes	yes	yes	yes	yes	no	no	yes	yes	yes
Vitritis	No	no	yes	yes	no	no	yes	yes	no	no	no
Vasculitis	No	no	no	no	Occlusive	no	no	no	no	no	no
Deviation in final VA from baseline	0	−10	−24	0	−7	0	−5	0	0	0	0
Tap and inject	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Aqueous culture	n/a	n/a	Negative	n/a	Negative	Negative	Negative	Negative	n/a	n/a	n/a
Vitreous culture	Negative	Negative	Negative	n/a	Negative	Negative	Negative	Negative	n/a	n/a	n/a
Faricimab lot number	B1502B25	B1505B01	B1505B01	B1505B02	B1527B01	B1525B01	B1507B16	B1510B01	B1510B01	B1509B15	B1509B15

Abbreviations: AMD, age-related macular degeneration; DME, diabetic macular edema; ETDRS, Early Trial Diabetic Retinopathy Study; IOP, intraocular pressure; VA, visual acuity.

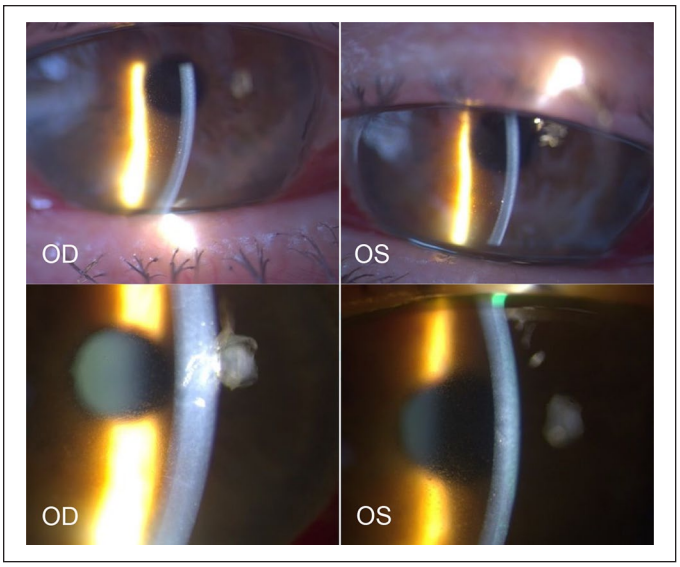

Figure 1. Slitlamp photographs of Patient 1's right eye (OD) and left eye (OS) demonstrate bilateral fine keratic precipitates.

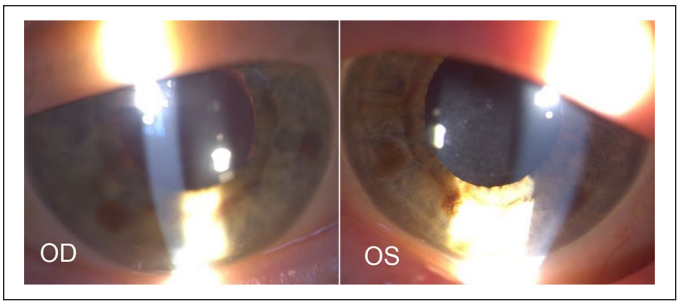

Figure 2. Slitlamp photographs of Patient 2's right eye (OD) and left eye (OS) demonstrate bilateral fine keratic precipitates.

restore vision. Two additional case reports[12,13] described occlusive vasculitis after faricimab injection, with associated vision loss and hypertensive uveitis.

Although we acknowledge that our cases could potentially be infectious endophthalmitis with negative cultures, we believe sterile inflammation is more likely. The delayed onset of symptoms after injection (median, 10 days) and keratic precipitates are atypical for endophthalmitis. In addition, 5 cases were bilateral, which is exceedingly rarely seen with endophthalmitis after an injection.[19] All eyes responded promptly to steroids, with 7 of 11 eyes regaining baseline VA. All patients receiving bilateral faricimab injections were administered doses from different lot numbers, reducing the likelihood of a manufacturing contamination issue. Notably, a systemic uveitic workup was not completed in these patients because the most likely cause was a drug-induced reaction.

Sterile inflammation in response to anti-VEGF agents is a recognized phenomenon, with both acute and delayed onset reactions reported.[20] Acute cases can mimic endophthalmitis, while cases of delayed onset may manifest weeks after injection, as seen with brolucizumab.[5] Reduced vision, floaters, and the presence of anterior chamber or vitreous cells are common in sterile inflammation, but pain, hypopyon, keratic precipitates, or trabeculitis are less frequent.[20]

The mechanism for sterile IOI remains speculative.[20] Various personal, drug-related, and manufacturing-related[21] factors have been proposed, including genetic susceptibility to autoimmunity and delayed type IV hypersensitivity. In the TENAYA and LUCERNE trials, drug-induced antibody formation was reported in 10% of patients at 20.1 weeks and at 28 weeks in 8.2% to 8.7% of patients in the YOSEMITE and RHINE trials,[22] but the clinical significance of anti-faricimab antibodies remains unclear. The preclinical trials assigned only 1 eye to faricimab treatment, but in real-world settings, patients are likely to require bilateral treatment. Our data demonstrate the incidence of IOI to be 8.5% (5/59) in patients receiving bilateral faricimab. We hypothesize that this may be related to higher cumulative dosing and the resultant increased concentration of antibodies. Further investigation is required to determine the underlying mechanism behind this observation.

Faricimab's bispecific antibody structure may also contribute to its higher IOI rates compared with traditional anti-VEGF agents. Ranibizumab has been noted to have a lower incidence of sterile IOI, thought to be due to the absence of a fragment crystallizable (Fc) region, which can be proinflammatory. Unlike ranibizumab, faricimab contains an Fc region that has been modified to reduce inflammatory risk.[20]

Faricimab is not supplied in a prefilled syringe. The process of drawing the medication into a syringe could lead to the release of silicone oil and subsequent inflammatory reactions.[23] The Manufacturer and User Device Experience database has also raised concerns regarding the manufacturing quality and sterility of the filter needles used in the injection process.[21] The exact pathophysiological mechanism of drug-induced inflammation is likely to be multifactorial, and further work is needed to illicit these mechanisms.

Faricimab has been in routine clinical use for approximately 2 years, and clinicians are still adapting to its safety profile. Although the reported overall incidence of faricimab-related IOI is low and comparable to aflibercept, our findings suggest the need for heightened vigilance for patients receiving bilateral injections, particularly within the first 6 injections.

In the UK, it is standard practice for patients undergoing IVT injection therapy to be managed in a virtual medical retina service. IOP measurements with a dilated slitlamp examination are recommended for patients before initiating faricimab treatment. In our cohort, 3 of 11 eyes demonstrated elevated IOP and uveitis without symptoms. The balance between the convenience of bilateral injections and the risk of bilateral inflammation, including vasculitis, must also be carefully considered.

When a patient presents with subacute symptoms, anterior or vitreous inflammation, the possibility of a drug-induced reaction should be promptly considered. In addition, education among patients, healthcare professionals administering injections, and other allied eye care professionals is needed regarding the warning signs of IOI to ensure timely access to eye care. We recommend all

patients be offered urgent evaluation when indicated, initiating corticosteroid treatment and close monitoring. These steps are essential to mitigate the risk of inflammatory or pressure-related complications and optimize visual outcomes.

Ethical Approval

The study of this type did not require ethical permission as it was viewed and registered as an audit, approved by the North of Scotland Ethics Committee.

Statement of Informed Consent

Written informed consent was obtained from all patients.

Declaration of Conflicting Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary Material

Supplementary material is available online with this article.

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