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ARTICLE

Faricimab in neovascular AMD: first report of real-world outcomes in an independent retina clinic

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PURPOSE: Assess short-term real-world outcomes in neovascular aged-related macular degeneration (nAMD) treated with novel faricimab.

METHODS: Retrospective case series of nine patients with nAMD (11 eyes) treated with faricimab between May and November 2022. Treatment-naïve patients and non-naïve patients underwent logMAR best corrected visual acuity (BCVA), optical coherence tomography (OCT) DRI OCT-1 Triton (Topcon Corp, Tokyo, Japan), ultra-widefield (UWF) and fundus autofluorescence (FAF) (California Optomap, Optos plc, Dunfermline, Scotland, UK). Previous treatment intervals, number of intravitreal injections, sub/intra retinal fluid (SRF/IRF), central retinal thickness (CRT) and presence/changes in pigment epithelial detachments (PEDs) were recorded.

RESULTS: Mean baseline BCVA and CRT values of patients who switched from other agents were 0.612 ± 0.75 logMAR and 256.16 ± 12.98 µm respectively, with a mean 36-day previous treatment interval. The median number of other previous anti-VEGF intravitreal injections was 8. Mean BCVA at one month significantly improved to 0.387 ± 0.54 logMAR, as well as CRT values which decreased to 245.43 ± 15.34 µm. In the 3 naïve patients, mean baseline BVCA and CRT values were 0.33 ± 0.29 and 874.67 ± 510.86 µm, respectively. At one month follow-up, mean BCVA improved to 0.30 ± 0.29 logMAR and mean CRT was 536.04 ± 36.15 µm. Overall, a significant improvement in BCVA of 0.21 ± 41 logMAR and 238.44 ± 114.9 µm was achieved at one month after the first faricimab intravitreal injection. In addition, a complete resolution of SRF was observed in 6 out of 8 eyes (75%) and of IRF in 2 out of 3 eyes (66.67%), respectively. Drusenoid PED morphology changes were observed in all patients and no drug-related adverse events were observed.

CONCLUSION: Real-world outcomes showed improvement in BCVA and anatomic parameters at an early timepoint, demonstrating the efficacy and durability of faricimab in nAMD patients. Larger numbers of patients and longer follow-up are needed to determine whether the loading dose is required in all, what percentage of patients experience an improvement, and whether improvement it is maintained.

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BACKGROUND

Since pegaptanib sodium (Macugen) was approved in 2004 for intravitreal therapy (IVT) [1], the introduction of medicines targeting vascular endothelial growth factor (VEGF) has substantially improved visual outcomes for patients with neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO) and diabetic retinopathy (DR) [2]. Despite the proven positive effect of these compounds, their molecules target only VEGF [3]. Response to antiVEGF therapy varies, and resistance, recurrence of the disease or non-response phenomena have all been observed [4]. Approximately 30% of patients are considered non-responders; it is possible that this could be due to underlying genetic variants rendering the individual less susceptible to antiVEGF medication; there is no clear explanation to date [5].

Real-world studies have shown that most patients are under-treated. The reasons for this are manifold and may include lack of compliance, health care capacity issues, or inadequate/inappropriate treatment protocols [6, 7]. Recent medical research has focused on new molecular targets to try to develop new agents with greater efficacy and duration of effect. Achieving this goal would enable a reduction in the need for repeated frequent intravitreal administration of the active agent resulting in, improved anatomical and functional response, greater compliance, with a reduction in demand on the clinical service.

Faricimab (Vabysmo™, Roche/Genetech, Basel, Switzerland) is a novel FDA (February 2022, USA), MHRA (May 2022, UK) and EMA (October 2022, EU) –approved agent administered via intravitreal injection designed to block both VEGF and angiopoietin-2 (Ang-2) in the treatment of nAMD and diabetic macular oedema (DMO) [8, 9]. It is the first bispecific antibody designed for intraocular use via intravitreal injection allowing for a single molecule to target two mediators [3]. The new target Ang-2 plays an important role in

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vascular diseases by regulating angiogenic functions as well as endothelial permeability [10, 11].

This next-generation biologically engineered bispecific molecule yields a higher efficacy using evidence from best corrected visual acuity (BCVA) measurements and anatomical improvement with a high safety profile as shown in various clinical trials (CTs) [12–15]. These attributes may offer potential advantages in the treatment of a range of retinal diseases. A multi-centre real-world safety and efficacy study (TRUCKEE) is currently underway [16]. However, no real-world results have been published so far.

The maximum recommended interval in between faricimab intravitreal injections based on CTs is Q16 weeks and is thus significantly longer than that of a one-compound anti-VEGF such as brolucizumab, aflibercept or ranibizumab [17]. Although CTs and real-world treatment efficacy have been studied extensively comparing ranibizumab and aflibercept [18–20], faricimab real-world results are not yet available.

Here, we present week four clinical outcomes from a real-world study in an independent specialised retina clinic to assess the safety, efficacy, and durability of faricimab administered as customised treatment in patients with nAMD. To the best of our knowledge, this is the first short-term real-world data report.

MATERIALS AND METHODS

An observational and retrospective study of eleven consecutive eyes (nine patients) was conducted to compare the efficacy and safety of faricimab in nAMD at an independent ophthalmic clinic specializing in vitreoretinal diseases in London, United Kingdom. The tenets of the Declaration of Helsinki were followed, and patients provided informed consent for participation.

All patients included in this review were over the age of 50 years and presented with nAMD. Treatment-naïve nAMD eyes as well as those which had already received treatment with other anti-VEGF intravitreal injections for nAMD were included. A minimum of 4-week follow-up was required to be included in this review.

All subjects were treated with at least one intravitreal injection of 0.05 ml faricimab 120 mg/ml between May 2022 and November 2022. Prior to the intravitreal therapy (IVT), all patients underwent a complete ophthalmological examination including best corrected visual acuity (BCVA) in logMAR, slit lamp biomicroscopy (Topcon SI-D701 slit-lamp, Topcon Corporation, Tokyo, Japan), non-contact intraocular pressure measurement (TRK-2P, Topcon Corporation, Tokyo, Japan), red/green and autofluorescence (AF) ultra-widefield fundus imaging (UWFI) (California Optomap, Optos plc, Dunfermline, Scotland KY11 8GR, UK), and macular optical coherence tomography (OCT) imaging (DRI OCT-1 Triton, Topcon Corp, Tokyo, Japan). OCT was used to assess the central retinal thickness (CRT) and foveal thickness (FT), and the presence of subretinal and/or intraretinal fluid (SRF /IRF), and drusenoid pigment epithelium detachment (dPED).

Faricimab was administered as an intravitreal 6 mg injection with varying treatment regimens depending on each case and based on pre-existing anti-VEGF therapy and response to faricimab. OCT scans at baseline and final follow-up were assessed by one fellowship-trained (FJVB) and retina specialist (PES).

In three eyes, an UWF fundus fluorescein angiography (FFA) with or without simultaneous swept-source OCT (SS-OCT) was performed as well (Optos California and Optos Silverstone, Optos PLC; Dunfermline, Scotland, United Kingdom).

Previous treatment intervals, the total number of intravitreal injections, BCVA, CRT, SRF, IRF and dPED data were collected and analysed using Excel (Microsoft, Redmond, WA, USA).

Signs of retinal toxicity such as retinal cotton-wool spots, haemorrhages, vasculitis or vascular sheathing were examined for at each visit in each patient.

RESULTS

A total of eleven eyes (nine patients) presenting with nAMD were treated with Vabysmo™ between May and November 2022. Median age was 75.44 years (range: 61 to 89) and five subjects were female (55.55%). Median follow-up time was 12.5 weeks (range: 4 to 24).

Table 1. Baseline patient characteristics with functional and anatomical outcomes at 1 month after a 1st faricimab intravitreal injection.

Functional and Anatomical Outcomes	Baseline	Present at 1 month
BCVA mean ± SD (logMAR)		
Naïve patients ($n = 3$)	0.33 ± 0.29	0.30 ± 0.29
Non-naïve patients ($n = 8$)	0.61 ± 0.75	0.39 ± 0.54
Total population ($n = 11$)	0.55 ± 0.73	0.34 ± 0.32
Central Retinal Thickness mean ± SD (µm)		
Naïve patients ($n = 3$)	874.67 ± 510.86	536.41 ± 352.15
Non-naïve patients ($n = 8$)	256.16 ± 12.98	245.43 ± 15.34
Total population ($n = 11$)	565.41 ± 341.38	326.97 ± 226.48
Subretinal Fluid (SRF)	8 (72.72%)	2 (18.18%)
Drusenoid PED	7 (63.63%)	4 (36.36%)
Intraretinal Fluid (IRF)	3 (27.27%)	2 (18.18%)
Subretinal Haemorrhage	3 (27.27%)	2 (18.18%)

The anatomical and functional features at baseline and at one month after the first faricimab intravitreal injection are summarized in Table 1.

Four eyes (cases 1, 7, 10 and 11) were treated with a loading dose of four monthly faricimab intravitreal injections and seven eyes (cases 2, 3, 4, 5, 6, 8, 9) underwent a treat and extent regimen from the beginning of their treatment.

Four eyes (36.36%) gained at least one line of vision, six eyes (54.54%) remained stable, and one eye (9.09%) lost one line of vision one month after the first faricimab intravitreal injection. Four of the eleven eyes (36.36%) presented with differing grades of macular atrophy or fibrosis which are known to limit the potential for visual recovery.

Three out of the eleven eyes (cases 9, 10, 11) were treatment-naïve eyes (27.27%). In them, mean baseline BVCA and CRT values were 0.33 ± 0.29 and 874.67 ± 510.86 µm, respectively. At one month follow-up, mean BCVA improved to 0.30 ± 0.29 logMAR and mean CRT was 536.04 ± 36.15 µm.

A total of eight eyes (72.72%) had other previous anti-VEGF intravitreal injections, such as ranibizumab (Lucentis) or aflibercept (Eylea™). The median number of previous intravitreal injections in them was eight (range 0–25). The reason for switching to faricimab in the nine non-naïve eyes was persistent SRF (50%), persistent SRF and IRF (25%), persistent IRF (12.50%) and persistent subretinal haemorrhage (12.50%). Mean baseline BCVA and CRT values of patients who switched from other agents were 0.612 ± 0.75 logMAR and 256.16 ± 12.98 µm respectively, with a mean 36-day previous treatment interval. The median number of other previous anti-VEGF intravitreal injections was 8. Mean BCVA at one month significantly improved to 0.387 ± 0.54 logMAR, and CRT values decreased to 245.43 ± 15.34 µm.

Mean BCVA of the complete sample at baseline was 0.55 ± 0.73 logMAR and at one-month follow-up 0.34 ± 0.32 logMAR. Four eyes (36.36%) gained at least one line of vision, six eyes (54.54%) remained stable, and one eye (9.09%) lost one line of vision one month after the first faricimab intravitreal injection. Overall average CRT at baseline was 565.41 ± 391.38 µm, which improved significantly to 326.97 ± 226.48 µm at one month. The FT at baseline and at one month were 236.41 ± 74.32 µm and 153.69 ± 35.40 µm, respectively.

Initially, SRF was present in eight eyes at baseline and completely resolved after the 1st faricimab intravitreal injection in six eyes (75%). Similarly, IRF observed in three eyes completely resolved in one eye (33.33%) one month after the first faricimab intravitreal injection. Furthermore, PEDs were present in eight eyes (72.72%) at the initial examination and morphology changes such as flattening were observed in all of them one month after the first faricimab (i.e., Cases 5–6, Fig. 1).

Most of the non-naïve patients (Cases 2, 3, 4, 5, 6, 8, 9) who underwent ranibizumab or aflibercept IVT every 4 to 8 weeks with

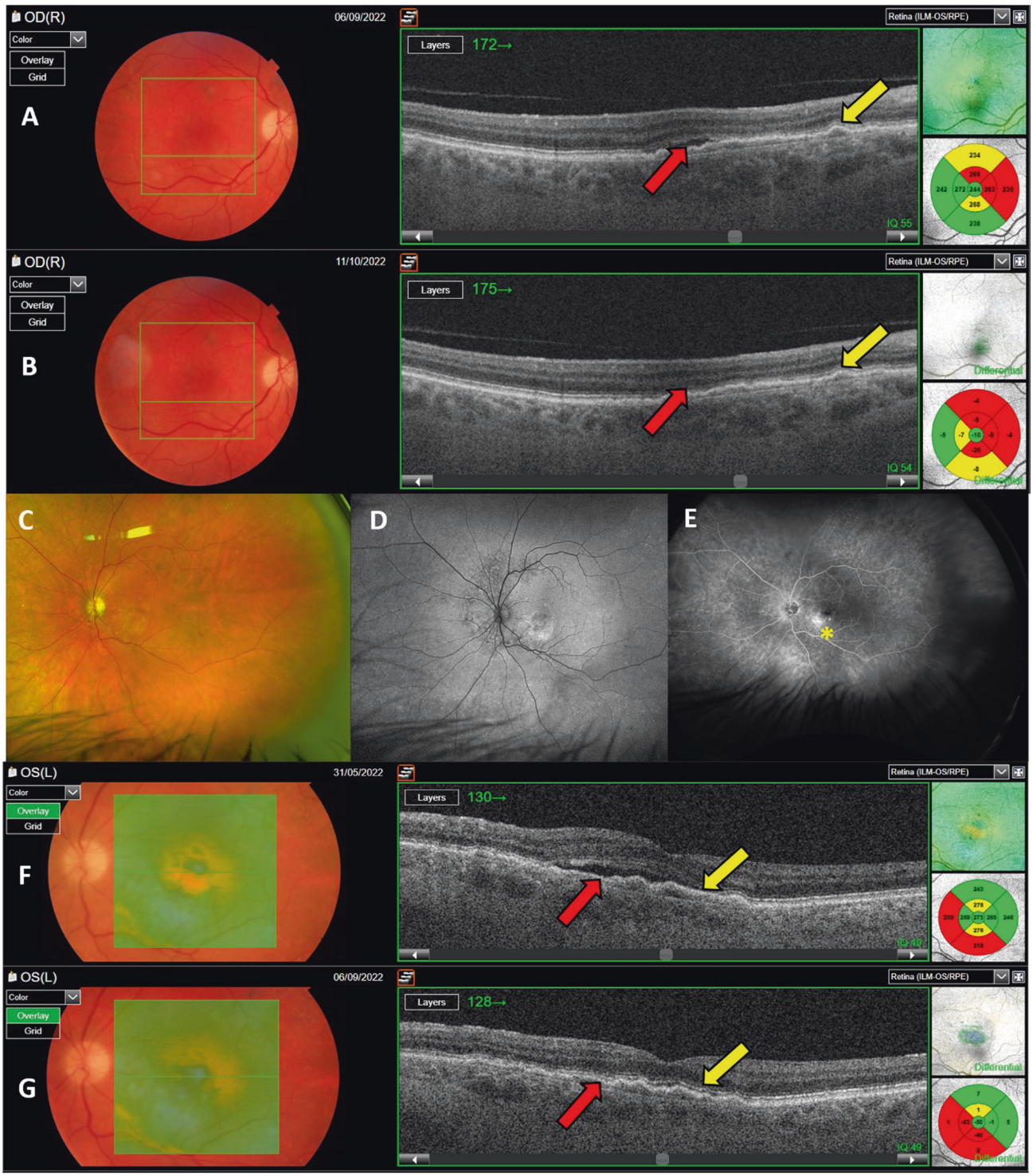

Fig. 1 Resolution of SRF and PED flattening after the initial intravitreal injection of faricimab. Case 5: A complete response to the treatment that lasted 10 weeks was observed in a 76-year-old male, who used to have Eylea™ intravitreal injections every 4 to 6 weeks. SRF resolution (red arrows) and PED flattening (yellow arrows) after the 1st faricimab is shown in **A** and **B**. Case 6: UWF RG (**C**) and FAF (**D**) scans demonstrated retinal pigment epithelium abnormalities in the fellow eye. An occult or type 1 CNV was observed on the UWF FFA (**E**). Below, comparative maps of macular topography and OCT images before faricimab injection (**F**) and 24-week follow-up after the first and only faricimab dose (**G**) shows resolution of SRF (red arrows) and modification of morphology and height of dPED (yellow arrows).

insufficient response had a better response to faricimab in terms of SRF and IRF resolution, as well as a flattening of the dPED at one month after the intravitreal injection. These results lasted more 10 weeks. In fact, a complete response after a 24-week period with an improvement in visual acuity, SRF resolution, and dPED morphology changes were observed in a 76-year-old male (Case 6), who had been undergoing aflibercept injections every 4 to 6 weeks due to choroidal neovascularisation (Fig. 1). Moreover, an improvement of visual acuity was observed. However, in a 76-year-old non-naïve female (Case 7), a course of 4 faricimab injections was needed to achieve a complete resolution of minimal SRF and reduction of dPED (Fig. 2).

The response to the treatment varied widely between the patients possibly due to several different nAMD phenotypes. For instance, a naive 71-year-old female (case 9), diagnosed with nAMD and possible polypoidal choroidal vasculopathy (PCV), had a resolution of SRF and flattening of multiple PEDs at one month after the first injection (Fig. 3). Thus, a treat and extent (T&E) regimen was discussed and agreed with the patient.

Faricimab was used to treat large subretinal, subRPE haemorrhages and fibrovascular PED in cases 1,10 and 11. A progressive resolution of a large subretinal and subRPE haemorrhage was observed after the loading dose of faricimab in all of them, as shown in Fig. 4 (Cases 10 and 11). For instance, case 11 (Fig. 4)

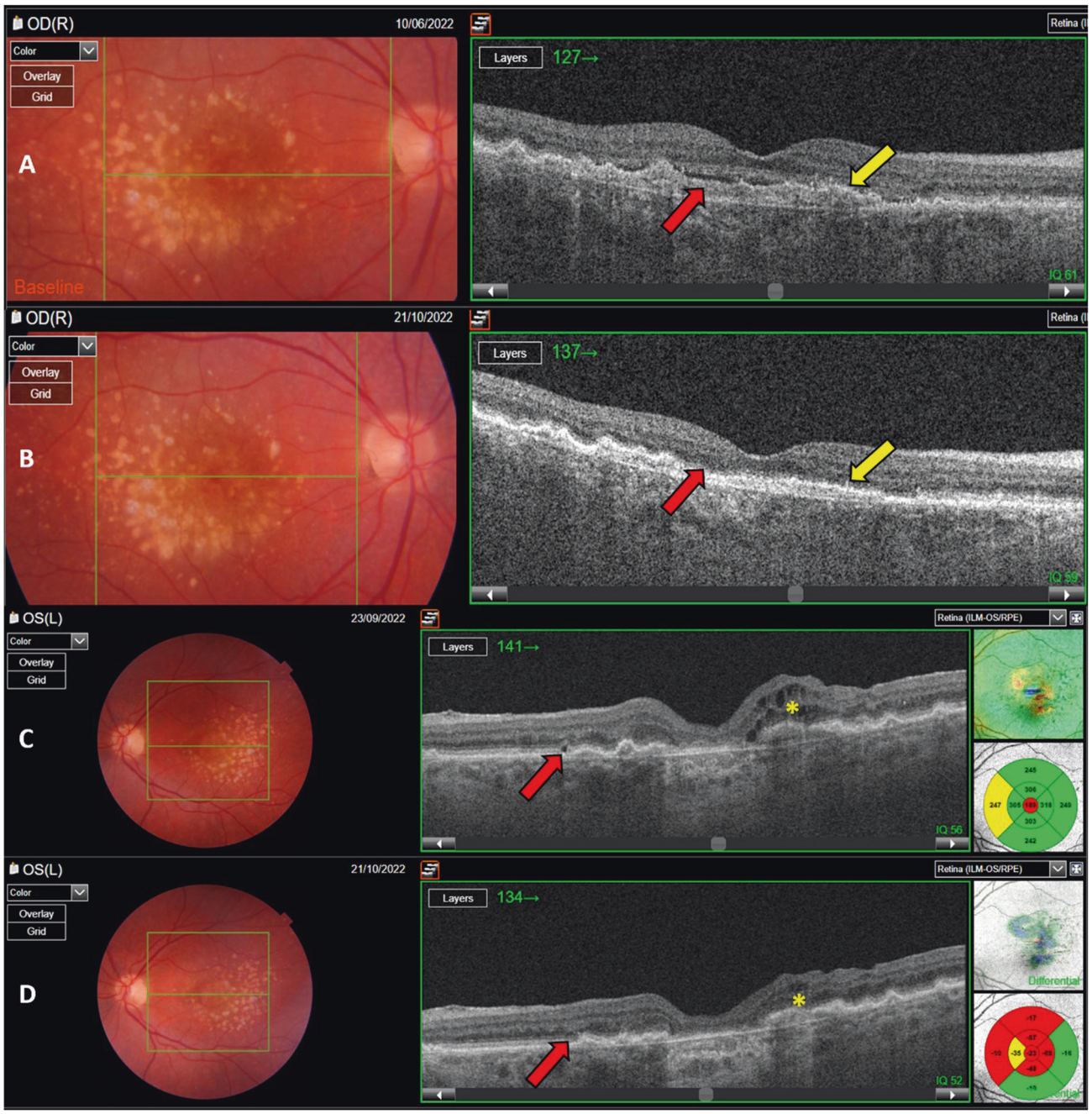

Fig. 2 Varying responses in different eyes to faricimab in the same patient. A, **B** (Case 7) The resolution of minimal SRF (red arrows) and reduction of dPED (yellow arrows) in a 76-year-old female with nAMD after the faricimab injections (**B**). However, a course of four faricimab intravitreal injections was needed. **C**, **D** Demonstrate SRF (red arrows) and IRF (yellow asterisks) resolution in the fellow eye (Case 8) at one month after the first faricimab injection.

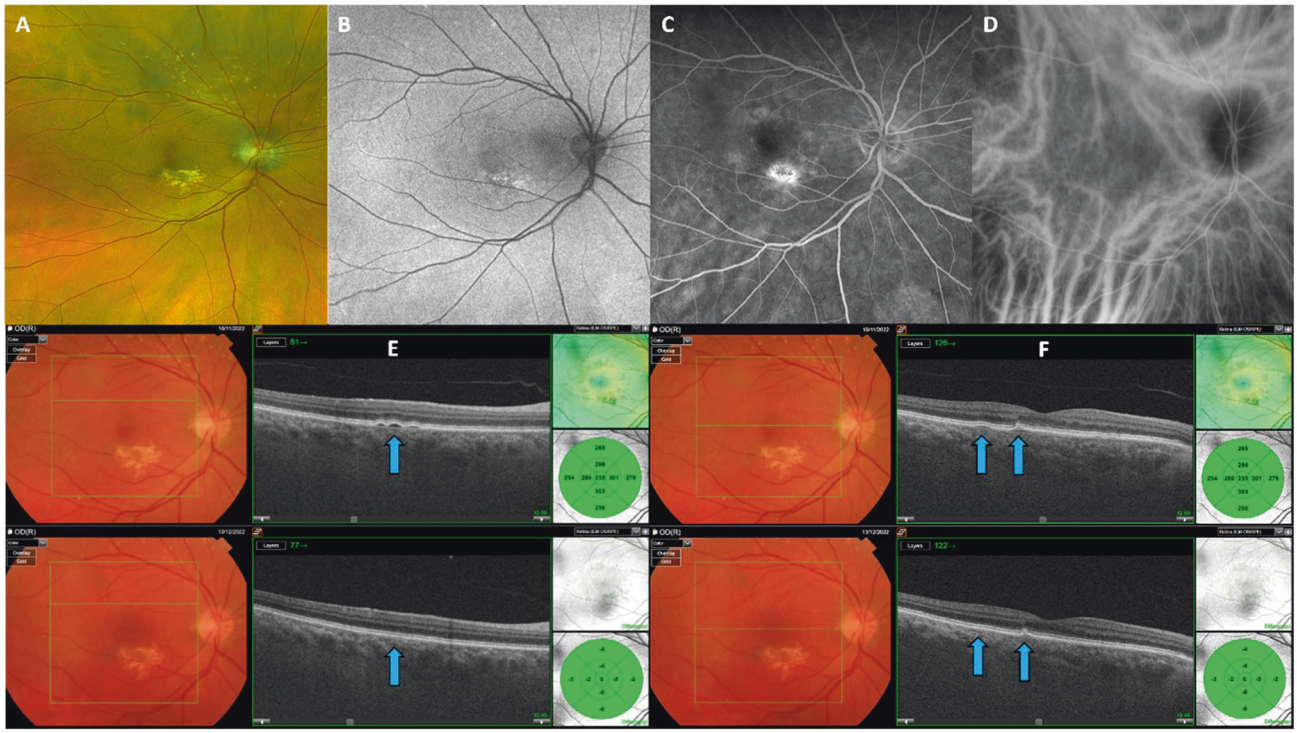

Fig. 3 Resolution of multiple PEDs after the first faricimab intravitreal injection. Case 9: Patient diagnosed with nAMD using multimodal and simultaneous imaging including UWF RG (**A**), FAF (**B**), FFA (**C**) and ICGA (**D**) with navigated SS-OCT. In **E** and **F**, a resolution of multiple PEDs was observed after the first injection of faricimab (blue arrows).

presented with an acute onset of a large fibrovascular PED which height decreased from 1458 µm to 1010 µm and the BCVA improved from 0.3 to 0.2 logMAR after the first faricimab injection.

No significant increase in central fibrotic or atrophic changes were observed subsequent to the faricimab intravitreal injections, nor were any cases of intraocular inflammation or systemic adverse events detected.

DISCUSSION

Anti-VEGF intravitreal therapy is the first choice of treatment for nAMD [21, 22]. Efficacy is variable and, in some cases, there is little or no response [4]. In addition, for those who do respond repeated frequent injections are usually required to maintain the desired effect [23]. Some cases may develop tachyphylaxis and fibrosis can also occur [4, 23, 24].

Faricimab is the first bi-specific antibody approved for intraocular use and inhibits both VEGF and angiopoietin 2 (Ang2), both of which are considered to be essential in the maintenance of vascular homeostasis [25]. We aimed to assess the effectiveness of the novel faricimab (Vabysmo^{TM}) in a real-world study in 11 consecutive eyes assessing BCVA as a functional outcome and OCT variables as anatomical ones (SRF, IRF, dPED, CRT, and FT).

This new compound is labelled for up to 16-week dosing intervals depending on response and following a loading dose of 4 monthly injections. However, in this group of patients, a treat-and-extend treatment regimen was used in seven eyes (64,64%), and only four eyes (36.36%) received the loading doses.

The AVENUE and STAIRWAY clinical trials demonstrated that faricimab was not inferior to ranibizumab and the treatment intervals were extended to 12 to 16 weeks for the treatment of nAMD [12, 26]. Previous studies using aflibercept have shown that extending treatment intervals beyond the manufacturer's recommended dosing regimen has been demonstrated to be effective [17, 27].

It is thought that the design of faricimab can lead to a more sustained and effective response to treatment. We demonstrated this in our small patient group, i.e., Case 5, a patient who had been previously undergoing 5–6 weekly intravitreal injections (IVI) of aflibercept for 3 years, had full resolution of the SRF after receiving only one faricimab injection and no signs of neovascular activity were observed for >24 weeks on OCT. Although our sample is small, it raises the question of the necessity of the initial loading dose of four monthly intravitreal injections of faricimab in patients already undergoing anti-VEGF therapy.

However, we realized that persistent SRF can be found even after three doses of faricimab, as seen for example in a non-naïve patient (Case 7). Thus, the need for loading doses and an increased frequency of treatment doses may be dependent on the phenotype of nAMD. A way forward would be to identify the response to therapy identifying specific OCT 'biomarkers' that will enable us to distinguish which treatment regimen is the most appropriate for each patient. This personalised medicine approach would be more cost-effective and reduce the number of appointments and IVI needed per year.

The mean BCVA in our patients increased up to 38.19% and four eyes (36.36%) gained at least one line of vision after the first IVI. These are very encouraging results since most of the here reported eyes (72.72%) were not treatment–naïve and had already undergone multiple anti-VEGF IVI prior to starting treatment with faricimab.

Our real-world results with faricimab in terms of improvement of BCVA and resolution of subretinal fluid or subretinal pigment epithelium haemorrhage are similar or even better when compared to other licensed anti-VEGF treatments at one month after the first injection [28]. Matsumoto et al. also showed significant BCVA improvement one month after the first injection of brolucizumab in nAMD patients [29], however, this IVT has been associated with ocular inflammation [30–32].

In addition, excluding the large fibrovascular PEDs and haemorrhages, we observed a significant reduction in CRT (more

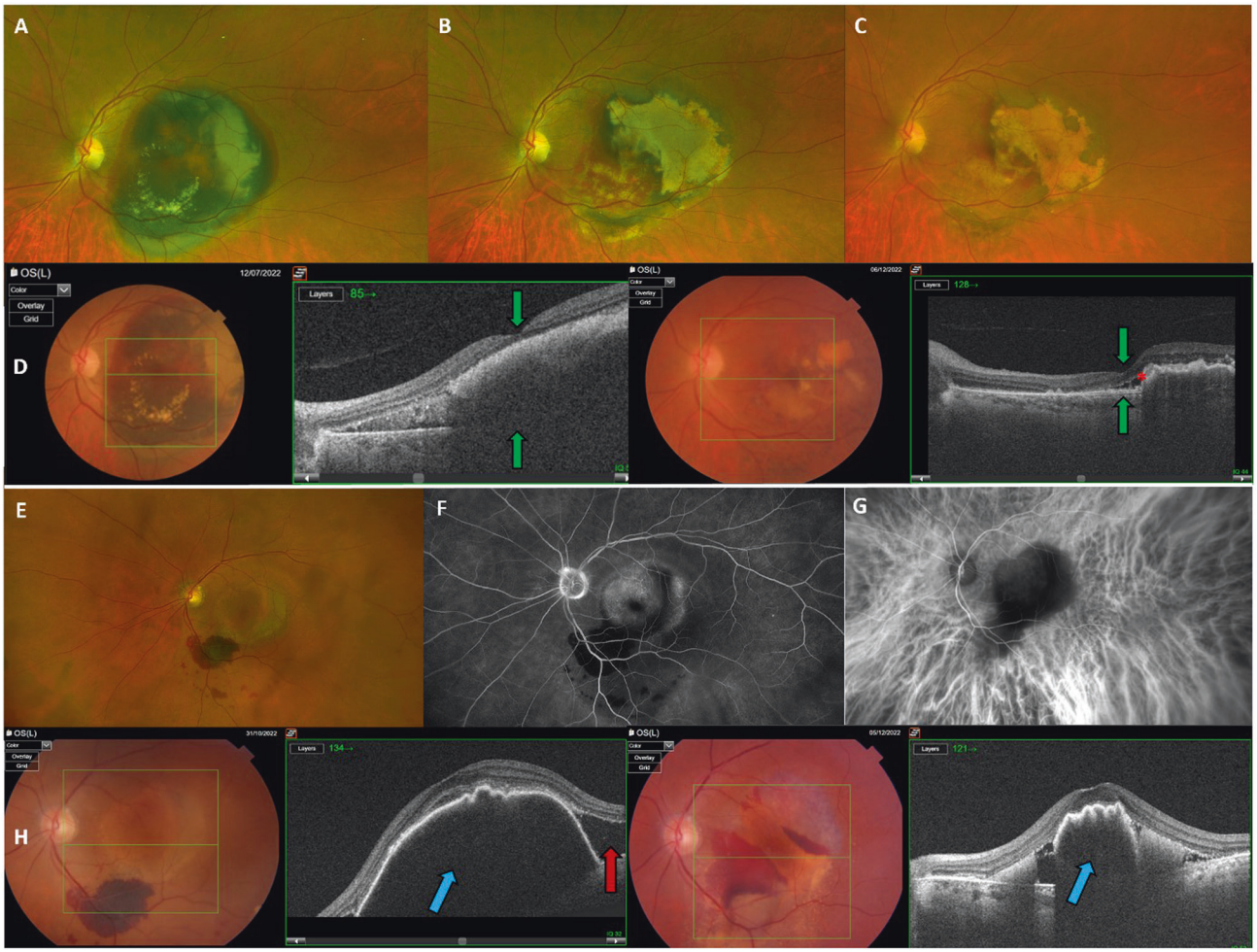

Fig. 4 Efficacy of faricimab in the resolution of subretinal and subRPE haemorrhages. Case 10: UWF RG images showed a progressive resolution of subretinal and subRPE haemorrhage in a nAMD patient, who was treated twice in one-monthly intervals with faricimab (**A**) at baseline, (**B**) at one month, (**C**) at two months. A significant and progressive reduction of the haemorrhage (green arrows) is also observed in SS-OCT after the faricimab loading phase (4 injections) treatment in spite of minimal SRF appearance (red asterisk) (**D**). Case 11: Large fibrovascular PED in a nAMD patient. The haemorrhage appears to be subretinal and sub-RPE in UWF RG, FFA and ICGA images (**E**, **F**, **G**). However, SS-OCT scans demonstrated a large PED with associated subretinal haemorrhage (blue arrow) and subretinal fluid (SRF) (red arrow), ruling out sub-RPE haemorrhage (**H**).

than 10 µm) and FT (more than 16 µm) in both naïve and resistant anti-VEGF nAMD eyes after the first faricimab injection. However, we should be cautious to interpret these findings, as a reduction in anatomical thickness may not necessarily be relevant to the long-term functional outcome [33].

We also observed a complete resolution of SRF and IRF at one month in 6 of the 8 eyes and 1 of the 3 eyes, respectively. It is known that IRF is associated with worse visual results in nAMD patients and with higher rate of atrophy and fibrosis [33]. Thus, despite our hopeful results, they must be valued in long term.

Drusenoid PED pathogenesis and its implication in nAMD is still unknown but it is though that they are associated with an increased risk of advanced AMD with atrophy or fibrosis development [34]. Thus, achieving a flattening or reduction in a PED early in disease might be of benefit. Javaheri et al. demonstrated that one-third of 586 eyes had a flattened PED after an initial ranibizumab injection [35]. Our results are similar, and we observed that 28.57% eyes which had a dPED at baseline achieved a complete flattened dPED at month one after a single injection of faricimab without recurrence. In addition, all eyes with the presence of dPED had at least a partial resolution. We also observed changes in the morphology of dPED, as Rispoli et al. (2021) described with Brolucizumab [36].

An important response with anatomical and functional improvements was noticed in three patients (Cases 1, 10 and 11) who presented with subretinal and/or subRPE haemorrhages at one month after faricimab treatment. Thus, this novel compound may be a useful agent in treating also extensive retinal haemorrhages, subRPE haemorrhages and fibrovascular PED. These are challenging conditions to treat, with limited evidence on the efficacy of available treatments. Of note, Case 11 developed an RPE tear, which is a known and expected potential complication when a PED is significantly elevated and can occur with or without anti-VEGF medication [37]. In this case, the RPE tear was not fovea-involving, and this patient experienced an improvement in vision following treatment with faricimab.

Further studies investigating this specifically would be helpful to see if this observation is confirmed.

In addition, we had the opportunity to compare the different responses to aflibercept and faricimab in different eyes of the same patient (89 y.o. female) (Case 4). The faricimab-treated eye had a better response to treatment and the advantage of intravitreal faricimab injection compared to other could be the greater affinity for VEGF-A in combination with the possibility of neutralizing Ang2, both of which have been implicated in angiogenesis [11, 25, 38–40].

We observed promising outcomes for visual acuity, safety, and central retinal thickness in both naïve and previously treated patients after faricimab injections. In addition, faricimab was well tolerated in all eyes (11 eyes) and no adverse events were observed.

There are several limitations to the study due to its retrospective nature, relatively small sample size and short follow-up. Moreover, we only had three treatment naïve eyes, while most eyes were previously treated with other anti-VEGF injections such as aflibercept or ranibizumab.

Further studies with larger patient numbers, and longer follow-up periods are needed to assess the efficacy of faricimab in nAMD and to help determine the need for loading doses in this patient group.

To the best of our knowledge, this is the first report of independent real-world outcomes looking at efficacy and safety using faricimab in nAMD. Reporting real-world data is indeed essential, as it provides a more comprehensive and practical understanding of how a particular intervention or treatment works in an everyday clinical setting, as highly regulated CTs may not reflect how they perform in real-world settings.

SUMMARY

What was known before

- Faricimab is the first bi-specific antibody approved agent administered via intravitreal injection designed to block both VEGF and angiopoietin-2 (Ang-2) in the treatment of nAMD and diabetic macular oedema (DMO).

What this study adds

- Real-world outcomes showed improvement in BCVA and anatomic parameters at an early timepoint, demonstrating the efficacy and durability of faricimab in nAMD patients.

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AUTHOR CONTRIBUTIONS

All authors contributed to the design, writing, critical review and approval the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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