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BRIEF REPORT

Early Effect of Intravitreal Faricimab on Hard Exudates in Diabetic Macular Oedema

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ABSTRACT

Introduction: Intravitreal faricimab is the first bispecific antibody to target vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2). In the study reported here, we examined the early effect of intravitreal faricimab on hard exudates (HEs) in patients with diabetic macular oedema (DMO).

Methods: Consecutive patients who were initiated on faricimab for centre-involving DMO associated with HEs between August 2022 and July 2023 were reviewed. Areas of HE were confirmed on colour fundus photographs taken at initiation of therapy and at the 6-month follow-up. ImageJ software was used for semi-automated segmentation and measurement of the HE area within the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Demographic data, including age, gender and ethnicity, as well as best-corrected visual acuity (BCVA), central retinal thickness (CRT) and macular volume (MV) were recorded.

Results: A total of 19 eyes from 16 patients were included in the study. Mean age of the cohort was 60.6 (range 49–71) years; ten eyes (53%) were treatment naïve. The median total HE area was reduced from 0.15 (interquartile range [IQR] 0.04–0.30) mm^2 to 0.10 (IQR 0.07–0.24) mm^2 by the 6-month follow-up. A greater reduction in total HE area was observed in treatment-naïve eyes (– 0.14 mm^2) compared with previously treated eyes (+0.05 mm^2), despite the former having a higher median baseline value (0.25 [IQR 0.15–0.47] mm^2 vs 0.05 [IQR 0.04–0.15] mm^2). Mean BCVA improved from LogMAR 0.26 ± 0.22 to 0.18 ± 0.19 ($p < 0.05$), while mean CRT and MV reduced from 413 ± 108 to 340 ± 95 µm ($p < 0.001$) and from 10.03 ± 1.41 to 9.20 ± 1.17 mm^3 ($p < 0.0001$), respectively.

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Conclusion: Intravitreal faricimab may be associated with reduction of HE area in DMO within 6 months of initiation, with greater effects in treatment-naïve eyes. Further studies with longer follow-up are warranted to determine the durability of HE resolution and its comparison to intravitreal steroids and other anti-VEGF agents.

Keywords: Hard exudates; Faricimab; Diabetic macular oedema

Key summary points
Why carry out this study?
The presence of hard exudates (HEs) poses a risk for poor visual outcomes in diabetic macular oedema
Based on early preclinical data, intravitreal faricimab may result in early clearance of HE due to its dual action on angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) receptors
This study aimed to evaluate the effect of faricimab on HEs in a multi-ethnic real-world population in a large retina practice
What was learned from the study?
Decrease in HE area was seen within 6 months of initiation of faricimab, accompanied by improvement in visual and anatomical outcomes
Longer-term comparative studies need to be performed to compare faricimab therapy with other intravitreal therapies for diabetic macular oedema

INTRODUCTION

Diabetic macular oedema (DMO) is a prevalent vision-threatening complication in diabetes mellitus [1]. It is a manifestation of the breakdown of the blood–retina barrier in diabetic retinopathy, leading to increased permeability of capillaries and leakage of microaneurysms within the macula [2]. Accompanying the permeation of fluid, lipids and lipoproteins may also extravasate into the outer plexiform layer, culminating in the formation of hard exudates (HEs) in DMO [3].

The presence of HEs has been established as an independent risk factor for visual loss in DMO [4]. Subfoveal exudates further diminish visual outcomes by increasing the risk of subretinal fibrosis [5]. Studies have confirmed an association between HEs and elevated serum cholesterol levels, with the commencement of lipid-lowering agents shown to reduce the development of HEs [4, 6]. Similarly, intraocular treatments for DMO, such as intravitreal anti-vascular endothelial growth factor (VEGF) and intravitreal dexamethasone injections, have also been demonstrated to reduce HEs [7–11].

Faricimab is the latest anti-VEGF agent that has gained approval from many regulatory authorities, including the Medicines and Healthcare products Regulatory Agency (MHRA) and the U.S. Food and Drug Administration (FDA), for treating DMO. Compared to its predecessors, faricimab is the only bispecific antibody, targeting both VEGF-A and angiopoietin-2 (Ang-2) [12]. The aim of the study report here was to evaluate the effects of intravitreal faricimab on HEs in patients with DMO.

METHODS

Participants

A retrospective review was performed to identify consecutive patients initiated on faricimab for centre-involving DMO between August 2022 and July 2023. Intravitreal faricimab 6 mg was administered in a treat-and-extend protocol, with an initial loading dose of four injections monthly and then reviewed 8 weeks after loading. If there was a good response, the injections were extended at 4-weekly intervals up to 16 weeks. At 16 weeks, if the DMO had resolved, patients were reviewed at 3 and 6 months before being discharged back to the diabetic eye clinic. If there was evidence of reactivation at any

point, reloading of faricimab would be considered at a senior clinician's discretion.

All patients initiated on faricimab for whom fundus photographs were available at baseline and within the 6 months of follow-up were included in this study. Colour fundus photographs taken up to 3 months before the initiation of faricimab were used to confirm the presence of HEs. These formed the 'baseline' images for the study. Subsequent fundus photographs taken within 6 months after the initiation of faricimab were used for the follow-up analysis. Demographic data, including age, gender, ethnicity and best corrected visual acuity (BCVA) at all time points, were obtained from electronic health records. Optical coherence tomography (OCT; Spectralis®; Heidelberg Engineering GmbH, Heidelberg, Germany) scans were used to ascertain the central retinal thickness (CRT) and macular volume (MV) at each time point.

The study was performed in accordance with the tenets of the Declaration of Helsinki and its later amendments. Due to the retrospective nature of the study and use of anonymised data, the requirement for informed consent was waived and ethical approval was not required. The study was registered locally as a retrospective audit.

Image analysis

Images were acquired with the Zeiss Claus 500 fundus imaging system (Carl Zeiss Meditec AG, Jena, Germany), with a field of capture of 133°, and with the Kowa nonmyd WX3D versatile retinal camera (Kowa Company Ltd, Nagoya, Japan), with a field of capture of 45°. For each eye, a series of images was obtained over the treatment course, with the Kowa or Clarus cameras being used interchangeably. The earliest acquired Kowa image for each patient was designated as the reference image. Approximately 45-degree crops from Clarus images, corresponding to the Kowa field of view, were obtained for registration with the reference image. Only patients with image series that contained at least one Kowa image and were of sufficient image quality were included. As suitable images were not available at every follow-up visit, the time point closest to the nominal 6-month follow-up was chosen, resulting in a total of 58 images from 16 patients (19 eyes).

All non-reference images in each eye's series were registered and rescaled to the reference image using the RniftyReg package in R [13]), with final alignment visually checked by a retina specialist (author CD) and adjusted as needed. The fovea was manually marked on each reference image using ImageJ software (Laboratory for Optical and Computational Instrumentation, University of Wisconsin–Madison, Madison, USA), and this location was replicated across all registered photographs within each series. Exudate segmentation was performed semi-automatically in ImageJ; adaptive contrast enhancement (CLAHE) was followed by Otsu colour thresholding and manual refinement on each image. This task was performed by one author (GO) and was subsequently validated by a retina specialist (CD). Subsequent operations were performed using Matlab R2021b (MathWorks, Natick, MA, USA). The Early Treatment Diabetic Retinopathy Study (ETDRS) grid areas were automatically generated based on the marked fovea location and image physical resolution (calculated as 4.5 µm/pixel), yielding 1/3/6 mmcircles (Fig. 1) For each image, exudate pixel counts within each ETDRS ring were converted to $mm.^2$. The minimum fovea–exudate distance in millimetres was also recorded. The pixel resolution in µm was calculated using the photograph's field-of-view (45°) and diameter in pixels, using the method described by Yao et al. [14]

Statistical Analysis

Statistical analysis was performed to compare outcomes from baseline to follow-up. In patients with more than one follow-up measurement, the measurement closest to the 6-month follow-up time point was used. Mean and median values were utilised for study outcomes depending on the distribution of the data, and the Wilcoxon matched-pairs test was used for comparison between time points. Due to the non-parametric nature of the data and potential non-linear relationship between variables, Spearman correlation was used to assess associations between HE, BCVA, CRT and MV.

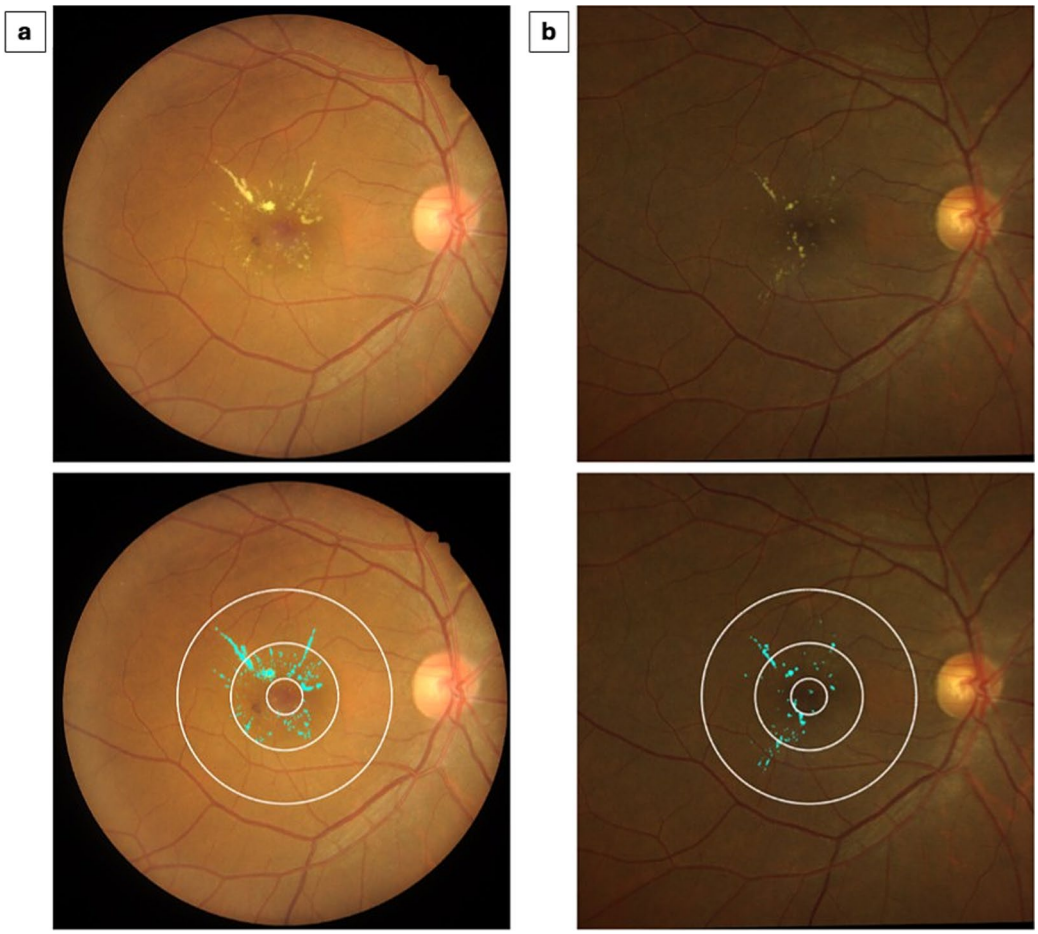

Fig. 1 Colour fundus photographs of the right eye of a patient with centre-involving diabetic macular oedema at initiation of faricimab therapy (**a**, top row) and within 6 months of therapy initiation (**b**, top row), with respective semi-automated segmentation of hard exudate within the Early Treatment Diabetic Retinopathy Study ring (bottom row)

RESULTS

Baseline Characteristics

In total, 19 eyes from 16 patients were included in this study (Table 1). The mean (± standard deviation [SD]) age of the 16 patients was 60.6 ± 5.3 years; nine (56%) patients were female and seven (44%) patients were male. The majority of patients were of South Asian ethnicity (7/16; 44%). Of the 19 eyes, ten (53%) were treatment-naïve, and nearly all previously treated eyes had received aflibercept injections. None of the patients had undergone focal macular laser treatment. Given the individualised nature of real-world follow-up visits, the mean follow-up was 4.54 ± 1.24 months, with eyes receiving a mean of 3.67 ± 1.33 faricimab injections.

Changes in HE Characteristics

The median HE area within the total ETDRS ring at baseline was 0.15 (interquartile range [IQR] 0.04–0.30) mm^2, which decreased to 0.10 (IQR 0.07–0.24) mm^2 at follow-up (Fig. 2). This reduction was not statistically significant ($p = 0.89$).

Table 1 Baseline characteristics of included patients

Baseline characteristics	*N*	%
No. of patients	16	
No. of eyes	19	
Mean age of included patients, years	60.6	
No. of patients in each of 10-year age categories		
40–49 years	1	6
50–59 years	7	44
60–69 years	7	44
70–79 years	1	6
Sex		
Male	7	44
Female	9	56
Race		
White	2	13
South Asian	7	44
Black African	2	13
Black Caribbean	2	13
Other	3	19
Treatment		
Treatment naïve	10	53
Previously treated	9	47
Intravitreal aflibercept	8	42
Intravitreal dexamethasone	2	11

Values in table are presented as frequency (*N*) with the percentage, with the exception of mean age, which is presented in years

The treatment-naïve group had a higher median total HE area at baseline compared with the group that had been previously treated (0.25 [IQR: 0.15–0.47] mm^2 vs 0.05 [IQR: 0.04–0.15] mm^2). Additionally, treatment-naïve eyes demonstrated a median reduction in total HE area within 6 months (– 0.06 mm^2, IQR: – 0.18 to 0.03), whereas previously treated eyes showed a median increase (+0.06 mm^2, IQR: – 0.03 to 0.09). The median distance between the closest HEs to the fovea in treatment-naïve eyes was 0.57 (IQR 0.45–0.66) mm at baseline; at follow-up, this distance decreased to 0.33 (IQR 0.12–0.54) mm (Tables 2, 3).

We also analysed the median HE area within each of the three ETDRS rings and observed a similar trend: reduction in the outer ring, a slight increase in the middle ring and minimal exudate at baseline and in the central 1-mm subfield ring at follow-up (Fig. 3).

Visual and Anatomical Outcomes

A statistically significant improvement in BCVA was observed from baseline to follow-up. The mean BCVA of all eyes improved from 0.26 ± 0.22 at baseline to 0.18 ± 0.19 at follow-up ($p = 0.02$). For treatment-naïve eyes, BCVA improved from 0.20 ± 0.14 to 0.15 ± 0.19, but this was not significant ($p = 0.26$). Similarly, anatomical reduction was demonstrated in treatment-naïve and previously treated cohorts throughout the follow-up period (Fig. 4). Mean (± SD) CRT reduced from 413 ± 108 to 340 ± 95 µm ($p < 0.001$) and mean MV was reduced from 10.03 ± 1.41 to 9.20 ± 1.17 mm^3 ($p < 0.0001$).

Spearman correlation analysis demonstrated no statistically significant associations between HE area and baseline or change in BCVA, CRT, or MV (all $p > 0.05$). However, moderate negative correlations approaching statistical significance were observed between baseline BCVA and HE area within the 6-mm ETDRS ring ($r = -0.45$, $p = 0.052$), as well as between change in CRT and change in HE area within the 1-mm ETDRS ring ($r = -0.45$, $p = 0.052$). All other correlations were weak and non-significant. (Tables 4, 5).

DISCUSSION

In this real-world retrospective study, we demonstrate an early reduction in HE area in eyes treated with faricimab for DMO as early as 6 months on colour fundus photography. This reduction was greatest in treatment-naïve eyes, despite the higher total HE area in these eyes at baseline. While not statistically significant, the

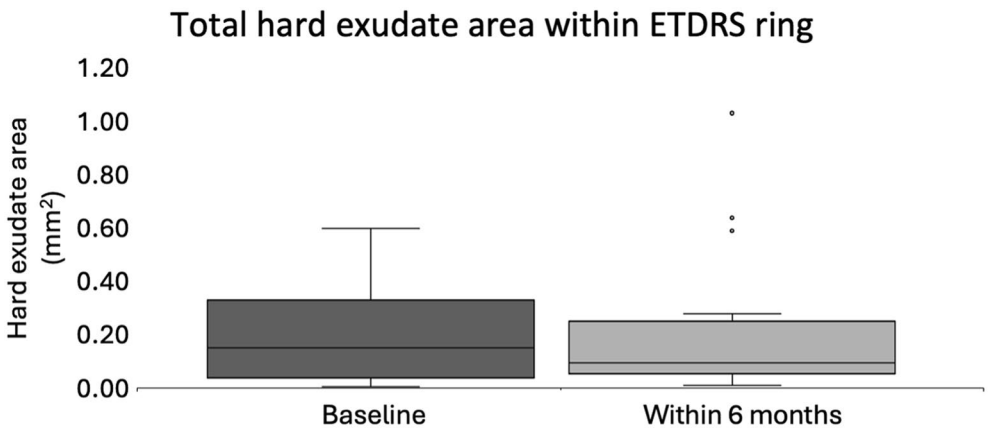

Fig. 2 Boxplot of total hard exudate area within the Early Treatment Diabetic Retinopathy Study (*ETDRS*) ring at baseline and following initiation of faricimab therapy

Table 2 Distance from fovea to the nearest hard exudate in treatment-naïve eyes at different time points

Eye	Distance from fovea to nearest hard exudate	
	Baseline (mm)	Follow-up (mm)
1	0.00	0.05
2	0.63	0.39
3	1.30	0.33
4	0.42	0.10
5	0.58	0.32
6	0.55	0.59
7	0.56	0.16
8	0.10	0.11
9	1.50	0.72
10	0.66	1.05

Table 3 Mean and median distance from fovea to the nearest hard exudate in treatment-naive eyes

Time point	Mean ± SD (mm)	Median (IQR) (mm)
Baseline	0.63 ± 0.47	0.57 (0.45–0.66)
6 months	0.38 ± 0.32	0.33 (0.12–0.54)

IQR Interquartile range, *SD* standard deviation

observed early reduction of HEs may indicate the mechanistic influence of Ang-2 inhibition in the clearance of HEs.

We hypothesised that faricimab would result in early clearance of HE based on preclinical evidence that Ang-2 and VEGF-A work synergistically to regulate vascular leakage and inflammation. Our cohort consists of consecutive, multi-ethnic, heterogeneous patients presenting to a large retina practice, suggesting that our findings are likely to be replicable and generalisable in larger, real-world cohorts.

Our findings align with post-hoc analyses of the YOSEMITE and RHINE clinical trials, which also evaluated the presence of HE on colour fundus photographs. Goldberg et al. reported fewer patients had HE by 12 months in the faricimab arm compared to the aflibercept arm [15]. Similarly, through the use of a deep learning algorithm to analyse OCTs, these authors demonstrated a greater reduction in HE volume and count by 6 months in the faricimab arm compared to the aflibercept arm [15].

Previous studies evaluating other anti-VEGF monotherapies, including ranibizumab, bevacizumab and aflibercept, have also reviewed the effects of these medicines on HE. Using OCT quantitative analyses, Srinivas et al. found that ranibizumab significantly reduced intraretinal HEs at month 12 following treatment initiation [16]. Similarly, post-hoc analyses of the DRCR protocol T trial, in which patients were

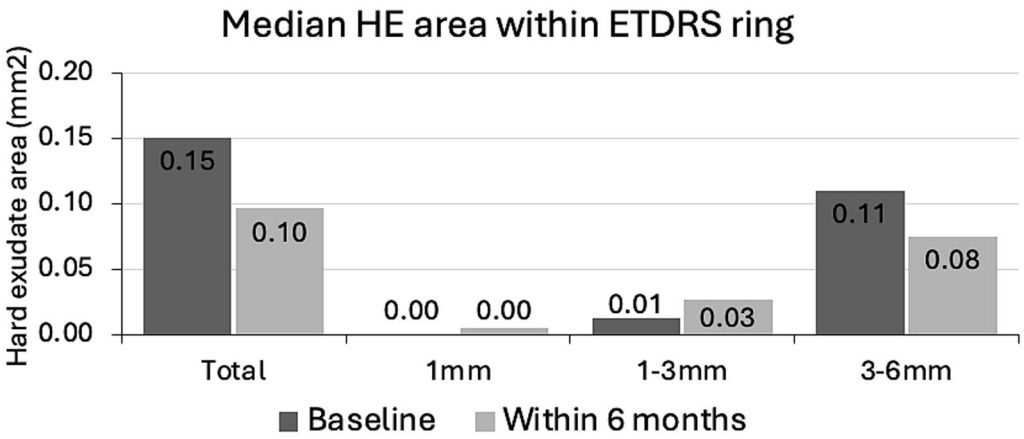

Fig. 3 Median hard exudate (*HE*) area within the Early Treatment Diabetic Retinopathy Study (*ETDRS*) ring at baseline and following initiation of faricimab therapy

randomly assigned to the aflibercept, bevacizumab or ranibizumab arm, noted a decrease in HEs by week 52, following an initial rise and peak at week 12 [17]. With colour fundus photographs, Domalpally et al. found that resolution of HE was apparent after 6 months of intravitreal ranibizumab injection [18]. In contrast, Jeon et al. found no benefit with intravitreal bevacizumab at 6 months using colour fundus photographs [19]. This discrepancy may be attributed to the fact that OCT imaging can discern HEs that are not apparent on colour fundus photographs, hence changes are elicited earlier than with colour fundus photography.

Multiple reports have demonstrated rapid reduction of HEs with intravitreal steroids such as triamcinolone and dexamethasone implants, with reductions demonstrated as early as 2 months post-treatment [7, 8, 10, 11, 20, 21]. Post-hoc analysis of the BEVORDEX trial elicited a greater resolution of HE at 12 months with intravitreal dexamethasone injection compared to bevacizumab, although this difference was not significant at 24 months [22]. This result is attributable to the anti-inflammatory properties of intravitreal steroids, in addition to their anti-angiogenic effects [23]. Work by Sohn et al. demonstrated that intravitreal triamcinolone reduced aqueous levels of inflammatory cytokines involved in DMO, such as IL-8, IP-10, MCP-1 and VEGF, compared to VEGF alone with bevacizumab [24].

Dual inhibition of Ang-2 and VEGF receptors may confer similar anti-inflammatory properties as demonstrated in in vivo studies [13, 25, 26]. In murine models, combined blockade of Ang-2/ VEGF was superior in reducing infiltration of subretinal inflammatory cells over VEGF or Ang-2 blockade alone [25]. Additionally, inhibition of Ang-2/ VEGF, as in faricimab therapy, may confer benefits over intravitreal steroid injections, which predispose patients to cataract and glaucoma development. Yoon et al. reported significant reductions in HE area within 1 month following dexamethasone implantation, but 45.7% of patients showed cataract progression, and 11% experienced intraocular pressure elevation [7].

In the present study, we also demonstrated that the changes in HE were accompanied by an improvement in visual acuity and a reduction in CRT and MV. Although negative correlations were observed with baseline BCVA and HE areas across in most ETDRS regions, none reached statistical significance. This result is consistent with those of previous studies reporting no significant association between BCVA and HE burden at baseline or following intravitreal ranibizumab [16, 18, 27]. The importance of early HE clearance in DMO may lie in its association with reduced risk of photoreceptor damage, which may not be captured by visual acuity measurement unless the fovea is involved. The presence of HE has

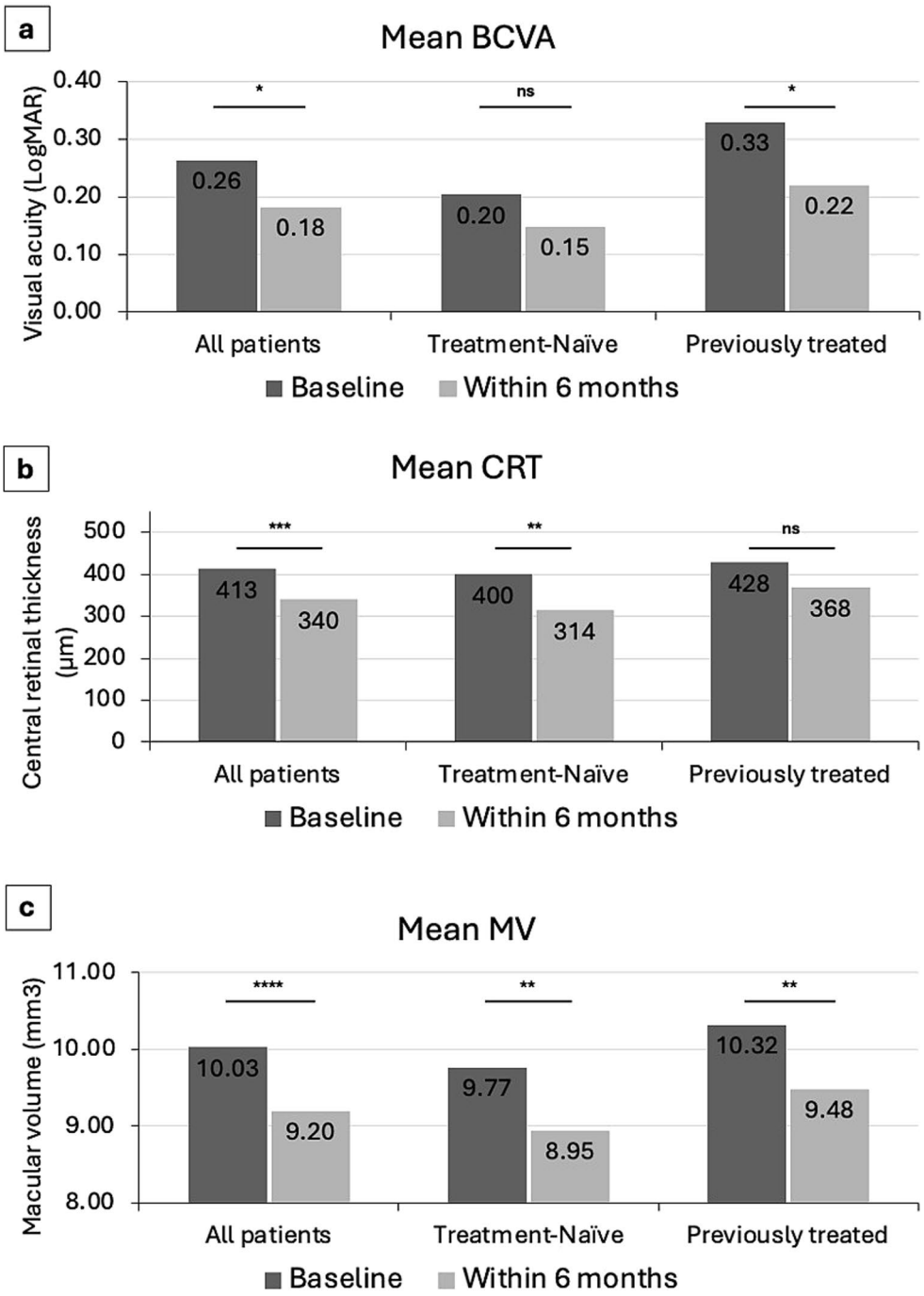

Fig. 4 Visual and anatomical outcomes at baseline and after initiating faricimab therapy. **a** Best corrected visual acuity (*BCVA*), **b** central retinal thickness (*CRT*), **c** macular volume (*MV*). Asterisks indicate a significant difference at $^{*}p < 0.05$, $^{**}p < 0.01$ $^{***}p < 0.001$, $^{****}p < 0.0001$. *ns* Not significant

been associated with recalcitrant macular oedema and worse prognosis for visual recovery, with Chew et al. demonstrating that HEs represented a significant risk factor for poor visual outcome in the ETDRS, after adjustment for the extent of macular oedema [5].

Table 4 Spearman correlation analysis of baseline clinical variables with baseline hard exudate area measurements within the Early Treatment Diabetic Retinopathy Study ring

Baseline clinical variable	Baseline HE area measurement	Correlation coefficient (*r*)	*p*-value
BCVA	1-mm ring	0.16	0.51
	3-mm ring	− 0.34	0.15
	6-mm ring	− 0.45	0.052*
	Total	− 0.35	0.14
CRT	1-mm ring	− 0.02	0.95
	3-mm ring	− 0.11	0.65
	6-mm ring	− 0.02	0.94
	Total	− 0.01	0.98
MV	1-mm ring	0.03	0.91
	3-mm ring	− 0.03	0.92
	6-mm ring	0.15	0.55
	Total	0.12	0.63

BCVA Best corrected visual acuity, *CRT* central retinal thickness, *HE* hard exudate, *MV* macular volume

*Significant correlation at $p = 0.052$

We observed moderate, but borderline significant, negative correlations between change in CRT and HE area within the 1-mm ETDRS ring ($\rho = -0.45$ and $p = 0.052$, respectively). This regional association is anatomically plausible as the CRT measurement is derived from the central 1-mm ETDRS subfield. In contrast, Srinivas et al. [16] and Pak et al. [17] reported significant associations between HE area and changes in CRT and MV following intravitreal ranibizumab. Compared to the present study, both of these studies had a longer follow-up duration of 12 months, which might have allowed for greater sensitivity to detect modest changes in HE dynamics and retinal thickness changes.

Despite promising trends, our study has a number of limitations, including its retrospective design and small sample size. The non-significant reduction in HE area in this study may be attributed to these factors, underscoring the need for larger, prospective studies with longer follow-up durations. A key limitation of this study is the lack of a control or active comparator group. As noted, anti-VEGF and intravitreal steroids have been established to reduce HEs and, therefore, the observed reduction in HEs in this study is not exclusive to faricimab. However, compared to other anti-VEGF agents, reductions in HEs were observed earlier in our study within 6 months. Due to variation in methodology, including differences in imaging modalities and treatment regimens, direct comparison across studies was not possible. Comparative studies are therefore needed to outline the auxiliary effects of Ang-2 blockade with faricimab.

Additionally, while the relationship of HEs between anatomical parameters such as MV and CRT was evaluated, other biomarkers, such as the presence of microaneurysms and subretinal fluid, were not fully explored in this study and warrant further investigation with the use of multi-modal imaging. We also recognise that DMO and HE area can fluctuate with systemic disease control, including the duration of disease and use of medications, regardless of intravitreal therapy. Unfortunately, biochemical tests to assess metabolic control, such as glycated haemoglobin (HbA1c) and lipid profiles, were not available for patients during the study period to further assess this dynamic. Therefore, future studies should aim to explore this further, as well as the potential benefits of combination therapy with steroids or lipid-lowering agents to enhance HE clearance. Investigating the synergistic effects of faricimab and dexamethasone, for example, could provide valuable insights into optimising treatment strategies for DMO.

A key limitation of colour fundus photograph processing is the differing physical resolutions between the Clarus (approx. 7 µm/pixel) and Kowa (4.5–6 µm/pixel) systems for the same 45° field, potentially influencing exudate segmentation fidelity: Clarus images are effectively lower in resolution and may appear less sharp. Moreover, the assumption of uniform resolution across each image is an approximation; however, as the analysis focuses on matched images of the same

Table 5 Spearman correlation analysis of changes in clinical variables with changes in HE area measurements within the Early Treatment Diabetic Retinopathy Study ring

Clinical variable	Change in the hard exudate area parameter	Correlation coefficient (*r*)	*p*-value
Change in BCVA	1-mm ring	0.14	0.56
	3-mm ring	0.08	0.76
	6-mm ring	− 0.21	0.38
	Total	− 0.08	0.74
Change in CRT	1-mm ring	− 0.45	0.052*
	3-mm ring	0.11	0.67
	6-mm ring	− 0.08	0.74
	Total	0.01	0.96
Change in MV	1-mm ring	− 0.32	0.18
	3-mm ring	0.14	0.57
	6-mm ring	− 0.21	0.39
	Total	− 0.15	0.54

BCVA Best corrected visual acuity, *CRT* central retinal thickness, *HE* hard exudate, *MV* macular volume

*Significant correlation at $p = 0.052$

eye, this is not expected to affect intra-eye comparison of exudate area.

CONCLUSION

In conclusion, our study offers preliminary evidence that faricimab may be associated with early HE reduction in DMO, particularly in treatment-naïve patients. Although the observed changes were not statistically significant, the trend towards improvement suggests a potential benefit that warrants further investigation. Given its dual mechanism of action, favourable safety profile and extended dosing interval, faricimab may represent a promising treatment option for exudative DMO, especially for patients at risk of steroid-related side effects. Future studies should directly compare faricimab with dexamethasone and other anti-VEGF agents to establish its role in the management of HEs in DMO.

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Author Contribution. Ameeta Kumar: data acquisition, statistical analysis, draft and revision. Busaraben Gandhi: data acquisition, statistical analysis, draft and revision. Arevik Ghulakhszian: data acquisition and analysis. Giovanni Ometto: data acquisition and analysis. Christiana Dinah: conception, study design, draft and revision.

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Data Availability. The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Christiana Dinah has received research grants from Apellis, NIHR, Roche and Topcon; is a consultant for AbbVie, Alimera Sciences, Apellis, Astellas, Bayer, Boehringer Ingelheim, Eyepoint, Roche and Ora Clinical; and has received clinical lecture fees from Alimera Sciences, Apellis, Astellas, Bayer, Boehringer Ingelheim, Eyepoint, Roche and Topcon. Ameeta Kumar, Busaraben Gandhi, Arevik Ghulakhszian and Giovanni Ometto have no competing interests.

Ethical Approval. The study was performed in accordance with the tenets of the Declaration of Helsinki and its later amendments. Due to the retrospective nature of the study and use of anonymised data, the requirement for informed consent was waived and ethical approval was not required. The study was registered locally as a retrospective audit.

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