Research Square

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Option of Switching to Intravitreal Faricimab in Refractory Wet Age-Related Macular Degeneration for Patients Requiring Continued Brolucizumab Treatment

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Research Article

Keywords: wet age-related macular degeneration, brolucizumab, faricimab, intravitreal injection, switching, vascular endothelial growth factor

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10883944/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

We evaluated changes in visual and anatomic outcomes in patients with difficult-to-treat wet age-related macular degeneration (wAMD) who were switched to faricimab from brolucizumab.

Methods

We conducted an IRB-approved retrospective chart review of patients with wAMD treated at Retinal Consultants P.C. across five clinical sites between July 2020 and May 2024. Patients with ambiguous diagnoses, a history of endophthalmitis or inflammatory disorders, surgery or photodynamic therapy, inadequate follow-up, or who did not receive the two drugs of interest sequentially were excluded. Best corrected visual acuity (BCVA), central subfield thickness (CST), and retinal fluid assessment were recorded for each treatment period and compared between faricimab and brolucizumab. Wilcoxon's signed-rank tests and McNemar's tests were used to assess significance.

Results

57 eyes were included. All patients had persistent or recurrent retinal fluid despite treatment with anti-VEGF therapy prior to initiating brolucizumab. Patients received a mean of 9.6 ± 4.9 IVB injections and 8.6 ± 6.6 IVF injections, with a mean treatment duration of 52.7 ± 35.9 and 59.3 ± 31.5 weeks for brolucizumab and faricimab, respectively. Neither BCVA or CST changed significantly from baseline following treatment with either agent. Average BCVA and CST were comparable on both IVB and IVF. However, complete fluid resolution occurred more frequently with faricimab than brolucizumab ($p = 0.01$). Treating retina specialists reported 75.4% of eyes had an improved response to faricimab.

Conclusions

Switching from brolucizumab to faricimab resulted in similar reductions in CST and BCVA, with higher rates of fluid resolution. These findings suggest that faricimab may serve as an effective alternative for patients who remain on brolucizumab with a history of treatment resistance.

Introduction

The clinical utility of anti-vascular endothelial growth factor (anti-VEGF) therapy in wet age-related macular degeneration (wAMD) lies in its targeted inhibition of angiogenesis and control of vascular permeability. For many years, agents such as bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea) have served as standard treatments. While these therapies are highly effective for many patients,[1] a subset continues to exhibit disease resistance and experience a high treatment

burden.[2,3] Second-generation agents such as brolucizumab (Beovu) and faricimab (Vabysmo), approved by the FDA in 2019 and 2022 respectively, aim to improve disease control and address these limitations.

Brolucizumab, a single-chain antibody fragment, is notable for its high VEGF binding affinity. It demonstrated non-inferiority to aflibercept in pivotal trials, and real-world reports have shown promising efficacy in patients with suboptimal responses to prior anti-VEGF therapies.[4–7] However, its clinical use has been limited by an unexpectedly high rate of vision-threatening vasculitis,[8] which appears to be linked to increased antigenicity and anti-drug antibody activity.[9,10] Faricimab has also demonstrated non-inferiority to aflibercept in clinical trials but has shown lower rates of vasculitis in real-world settings.[11,12] As a dual inhibitor of VEGF and angiopoietin-2 (Ang-2), it can maintain visual acuity and anatomic outcomes (e.g., central subfield thickness reduction) over longer treatment intervals, offering a potential alternative for patients with refractory disease.[13]

Data directly comparing outcomes in patients switched from brolucizumab to faricimab are limited. To date, only two retrospective analyses have examined this treatment sequence, reporting stable visual acuity and modest anatomic responses following the switch to faricimab in a heterogenous population, including responsive, refractory, and naïve patients.[17,19] The objective of this study was to specifically evaluate patients with wAMD who had persistent or recurrent intra- or subretinal fluid (SRF) on optical coherence tomography (OCT) despite frequent injections (4–6 weeks) on a first-generation agent. In this population, we identified patients who were subsequently placed on brolucizumab, in order to determine whether faricimab could be a reasonable alternative in patients with refractory wAMD.

Methods

Study Design

This retrospective chart review of patients with refractory wAMD was conducted between July 2020 and May 2024 across five Retina Consultants P.C. clinical sites. Eligible patients were identified via drug codes and data was extracted from de-identified electronic medical records (EMR) to assess treatment responses. This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study protocol was reviewed and approved by the Quinnipiac University Institutional Review Board.

Study Population

Patients were identified and included in the study if they met the following inclusion criteria: a) had a diagnosis of wAMD confirmed by a retina specialist, b) demonstrated an inadequate response to a first-generation anti-VEGF agent marked by persistent or recurrent intraretinal or subretinal fluid, c) subsequently underwent transition from brolucizumab to faricimab in sequence, and d) had a minimum of one follow-up visit after receiving each drug. Refractory disease was defined as persistent IRF or SRF

after a minimum of three sequential injections on a first-generation anti-VEGF, or recurrent SRF and/or IRF after a 4–6 week duration, which requires a frequent injection burden. Study size was determined by the number of eligible patients meeting this inclusion criteria during the study period. All patients demonstrated treatment-refractory disease on anti-VEGF therapy prior to brolucizumab. Patients were excluded from the study if they had a) ambiguous diagnoses (such as central serous chorioretinopathy), b) a history of endophthalmitis or other intraocular inflammatory disorders, c) underwent ocular surgery or photodynamic therapy prior or during treatment, or d) had insufficient follow-up. Patients who remained on brolucizumab without transition to faricimab were not included in this study, as we aimed to evaluate outcomes following the switch in treatment.

Data Collection

Patient data was extracted from NexTech EMR. Demographic variables of interest included age, sex, and race. Treatment-related variables included number of injections, duration of treatment period, and reasons for discontinuing intravitreal brolucizumab (IVB) and intravitreal faricimab (IVF) (where applicable). Best corrected visual acuity (BCVA), central subfield thickness (CST), fluid status (categorized as resolved, improved, unchanged, or recurrent), and injection interval were recorded at baseline, after the first three injections, and as an average across the entire treatment period for each drug. BCVA was reported as a Snellen fraction and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Central subfield thickness (CST) was obtained from OCT imaging at each visit, and an average was similarly recorded across the entire treatment period on each drug. The presence or absence of complete fluid resolution while being treated with each drug was assessed based on fundoscopic exam findings and OCT imaging. Comparative drug response was determined retrospectively using the treating retina specialist's OCT interpretation, documented clinical assessment, as well as the impression and plan under the related diagnosis associated with treatment.

Statistical Analysis

Data was documented using Microsoft Excel (Microsoft Corporation, Redmond, WA) and analyzed using IBM SPSS Statistics Version 29.0.1.0, Python (Python Software Foundation, version 3.12.4), and R (R Core Team, version 4.2.2). Demographic and treatment data, including race, age, sex, number of injections, and treatment duration were summarized using descriptive statistics (mean and standard deviation). For continuous variables, normality was assessed using the Shapiro-Wilk test and non-parametric testing with paired Wilcoxon signed-rank test was performed. Categorical variables were analyzed using McNemar's test for paired comparisons (e.g., fluid resolution) and one-sided binomial test for cohort-level assessments (e.g., holistic assessment). P values were adjusted for multiple comparisons using the Benjamini-Hochberg method, with adjusted $p < 0.05$ considered statistically significant.

Results

Patient Demographics and Baseline Characteristics

Table 1 lists participant characteristics. A total of 57 eyes from 57 patients with wAMD were included in the analysis. All eyes were transitioned to brolucizumab because of active retinal fluid despite first-generation anti-VEGF treatment, which was followed by sequential transition to intravitreal faricimab. The most common reason for switching was persistent or worsening fluid in the eye (80.7%). Among the 46 eyes transitioned from brolucizumab to faricimab due to persistent retinal fluid, the predominant fluid subtype was subretinal fluid (SRF), identified in 35 eyes (76.1%). Intraretinal fluid (IRF) was documented in 7 eyes (15.2%), IRF and SRF together were identified in 3 eyes (6.5%), and 1 eye (2.2%) had the presence of subretinal hemorrhage (SRH). Other reasons for switching to faricimab included intraocular inflammation (10.5%), being unable to extend the treatment interval (3.5%), concern for vasculitis risk while on IVB (3.5%), and retinal pigment epithelium tear (1.8%). (Table 2). The mean age of the cohort was 81.0 ± 9.9 years, and 27 patients (47.4%) were female. All patients initially received brolucizumab due to its earlier approval, followed by faricimab. Patients received a mean of 9.6 ± 4.9 IVB injections and 8.6 ± 6.6 IVF injections. Mean treatment duration was 52.7 ± 35.9 weeks for brolucizumab and 59.3 ± 31.5 weeks for faricimab. After receiving brolucizumab followed by faricimab, 15 patients (26.3%) discontinued faricimab and switched back to brolucizumab or a new drug altogether (high-dose aflibercept, bevacizumab, ranibizumab).

Table 1
Demographic and ocular profiles of study participants.

Patients (*n* = 57)	
Mean age ± SD (years)	81.0 ± 9.9
Sex (%)	
Female	27 (47.4)
Male	30 (52.6)
Race (%)	
White	54 (94.7)
Black	3 (5.3)
Comorbidities (%)	
Dyslipidemia	28 (49.1)
Hypertension	34 (59.6)
Diabetes mellitus	12 (21.1)
Eyes (*n* = 57)	
Mean injection interval in 12 months prior ± SD (weeks)	6.4 ± 2.9
Mean no. prior intravitreal drugs ± SD	1.5 ± 0.6
Last intravitreal drug before switching to brolucizumab (%)	
Aflibercept 2 mg	52 (91.2)
Ranibizumab	5 (8.8)

SD, standard deviation.

Table 2

Treatment exposure in study participants.

Drug #1: Brolucizumab	
Mean no. IVB injections ± SD	9.6 ± 4.9
Mean IVB treatment duration (weeks) ± SD	52.7 ± 35.9
Reason for IVB discontinuation (%)	
Persistent or recurrent fluid	46 (80.7)
Sterile intraocular inflammation	6 (10.5)
Inability to extend interval	2 (3.5)
Concerns about vasculitis risk	2 (3.5)
RPE rip	1 (1.8)
Drug #2: Faricimab	
Mean no. IVF injections ± SD	8.6 ± 6.6
Mean IVF treatment duration (weeks) ± SD	59.3 ± 31.5
Total no. IVF discontinuations (%)	15 (26.3)
Reason for IVF discontinuation (% of 15)	
Persistent or recurrent fluid	12 (80.0)
Inability to extend interval	1 (6.7)
Endophthalmitis	1 (6.7)
No insurance coverage	1 (6.7)
Follow-up	
Treatment at last follow-up (%)	
Faricimab	42 (73.7)
Aflibercept 8 mg	8 (14.0)
Brolucizumab	2 (3.5)
Aflibercept 2 mg	2 (3.5)
Bevacizumab	1 (1.8)
Ranibizumab	1 (1.8)
Thermal laser	1 (1.8)

RPE, retinal pigment epithelium; SD, standard deviation.

Functional and Anatomic Outcomes

Visual and anatomic outcomes were evaluated based on treatment-specific baselines, defined as the visit immediately preceding administration of either brolucizumab or faricimab. Baseline BCVA for brolucizumab was 0.62 ± 0.58 logMAR and baseline CST was 364.5 ± 104.2 μm. Although BCVA was not significantly changed following the first three injections of brolucizumab, CST was significantly reduced after the first, second, and third injections compared to baseline. Baseline BCVA for faricimab was 0.61 ± 0.54 and CST was 341.8 ± 104.8 μm. Although BCVA was not significantly changed following the first three injections of brolucizumab and faricimab, CST was significantly reduced compared to baseline after the second injection. Fluid resolution increased over the first two injections before a decrease after the third injection of brolucizumab. On the other hand, fluid resolution increased over the first three injections of faricimab.

Overall treatment outcomes on brolucizumab and faricimab are compared in Table 4. During the course of treatment with brolucizumab, average BCVA across all injections was 0.58 ± 0.49 logMAR, which was not significantly different from the average BCVA on faricimab (0.65 ± 0.58 logMAR, $p = 0.63$). Average CST on brolucizumab (344.5 ± 95.3 μm) and faricimab (334.1 ± 99.2 μm) were also comparable ($p = 0.24$). However, more patients were able to achieve sustained resolution of fluid with faricimab than brolucizumab ($p = 0.01$). Patients seemed to tolerate a slightly extended interval with faricimab (8.4 ± 2.6 weeks vs. 7.9 ± 3.3 weeks on brolucizumab), but this finding was not statistically significant ($p = 0.06$).

Table 3

Visual and anatomic outcomes after subsequent IVB and IVF injections. VA, CST, and fluid resolution after the first three injections of each drug are compared to baseline. Bold font indicates significance.

Injection	Mean VA (logMAR) ± SD	Adj. p-value	Mean CST (μm) ± SD	Adj. p-value	Fluid resolution, n (%)
Baseline	0.62 ± 0.58	-	364.5 ± 104.2	-	0/57 (0.0)
Brolucizumab					
After 1st IVI	0.62 ± 0.62	0.89	**339.7 ± 113.0**	**0.005**	4/57 (7.0)
After 2nd IVI	0.66 ± 0.69	0.89	**346.9 ± 134.5**	**0.005**	7/51 (13.7)
After 3rd IVI	0.56 ± 0.45	0.19	**347.3 ± 101.8**	**0.012**	5/48 (10.4)
Faricimab					
After 1st IVI	0.62 ± 0.57	0.89	**324.6 ± 90.2**	**0.001**	3/57 (5.3)
After 2nd IVI	0.65 ± 0.62	0.89	**326.8 ± 111.1**	**0.005**	7/53 (13.2)
After 3rd IVI	0.64 ± 0.62	0.93	**331.2 ± 115.2**	**0.005**	11/52 (21.2)

Adj, adjusted; CST, central subfield thickness; IVI, intravitreal injection; SD, standard deviation; VA, visual acuity.

Table 4

Comparison of overall outcomes on brolucizumab and faricimab.

Outcome	Brolucizumab	Faricimab	p-value
Mean VA across all injections (logMAR) ± SD	0.58 ± 0.49	0.65 ± 0.58	0.63
Mean CST across all injections (μm) ± SD	344.5 ± 95.3	334.1 ± 99.2	0.24
No. with sustained fluid resolution (%)	**6/57 (10.5)**	**18/57 (31.6)**	**0.01**
Mean injection interval (weeks) ± SD	7.9 ± 3.3	8.4 ± 2.6	0.06

Adj, adjusted; CST, central subfield thickness; IVI, intravitreal injection; SD, standard deviation; VA, visual acuity.

Fluid Resolution

Complete fluid resolution was observed in 18/57 eyes (31.6%) following treatment with faricimab compared to 6/57 eyes (10.5%) after treatment with brolucizumab (p = 0.01), indicating a favorable anatomic response following the switch to faricimab (Table 4).

Treating retina specialists provided a subjective comparative assessment of overall drug efficacy for all patients in this cohort. Complete fluid resolution was observed in 18/57 eyes (31.6%) during faricimab treatment compared with 6/57 eyes (10.5%) during brolucizumab treatment (p = 0.01), indicating greater fluid control during the faricimab treatment period (Table 4).

Conclusions

In this study, we evaluated functional and anatomic outcomes in patients with refractory wAMD who were switched from brolucizumab to faricimab. This was a challenging patient population, as all 57 eyes demonstrated persistent or recurrent retinal fluid despite use of prior anti-VEGF therapy, representing a hard-to-treat subgroup with treatment resistance. In our comparison, neither IVB nor IVF yielded significant improvements in VA or CST from treatment-specific baselines; however, there were reductions in CST while on both treatments. These findings suggest that faricimab was associated with comparable anatomic and visual outcomes to brolucizumab in this hard-to-treat subset of patients. We also found increased fluid resolution during treatment with faricimab. Despite a lack of significant change in VA while on faricimab, improved fluid resolution may still indicate increased control of disease activity. Thus, our findings do not emphasize superiority of one drug over the other, but indicate faricimab may be a potential alternative treatment for patients who remain on brolucizumab.

Previous studies examining an IVB to IVF switch reinforce the findings in the present study. One study reported stable BCVA and reductions in CST after switching to faricimab.[16] Another study similarly found decreases in CST with no significant changes in BCVA following the switch over a 9-month period.[17] These studies support the use of faricimab following the switch; however, these studies include treatment-naïve or treatment-responsive patients as well, while our study represents a defined, treatment-resistant subgroup, which is less likely to tolerate a non-IVB drug. Our findings expand upon what was previously found in these studies about the switch to faricimab, demonstrating improved fluid control specifically in a hard-to-treat patient population but also showing comparable outcomes on both treatments.

The lack of significant improvement in BCVA despite reductions in CST and improved fluid resolution on each treatment is not a sign of limited response or statistical incongruity and has been previously documented.[18–20] Prior literature has described several plausible explanations for possible discrepancies between visual acuity and fluid resolution, including baseline disruption of the photoreceptors, existing integrity of key retinal layers, and type and location of the fluid (i.e. subretinal vs. intraretinal fluid).[21] Consequently, visual outcomes in eyes that have demonstrated chronic disease may not be solely associated with CST changes or fluid resolution, but more determined by the degree of

baseline photoreceptor degeneration.[22] The eyes in our cohort similarly had longstanding disease, that may result in minimal gains in BCVA despite fluid resolution.[23]

The type of residual fluid was particularly relevant in our cohort, where the majority of patients were switched from brolucizumab to faricimab due to documented persistent SRF. Despite this documented fluid, there was a lack of significant changes in BCVA observed during the study treatment period. Prior literature has suggested that SRF is associated with a better visual prognosis and may even have a protective effect against progressive vision loss and macular atrophy[24]. In contrast, IRF has been described as linked to poor visual outcomes and requiring more aggressive treatment[24–25]. The predominance of SRF as a reason for switching in our cohort may contribute to the disconnect between improved fluid control and VA and CST changes. These eyes may have had preserved visual function despite the SRF, resulting in less quantifiable improvement from that baseline even following fluid resolution. Therefore, absence of significant changes in BCVA within our treatment-refractory patient subset can be interpreted in the context of chronic ongoing disease as well as fluid subtype. Future studies may benefit from investigating whether fluid subtype modifies response to treatment, particularly in treatment-resistant patient subsets.

The transition from brolucizumab to faricimab also becomes relevant when considering the association of brolucizumab with retinal vasculitis and intraocular inflammation (IOI). While small (3.3%), the risk of vasculitis with IVB use persists, even years after use, and is especially pertinent in a population requiring frequent treatment.[20] In our cohort, no patients developed retinal vasculitis or intraocular inflammation following the transition to faricimab. However, due to the sample size and retrospective design it is not possible to derive conclusions about long-term comparative safety between the two agents.

There are several limitations to this study. First, the small sample size may reduce generalizability of our findings. Second, variability in patient follow-up and injection interval may influence outcomes. As a retrospective study, there may be a subset of patients who remained on brolucizumab and were not subsequently trialed on faricimab, resulting in potential selection bias. Lastly, there remains the concept of non-VEGF mediated disease. Whether the population chosen truly suffers from wAMD or a different disease process entirely, which may account for treatment “resistance,” is unknown. Emerging evidence suggests the role of alternative pathways, such as Ang-2 mediated vascular instability,[33,34] monocyte and macrophage-promoted arteriolar arteriogenesis,[35,36] and the pro-inflammatory effects of integrin signaling, as contributing to treatment resistance in this disease.[37] The added disease responsiveness to IVF may be due to these alternative pathway mechanisms, or because this sub-group includes patients with a non-typical wAMD diagnosis; however, this mechanism was not directly investigated in this present study. Nonetheless, our study conclusions at least support equivalent disease control after switching to faricimab in this unique patient subset. These findings demonstrate that faricimab may be a suitable alternative for brolucizumab for patients with persistent or recurrent disease.

Declarations

Consent to Participate:

Given the retrospective nature of this study, the requirement of informed consent was waived.

Consent for Publication:

Not applicable.

Declarations
of Conflicting Interest: Tavish Nanda, MD: Consultant – Genentech, Regeneron. All other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Statement

The authors received no financial support for the research, authorship, and/or publication of this article.

Funding Statement:

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of Interest:

Tavish Nanda, MD: Consultant – Genentech, Regeneron. All other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contribution

R.P. obtained IRB, conducted chart review, collected and organized clinical data, contributed to statistical analysis, drafted manuscript, revised manuscript following multiple rounds of revision. A.P. contributed to statistical analysis, prepared tables and figures, and revised the manuscript over multiple rounds. T.N. conceived and supervised the study, contributed to study design, and critically revised the manuscript. All authors reviewed the manuscript.

Acknowledgements:

We thank Richard Feinn, PhD., for statistical guidance and assistance.

Ethical Approval

Statement: This study was approved by the Quinnipiac University Institutional Review Board (IRB #10924) on July 16, 2024.

Informed Consent

Statement: Given the retrospective nature of this study, the requirement of informed consent was waived.

Data Availability

The data from this study are not publicly available due to privacy and confidentiality restrictions associated with patient electronic medical records. De-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional review board approval.

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