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BRIEF REPORT

Faricimab in Neovascular AMD Complicated by Pigment Epithelium Detachment: An AI-Assisted Evaluation of Early Morphological Changes

Daniele Veritti · Valentina Sarao · Marco Gonfiantini · Leopoldo Rubinato · Paolo Lanzetta

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ABSTRACT

***Introduction*:** This study investigates the early temporal changes in pigment epithelial detachment (PED) morphology following treatment with faricimab in patients with neovascular age-related macular degeneration (nAMD). Utilizing an artificial intelligence (AI)-assisted approach, we provide a detailed quantification and characterization of the dynamics of these morphological changes.

***Methods*:** A prospective observational study was conducted on 22 eyes from 22 treatment-naïve patients with nAMD-associated PED (presenting either type 1 or type 3 macular neovascularization). Participants were administered intravitreal faricimab (6 mg) at baseline and at days 30, 60, and 90. Comprehensive ophthalmic evaluations and spectral-domain optical coherence tomography (SD-OCT) imaging were conducted at baseline and at seven additional follow-up visits on days 1, 7, 14, 30, 60, 90, and 120. An AI-based automated segmentation algorithm was utilized to precisely quantify changes in PED volume, alongside intraretinal (IRF) and subretinal fluid (SRF) volumes, at each time point.

***Results*:** Treatment with faricimab resulted in a significant reduction in mean PED volume, with an average decrease of 12% at day 1, 29% at day 7, 51% at day 14, 68% at day 30, 72% at day 60, 79% at day 90, and 84% at day 120 ($p<0.0001$ for all time points). Similarly rapid and marked reductions were noted in both mean IRF (23.5% at day 1, 90.7% at day 14) and SRF (14.4% at day 1, 91.2% at day 14) volumes. The study also showed a statistically significant improvement in best-corrected visual acuity (BCVA) over the follow-up period, correlating with the reduction in PED volume.

***Conclusion*:** Faricimab demonstrates early and significant efficacy in improving PED architecture in patients with nAMD. The rapid morphological improvements observed in this study suggest faricimab may represent a valid therapeutic option for PEDs associated with nAMD.

Keywords: Artificial intelligence; Faricimab; Neovascular age-related macular degeneration; Pigment epithelium detachment

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D. Veritti · V. Sarao · M. Gonfiantini · L. Rubinato · P. Lanzetta (✉)
Department of Medicine-Ophthalmology, University of Udine, Udine, Italy
e-mail: paolo.lanzetta@uniud.it

V. Sarao · P. Lanzetta
Istituto Europeo di Microchirurgia Oculare–IEMO, Udine and Milan, Italy

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Key Summary Points

Why carry out this study?

Pigment epithelium detachment (PED) is commonly observed in patients with neovascular age-related macular degeneration (AMD), significantly increasing the need for consistent anti-VEGF treatments and highlighting an unmet need for more effective therapies.

The study aimed to evaluate the effectiveness of faricimab, a dual-targeting molecule, in improving the morphological parameters of PED and retinal fluids in patients with neovascular AMD through the use of artificial intelligence for segmentation and quantification.

What was learned from the study?

Faricimab leads to a rapid and significant improvement in retinal fluid volumes and PED morphology for patients with neovascular AMD.

Faricimab offers a promising treatment alternative for managing PEDs in patients with neovascular AMD.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) stands as a predominant cause of irreversible vision loss [1–4]. A hallmark of nAMD is the development of pigment epithelial detachment (PED), a critical pathological feature evident in approximately 30% to 80% of nAMD cases [5]. The detachment of the retinal pigment epithelium (RPE) from the underlying Bruch's membrane, driven by fluid accumulation and vascular proliferation, manifests in several clinical forms. The most common include serous, hemorrhagic, and fibrovascular. Serous PEDs, marked by serous fluid buildup, and fibrovascular PEDs, characterized by fibrovascular tissue growth, are closely associated with type 1 and type 3 macular neovascularization (MNV) [6]. They present a substantial therapeutic challenge, as anti-vascular endothelial growth factor (anti-VEGF) therapies often show limited efficacy in resolving PEDs compared to their impact on intraretinal (IRF) and subretinal fluid (SRF) [7–9]. The sub-RPE compartment appears to be relatively isolated, and fluid in this space often demonstrates a suboptimal response to anti-VEGF therapy. It has also been observed that sub-RPE fluid is more persistent than IRF and SRF and typically requires more frequent anti-VEGF treatment regimens [10].

Faricimab is a bispecific antibody that binds and inhibits both VEGF-A and angiopoietin-2 (Ang-2), recently approved for the treatment of nAMD and diabetic macular edema. By blocking these two key pathways in MNV pathogenesis, faricimab offers dual angiogenic targeting, not only addressing the neovascular elements but also contributing to vascular stabilization, potentially improving PED management [11, 12].

In this context, our study aims to explore the early changes in PED morphology following faricimab treatment in patients with nAMD. Employing artificial intelligence (AI)-assisted analysis, we quantitatively assess PED volume and fluid accumulation in the subretinal and intraretinal compartments, providing a detailed evaluation of faricimab's impact on PED architecture in nAMD.

METHODS

Study Design and Participants

This prospective, observational study was conducted between March 2023 and December 2023 at the Department of Medicine–Ophthalmology, University of Udine, Italy, and included consecutive, treatment-naïve patients with neovascular age-related macular degeneration (nAMD) presenting type 1 or type 3 macular neovascularization (MNV) associated with pigment epithelial detachment (PED). Type II MNV was excluded because it does not typically present with PED, which could introduce confounding variables and affect comparability with previous studies

focusing on PED-related treatments. Consistent with previous studies, PED was defined as a pigment epithelial elevation exceeding 400 µm in width and 75 µm in height, or over 200 µm in height on spectral-domain optical coherence tomography (SD-OCT) [13]. PEDs were further categorized based on their reflectivity patterns on SD-OCT imaging as follows: predominantly serous PEDs comprising ≥ 50% serous fluid by volume showing optically empty spaces with minimal internal reflectivity; purely fibrovascular PEDs demonstrating peaked contours with moderately reflective internal structure; predominantly fibrovascular PEDs comprising ≥ 50% fibrovascular tissue by volume. In ambiguous cases, the dominant component of the PED was determined based on corresponding multimodal imaging with fluorescein angiography (FA) and indocyanine green angiography (ICGA).

Treatment Protocol

Patients received intravitreal injections of faricimab (6 mg) at baseline (day 0), and subsequently at days 30, 60, and 90, as per label.

Assessment Schedule

Comprehensive ophthalmic evaluations were conducted at baseline and subsequent visits (days 1, 7, 14, 30, 60, 90, and 120) post-treatment. These included best-corrected visual acuity (BCVA) measurements with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, fundus examination, and SD-OCT imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany). A density map program 20° × 20° with high-speed mode and follow-up settings was utilized for consistent imaging of the macula. Baseline evaluations also included FA and ICGA for detailed MNV and PED characterization.

Automated Quantification of Retinal Fluid

Retinal fluid segmentation was performed using the Fluid Monitor software (RetInSight, Vienna, Austria), an artificial intelligence-based system for automated segmentation of IRF, SRF, and PEDs. It employs a deep convolutional neural network that has undergone extensive validation across multiple cohorts and grading centers [14, 15]. For each OCT B-scan, the software performs a pixel-wise classification to delineate regions of IRF, SRF, and PED from normal retinal tissue. The neural network was trained on a diverse dataset of pathology-confirmed OCT scans annotated by expert graders. Quantitative outputs from the software include total fluid volume for IRF, SRF, and PED in the central 6-mm area. Built-in quality control measures, such as the *Q*-score, provide a per-scan indication of segmentation accuracy. This tool has demonstrated a significant correlation with manual grading for total fluid volumes (Pearson $r = 0.908$) and high sensitivity in detecting pathologic fluid-related retinal thickness changes [14, 15]. However, segmentation errors were monitored through a combination of automated quality assessments and manual review. An expert reviewer (VS) manually inspected automated segmentation outputs, correcting gross errors to ensure analysis accuracy.

Statistical Analysis

Statistical analyses were conducted to evaluate the changes in BCVA and fluid characteristics over time, using non-parametric tests due to the non-normal distribution of the data. The Friedman test was employed for repeated measures, and Spearman's rank correlation was used to assess relationships between variables. Descriptive statistics summarized baseline characteristics and treatment outcomes. Additionally, two multiple regression models were used: one to evaluate the impact of PED volume, SRF, and IRF on BCVA, and another to assess the relationship between changes in these fluid volumes and changes in BCVA. These models included BCVA and changes in BCVA as the dependent variables, respectively, and PED, SRF, and IRF volumes and their changes as independent variables to estimate their real impact on visual acuity. Results with two-sided p-values ≤ 0.05 were considered statistically significant.

Ethical Considerations

This study was approved by the IEMO institutional review board (reference number: 2024.0430/f) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

Patient Demographics and Baseline Characteristics

A total of 22 eyes (22 patients) with nAMD and PED were enrolled in the study. The average age of the participants was 74 years, with a majority (73%) presenting with type 1 MNV. All PEDs were located in the center 1 mm. Baseline characteristics are summarized in Table 1.

Faricimab Treatment and Patient Disposition

All patients received intravitreal injections with faricimab at the prespecified intervals. The response to treatment was available over a 120-day period with clinical assessments at baseline and at 1, 7, 14, 30, 60, 90, and 120 days for all patients.

Changes in PED, SRF, and IRF Volume

A significant time effect was observed with repeated-measures analysis of variance (ANOVA) for PED volume reduction after treatment with faricimab ($p<0.0001$). On average, PED volume decreased by 12% on day 1, 29% on day 7, 51% on day 14, 68% on day 30, 72% on day 60, 79% on day 90, and 84% on day 120. Post hoc comparisons showed a statistically significant change from baseline at every time point ($p<0.0001$). The study also showed a statistically significant and rapid reduction in both SRF and IRF volumes as early as 1 day after initial treatment ($p<0.0001$). Changes in the PED morphology and associated features are summarized in Table 2, Fig. 1, and Figures S1–S5.

In assessing the evolution of PED volume among different PED subtypes over time, a linear regression model with interaction terms was employed. The model accounted for the effects of time, PED subtype, and the interaction between time and each subtype. The analysis revealed significant variance in PED volume changes across different subtypes. Specifically, the "predominantly serous" subtype showed a statistically significant different trend in PED volume over time (interaction term coefficient = −7.1876, $p<0.01$) relative to the other subtypes. These results suggest a unique trajectory in PED volume changes for the predominantly serous subtype over the observed time period, indicating potential subtype-specific responses or progression patterns in PED volume changes (Fig. 2).

Visual Acuity Outcomes

There was a statistically significant improvement in BCVA over the course of follow-up ($p<0.001$). The average gain in BCVA was +2.3, +3.7, +5.2, +5.6, +8.3, +8.0, and +9.1 ETDRS letters on days 1, 7, 14, 30, 60, 90, and 120, respectively (Table 2). Post hoc comparisons with the baseline showed that these improvements were statistically significant from day 7 onwards (Fig. 3).

The multiple regression analysis demonstrated that IRF significantly impacts visual acuity, with IRF volume showing a statistically significant negative effect on BCVA ($\beta=-0.0354$, $p<0.05$). Additionally, when evaluating changes in fluid volumes, we found that the reduction in PED volume was significantly associated with improvement in visual acuity ($\beta=0.0017$, $p<0.05$).

Safety and Tolerability

Faricimab was well tolerated, with no serious adverse events reported. No patient experienced a vision loss of more than five ETDRS letters at any time point. No cases of RPE tear, intraocular inflammation, or retinal vasculitis occurred.

Table 1 Baseline characteristics

Characteristic		Total cohort ($N = 22$)
Age (years), mean ± SD		74.3 ± 8.2
Gender (%)		Male–46%, female–54%
MNV type, *n* (%)	Type 1	16 (72.7%)
	Purely fibrovascular PED	5 (31.3%)
	Predominantly fibrovascular	8 (50%)
	Predominantly serous	3 (18.7%)
	Type 3	6 (27.3%)
	Purely fibrovascular PED	0 (0%)
	Predominantly fibrovascular	1 (16.7%)
	Predominantly serous	5 (83.3%)
PED type, *n* (%)	Purely fibrovascular	5 (22.7%)
	Predominantly fibrovascular	9 (40.9%)
	Predominantly serous	8 (36.4%)
Baseline BCVA (ETDRS letters), mean ± SD		56.1 ± 12.1
PED volume (nL), mean ± SD (range) median (IQR)		2137 ± 966 (749–4301) 2072 (1107)
IRF volume (nL), mean ± SD (range) median (IQR)		63 ± 71 (0–307) 25 (128)
SRF volume (nL), mean ± SD (range) median (IQR)		920 ± 632 (12–2236) 979 (880)
Maximum PED height (μm), mean ± SD (range) median (IQR)		370 ± 136 (182–768) 67 (101)

SD standard deviation; *MNV* macular neovascularization; *PED* pigment epithelium detachment; *BCVA* best-corrected visual acuity; *ETDRS* Early Treatment Diabetic Retinopathy Study; *IRF* intraretinal fluid; *IQR* interquartile range; *SRF* subretinal fluid

DISCUSSION

The management of nAMD-associated PED represents a significant clinical challenge [5].

In this prospective case series, we demonstrate the ability of faricimab to significantly enhance the morphological characteristics of PEDs associated with type 1 and type 3 MNVs. Through the utilization of a validated deep learning algorithm for precise segmentation, we were able to delineate these structural gains at an unprecedented temporal granularity, capturing significant decreases in PED and fluid volumes as early as 1 day following the initial faricimab injection. These morphological improvements steadily continued through the observation period of 4 months, accompanied by significant and sustained gains in BCVA. In our series, the baseline IRF volume was minimal, indicative of the MNV included. Nonetheless, a marked response to therapy was observed. with a reduction of

Table 2 Temporal dynamics of PED volume, SRF, IRF, and maximum PED height in response to faricimab treatment

	Time (days)						
	1	**7**	**14**	**30**	**60**	**90**	**120**
BCVA (ETDRS letters)							
Mean (SD) variation	+2.3 (7.5)	+3.7 (6.7)	+5.2 (5.0)	+5.6 (4.6)	+8.3 (8.7)	+8.0 (8.3)	+9.1 (8.8)
PED volume (nL)							
Mean (SD) variation	−248 (244)	−618 (403)	−1078 (657)	−1450 (1088)	−1542 (1099)	−1688 (1042)	−1786 (989)
Median variation (IQR)	−246 (359)	−594 (478)	−1003 (544)	−1143 (1012)	−1145 (1086)	−1508 (917)	−1786 (1010)
Mean percentage variation	−11.6%	−28.9%	−50.5%	−67.9%	−72.2%	−79.0%	−83.6%
SRF volume (nL)							
Mean (SD) variation	−132 (212)	−549 (414)	−839 (606)	−911 (627)	−913 (630)	−916 (632)	−916 (631)
Median variation (IQR)	−65 (265)	−509 (482)	−845 (776)	−959 (864)	−967 (868)	−971 (873)	−968 (870)
Mean percentage variation	−14.4%	−59.7%	−91.2%	−99.0%	−99.3%	−99.6%	−99.6%
IRF volume (nL)							
Mean (SD) variation	−14 (19)	−45 (48)	−57 (66)	−59 (68)	−59 (71)	−58 (70)	−59 (69)
Median variation (IQR)	−10 (26)	−25 (93)	−22 (112)	−25 (119)	−17 (122)	−17 (118)	−25 (117)
Mean percentage variation	−23.5%	−71.9%	−90.7%	−94.7%	−93.7%	−92.1%	−94.2%
Maximum PED height (μm)							
Mean (SD) variation	−59 (89)	−110 (79)	−148 (97)	−198 (162)	−225 (164)	−256 (153)	−264 (148)
Median variation (IQR)	−51 (62)	−86 (82)	−142 (68)	−155 (63)	−196 (98)	−229 (91)	−224 (80)
Mean percentage variation	−16.2%	−29.7%	−40.1%	−53.5%	−60.8%	−69.4%	−71.4%

BCVA best-corrected visual acuity; *IQR* interquartile range; *IRF* intraretinal fluid; *PED* pigment epithelium detachment; *SD* standard deviation; *SRF* subretinal fluid

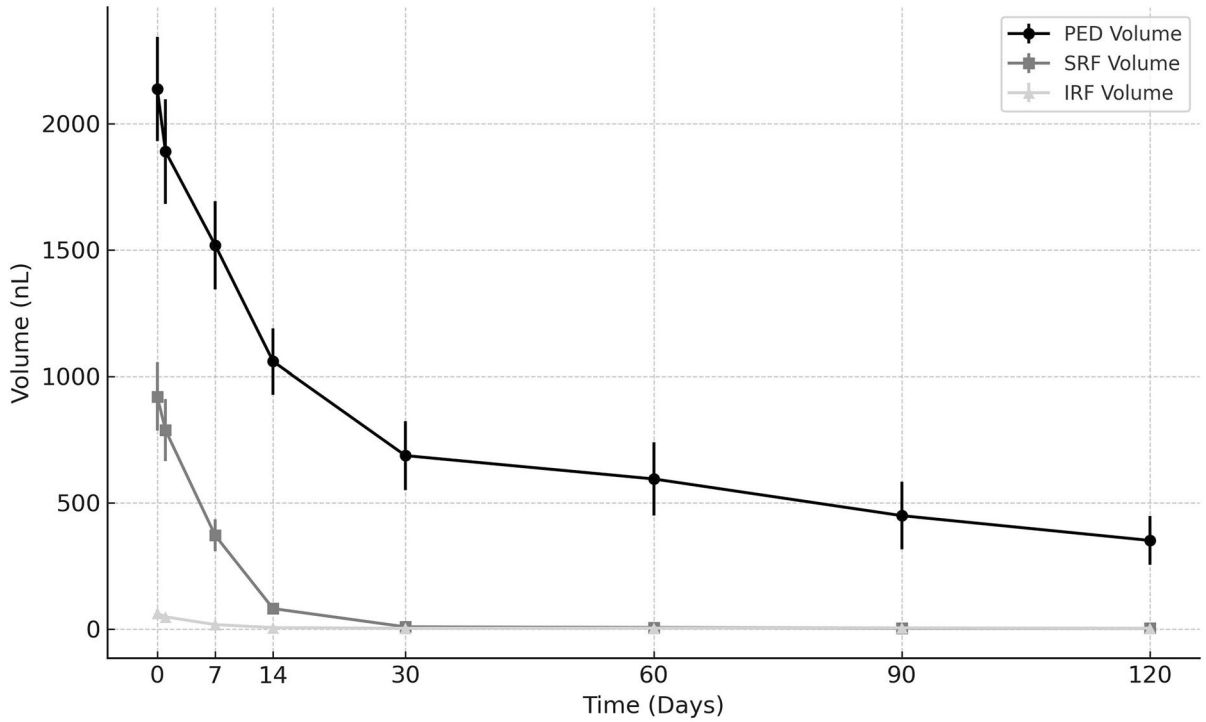

Fig. 1 Mean IRF, SRF, and PED volumes over time

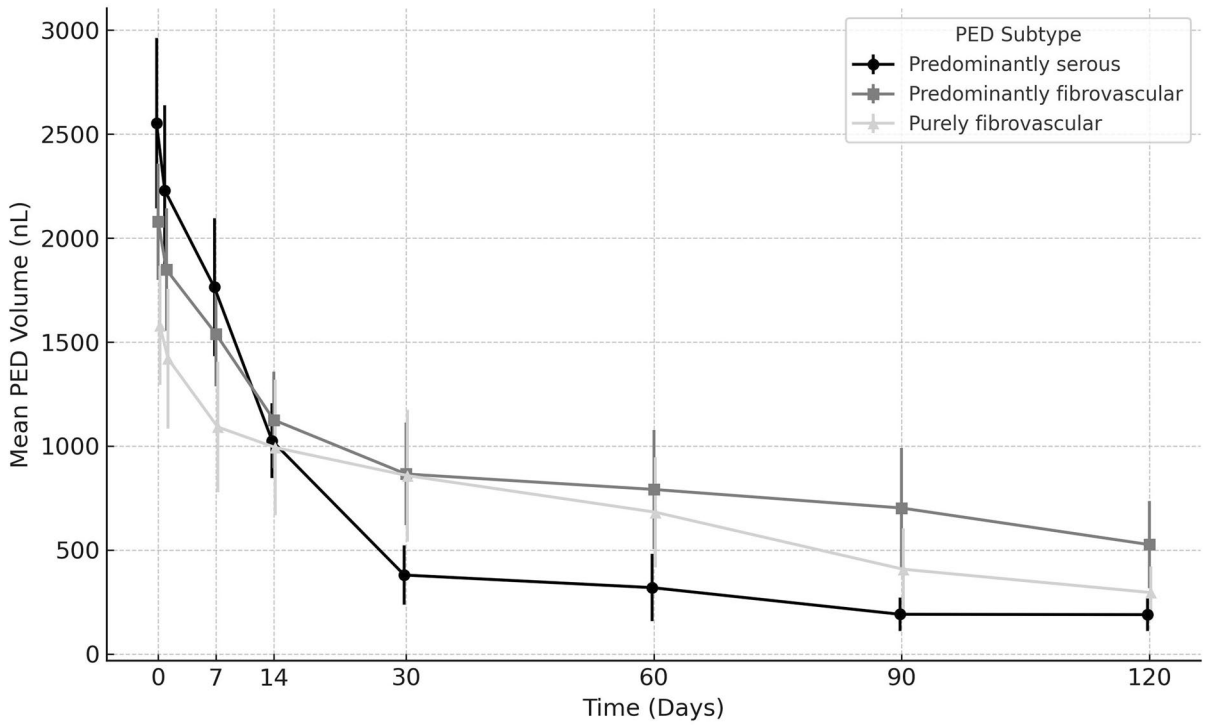

Fig. 2 Comparison of PED volume over time among different PED subtypes

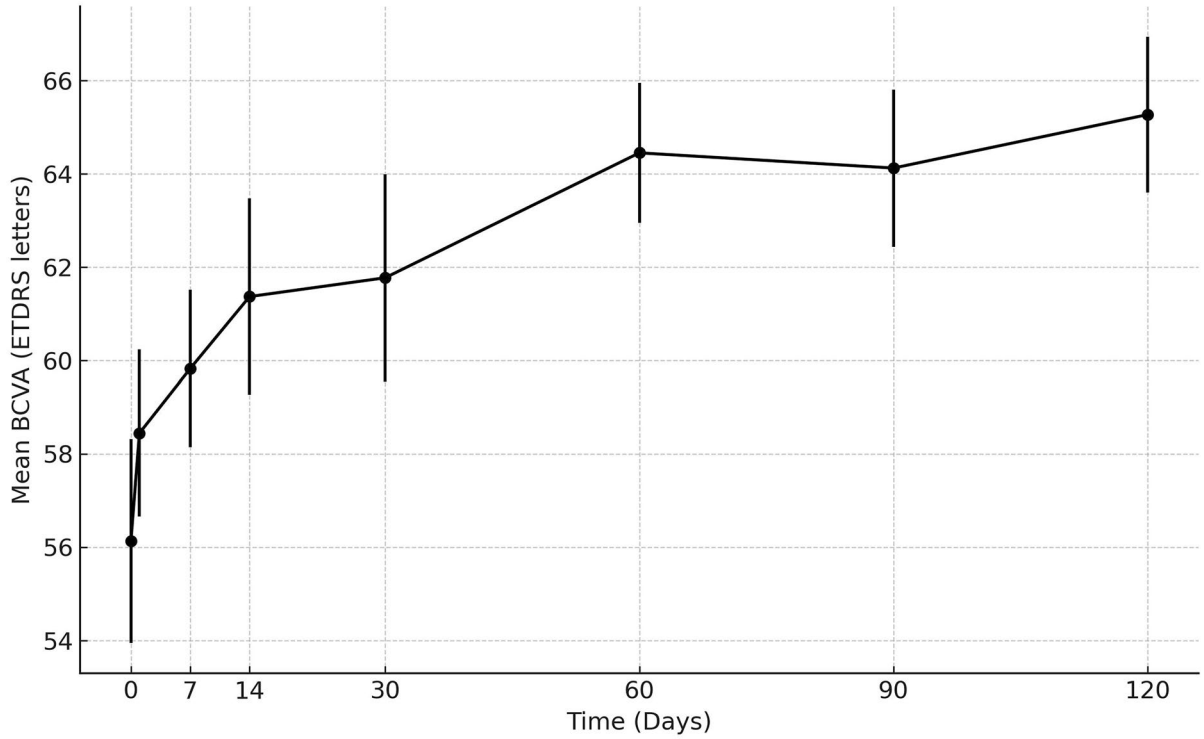

Fig. 3 Mean BCVA over time

over 90% in IRF volume evident as early as 2 weeks following the initial faricimab injection. Conversely, the baseline subretinal fluid (SRF) volume was significantly greater, yet it similarly exhibited a rapid decrease of over 90% within 2 weeks post-injection. The dynamics of PED volume reduction differed, with a decrease of approximately 50% observed at the 2-week mark. This gradual improvement in PED lesions, compared to the swift resolution of IRF and SRF, was anticipated, as the AI-based quantification of IRF and SRF exclusively accounts for optically empty spaces on OCT, whereas PED volume measurement also encompasses the fibrovascular component, whose nature impedes a rapid and complete resolution.

The sub-RPE compartment in nAMD constitutes an isolated space that appears to exhibit a limited therapeutic response to selective VEGF inhibition, frequently necessitating more intensive anti-VEGF treatment regimens [10]. By simultaneously inhibiting the VEGF and Ang-2 pathways that drive pathologic angiogenesis and vascular leakage, faricimab offers dual angiogenic targeting to counter the key mechanisms underlying PED formation [16–19]. Compared to selective VEGF inhibitors, additional Ang-2 blockade by faricimab may more effectively restrict inflammatory mechanisms linked to vascular permeability and fluid accumulation in the sub-RPE space [20] based on preclinical evidence [18]. Data delineating the actual capacity of available anti-VEGF agents to penetrate the sub-RPE space are currently lacking but would be worthwhile and a line of investigation potentially leading to substantial clinical benefits. In our series, mean PED volume decreased substantially from baseline by 12% at day 1, 29% by day 7, 51% by day 14% and 68% at 1 month following faricimab initiation. Of note, the mean 84% decrease from baseline at 4 months is greater than values reported in studies evaluating anti-VEGF therapy with other agents. In the HARBOR study, which assessed the efficacy and safety of intravitreal ranibizumab administered at two dosages (0.5 and 2.0 mg) and under two regimens (fixed monthly and flexible pro re nata), the aggregated mean reduction in

PED volume by the fourth month was approximately 55% [15]. In the HAWK and HARRIER trials, which evaluated the efficacy and safety of intravitreal brolucizumab versus aflibercept in treatment-naïve patients with neovascular AMD, the resolution of PED volume reached 68–79% of its baseline volume [21]. Moreover, our data on reduction of mean PED height can also be favorably compared to findings from other large studies. In the HARBOR trial, with a mean baseline PED height of approximately 280–290 µm, ranibizumab 0.5 mg led to a decrease of about 120–130 µm at 1 month and 130–140 µm at 4 months [22]. In the TENAYA and LUCERNE studies, starting from a baseline mean PED height of 248 µm, aflibercept 2 mg yielded a reduction of about 63 µm at 1 month and 74 µm at 4 months. Faricimab 6 mg, from a baseline mean height of 258 µm, lowered PED height by 74 µm at 1 month and 87 µm at 4 months [23]. In contrast, our study demonstrated more pronounced reductions in mean PED height using faricimab 6 mg, measuring 198 µm at 1 month and 265 µm at 4 months. These marked differences may be partially attributable to the higher baseline mean PED height of 370 µm observed in our cohort. Furthermore, the distribution of specific PED subtypes was not reported in the cited randomized clinical trials.

Our study shows a distinct response pattern in different PED subtypes, with the "predominantly serous" subtype demonstrating a unique trajectory in PED volume changes. This observation aligns with previous literature, emphasizing the heterogeneity in PED response to treatment across different subtypes [24]. So, an imbalance in proportions of this subtype could also account for some variability across studies. Similarly, the prevalence of type 3 MNV was not disclosed. As the approximately one third of eyes in our series with type 3 lesions exhibited the greatest PED volume decreases, differential distributions of MNV types may explain some variance in treatment responses.

Such rapid and significant reductions in PED volume observed in our study may translate into long-term functional gains, as studies have strongly linked early subsidence in PED severity to positive long-term visual acuity outcomes [25]. The positive correlation between PED volume decrease and BCVA improvement that we found in our study further reinforces the clinical relevance of PED as a biomarker for treatment efficacy, aligning with prior findings that have linked PED resolution with visual acuity gains [26, 27]. The impact of IRF and SRF on visual acuity has been extensively researched, with evidence indicating that IRF has a significantly more detrimental effect on visual acuity than SRF. Our observations are consistent with these findings. [28] The use of automated segmentation tools offers significant advantages in efficiency, reproducibility, and precision in quantifying pathological volumes from OCT imaging. Our study demonstrates the feasibility and utility of incorporating such AI-assisted analysis into the assessment of treatment response. Further validation studies comparing the performance of automated grading solutions like the RetInSight Fluid Monitor against expert manual annotation would lend additional support to their integration into research and clinical workflows. By enabling accurate, automated quantification of pathological volumes, these technologies provide invaluable insights into the effects of available and emerging therapies on retinal morphology and potentially empower clinicians to make more informed decisions, tailoring interventions to the individual characteristics of each patient's condition.

The excellent safety profile and tolerability of faricimab observed in our study, as evidenced by the absence of serious adverse events, including RPE tears, add to the growing body of evidence supporting its use in clinical practice.

Several limitations of the present study warrant consideration. First, the non-randomized, uncontrolled observational design precludes comparative efficacy analysis against other anti-VEGF agents. While the considerable anatomic improvements observed here provide early optimism for faricimab's therapeutic potential in PEDs, data from head-to-head trials are needed to determine if the dual Ang-2 and VEGF-A blockade confers additive benefits over inhibition of VEGF-A alone. Additionally, the single-center nature and relatively small sample size raise the possibility of selection and investigator bias, limiting generalizability. The duration of follow-up was also limited. Longer-term

data would offer further validation of faricimab durability. Finally, our cohort comprised only treatment-naïve patients. Evaluating faricimab's efficacy in eyes with prior anti-VEGF exposure will provide valuable insights on its utility in real-world clinical settings.

CONCLUSION

In conclusion, our high-resolution temporal analysis sheds light on the kinetics of PED morphological response soon after faricimab treatment. The rapid and significant morphological improvements, coupled with enhanced visual outcomes and a favorable safety profile, position faricimab as a valuable therapeutic option in the treatment of PEDs associated with nAMD.

Author Contributions. Conception and design of study: Daniele Veritti and Valentina Sarao. Acquisition/analysis/interpretation of data: Marco Gonfiantini, Leopoldo Rubinato, and Daniele Veritti. Drafting/critical revision: Daniele Veritti, Valentina Sarao, and Paolo Lanzetta. Agreement to be accountable for all aspects of the work: Daniele Veritti, Valentina Sarao, Marco Gonfiantini, Leopoldo Rubinato, and Paolo Lanzetta.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Daniele Veritti is consultant for Bayer, Novartis, and Roche. Valentina Sarao is consultant for Bayer, I-Care, and Roche. Marco Gonfiantini and Leopoldo Rubinato declare that they have no competing interests. Paolo Lanzetta is consultant for Aerie, Allergan, Apellis, Bausch & Lomb, Bayer, Biogen, Boehringer Ingelheim, I-Care, Genentech, Novartis, Ocular Therapeutix, Outlook Therapeutics, and Roche.

Ethical Approval. This study was approved by the IEMO institutional review board (reference number: 2024.0430/f) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients for both the participation in the study and the publication of the results.

REFERENCES

1. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol. 1984;102:1640–2.

2. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol. 2003;48:257–93.

3. Veritti D, Sarao V, Lanzetta P. Neovascular age-related macular degeneration. Ophthalmologica. 2012;227(Suppl 1):11–20.

4. Veritti D, Sarao V, Soppelsa V, Danese C, Chhablani J, Lanzetta P. Managing neovascular age-related macular degeneration in clinical practice: systematic review, meta-analysis, and meta-regression. J Clin Med. 2022;11:325.

5. Cheong KX, Teo KYC, Cheung CMG. Influence of pigment epithelial detachment on visual acuity in neovascular age-related macular degeneration. Surv Ophthalmol. 2021;66:68–97.

6. Rispoli M, Cennamo G, Antonio LD, et al. Practical guidance for imaging biomarkers in exudative age-related macular degeneration. Surv Ophthalmol. 2023;68:615–27.

7. Freeman WR, Kozak I, Yuson RMS, Nigam N, Cheng L, Mojana F. Prognosti implications of pigment epithelial detachment in bevacizumab (Avastin)-treated eyes with age-related macular degeneration and choroidal neovascularization. Retina. 2011;31:1812–8.

8. Veritti D, Sarao V, Parravano M, Arias L, Varano M, Lanzetta P. One-year results of aflibercept in vascularized pigment epithelium detachment due to neovascular AMD: a prospective study. Eur J Ophthalmol. 2017;27:74–9.

9. Veritti D, Macor S, Menchini F, Lanzetta P. Effects of VEGF inhibition on retinal morphology, neovascular network size, and visual acuity in patients with vascularized pigment epithelium detachment because of occult choroidal neovascularization. Retina. 2013;33:982–9.

10. Schmidt-Erfurth U, Waldstein SM, Deak GG, Kundi M, Simader C. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. Ophthalmology. 2015;122:822–32.

11. Khanani AM, Guymer RH, Basu K, et al. TENAYA and LUCERNE: rationale and design for the phase 3 clinical trials of faricimab for neovascular age-related macular degeneration. Ophthalmol Sci. 2021;1: 100076.

12. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022;399:729–40.

13. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. Ophthalmology. 2016;123:1521–9.

14. Gerendas BS, Sadeghipour A, Michl M, et al. Validation of an automated fluid algorithm on real-world data of neovascular age-related macular degeneration over five years. Retina. 2022;42:1673–82.

15. Schmidt-Erfurth U, Vogl WD, Jampol LM, Bogunović H. Application of automated quantification of fluid volumes to anti-VEGF therapy of neovascular age-related macular degeneration. Ophthalmology. 2020;127:1211–9.

16. Hussain RM, Neiweem AE, Kansara V, Harris A, Ciulla TA. Tie-2/Angiopoietin pathway modulation as a therapeutic strategy for retinal disease. Expert Opin Investig Drugs. 2019;28:861–9.

17. Ferro Desideri L, Traverso CE, Nicolò M. The emerging role of the Angiopoietin-Tie pathway as therapeutic target for treating retinal diseases. Expert Opin Ther Targets. 2022;26:145–54.

18. Nair AA, Finn AP, Sternberg P Jr. Spotlight on faricimab in the treatment of wet age-related macular degeneration: design, development and place in therapy. Drug Des Dev Ther. 2022;16:3395–400.

19. Yen WT, Wu CS, Yang CH, Chen YH, Lee CH, Hsu CR. Efficacy and safety of intravitreal faricimab for neovascular age-related macular degeneration: a systematic review and meta-analysis. Sci Rep. 2024;14:2485.

20. Canonica J, Foxton R, Garrido MG, Lin CM, Uhles S, Shanmugam S, et al. Delineating effects of angiopoietin-2 inhibition on vascular permeability and inflammation in models of retinal neovascularization and ischemia/reperfusion. Front Cell Neurosci. 2023;17:1192464.

21. Schmidt-Erfurth U, Mulyukov Z, Gerendas BS, et al. Therapeutic response in the HAWK and HARRIER trials using deep learning in retinal fluid volume and compartment analysis. Eye. 2023;37:1160–9.

22. Javaheri M, Hill L, Ghanekar A, Stoilov I. Changes in treatment-naive pigment epithelial detachments associated with the initial anti-vascular endothelial growth factor injection: a post hoc analysis from the HARBOR trial. JAMA Ophthalmol. 2021;139:219.

23. Greater reduction in pigment epithelial detachment size with faricimab vs aflibercept during head-to-head dosing in patients with neovascular age-related macular degeneration. Medically strengthening scientific exchange. Available from https://medically.gene.com/global/en/unrestricted/ophthalmology/APVRS-2023/apvrs-2023-presentation-lai-greater-reduction-in-pigmen.html.

24. Barth T, Reiners M, Zeman F, Greslechner R, Helbig H, Gamulescu MA. Anti-VEGF-therapy of fibrovascular and serous-vascularized pigment epithelial detachment in neovascular AMD: a retrospective five-year-analysis. Ophthalmologe. 2021;118:1255–63.

25. Cheong KX, Grewal DS, Teo KYC, Gan ATL, Jaffe GJ, Cheung GCM. The relationship between pigment epithelial detachment and visual outcome in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Eye. 2020;34:2257–63.

26. Selvam A, Shah S, Singh SR, et al. Longitudinal changes in pigment epithelial detachment composition indices (PEDCI): new biomarkers in neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2023. https://doi.org/10.1007/s00417-023-06335-3.

27. Sarraf D, Khanani AM, Sadda SR, et al. Pigment epithelial detachment thickness and variability affects visual outcomes in patients with neovascular age-related macular degeneration. Retina. 2024;44:10–9.

28. Nawash B, Ong J, Driban M, et al. Prognostic optical coherence tomography biomarkers in neovascular age-related macular degeneration. J Clin Med. 2023;12(9):3049.