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ORIGINAL RESEARCH

Evaluating Faricimab in Treatment-Naive Neovascular Age Related Macular Degeneration: A Retrospective Analysis of Real-World Data

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Purpose: To evaluate the efficiency and safety of Faricimab on treatment-naive neovascular age related macular degeneration (nAMD) in a real world UK clinic.

Patients and Methods: This single centre, retrospective note review was conducted on treatment-naive patients with nAMD. The data collected included demographics, best corrected visual acuity (BCVA), central macular thickness (CMT), total retinal fluid (TRF), the presence of intraretinal fluid (IRF) and subretinal fluid (SRF).

Results: A total of 66 eyes from 62 patients were analysed. The average age was 77 years (range 36–91) and 54% of patients were female. After the first dose of faricimab, the average BCVA improved by 0.05 LogMAR (+2.5 letters), the average CMT decreased by 65.9µm and 41% of patients were found to be inactive. The follow-up intervals after the third loading dose were divided into 2 subsets of 4 and 8 week extensions. The 4 week extension subset saw a smaller improvement in BCVA (+3 letters) than the 8 week extension (+6 letters) while both had an average decrease in CMT by 86.6 µm. The total retinal fluid decreased by 45% and 70.7%, leaving only 30% and 12.2% residual intraretinal fluid (IRF) and 30% and 24.4% residual subretinal fluid (SRF), respectively. Over a ten-month period, the average number of injections received was 6.6, including 3 initial loading doses. There was only one reported case of an adverse event out of 66 eyes (1/66, 1.5%).

Conclusion: Three loading doses of Faricimab appear efficacious and safe for the treatment of nAMD.

Plain language Summary: What is already known on this topic:

(1) Faricimab is recombinant humanised bispecific IgG monoclonal antibody which binds and neutralises both VEGF-A and angiopoietin-2 (VEGFA and ANG2).
(2) Clinical trials have reported faricimab dosing intervals of up to Q16W.

What this study adds:

(1) To offer a glimpse into real-world effectiveness and safety of faricimab beyond the constraints of a randomised controlled study in treatment naïve nAMD patients.
(2) Presents results derived from implementing a "Treat and Extend" algorithm with faricimab in nAMD management, showcasing its beneficial impact on the strategic planning and execution of patient care.

How this research may affect research, practice or policy:

- Faricimab should be seen as a viable therapy in treatment-naive patients with nAMD.
- Employing a shortened loading regimen of three doses presents no discernible detriment to treatment efficacy when compared to the established four-dose schedule.

Keywords: treatment-naïve, nAMD, Faricimab, dosing interval

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Introduction

Age-related macular degeneration (AMD) is a significant and increasing public health concern due to an ageing demographic throughout the developed world.[1] Neovascular AMD (nAMD) is an advanced form of this disease, characterised by the abnormal growth of nascent leaky blood vessels beneath the macula, leaking retinal fluid causing vision impairment and, if left untreated, irreversible vision loss.[2] Owen et al, using 2007–2009 UK population data found that the incidence of nAMD was 2.3 per 1000 females and 1.4 per 1000 males, though this was projected to rise.[3] Managing this condition places a substantial strain on resources and healthcare economics, highlighting significant unmet needs. The current standard of care for nAMD is anti-VEGF therapy.[1,2] Recent advancements in treatment modalities have sparked interest in optimising outcomes for patients with nAMD. Among these advancements, faricimab, a novel anti-angiogenic agent, has emerged as a promising therapeutic option.[4]

To date, most of the literature has been reported in switch patients.[5–18] This study focuses on the outcomes of faricimab treatment in a cohort of treatment-naïve nAMD patients in the coastal city of Swansea, Wales. The economic burden and prevalence of this condition coupled with the progressive nature of nAMD, underscore the importance of understanding the real-world efficacy and safety profile of faricimab.

Significance of the Study

The introduction of faricimab has introduced a dual blockade mechanism targeting both vascular endothelial growth factor (VEGF) and angiopoietin-2 pathways.[4] This dual inhibition holds the potential to enhance the durability and efficacy of anti-angiogenic treatment in nAMD. However, real-world evidence specific to treatment-naïve patients in the UK remains limited.

The TENAYA and LUCERNE trials, randomly assigned a faricimab group to receive a 6.0mg intravitreal injection every 4 weeks for a total of 4 injections as their loading protocol.[19,20] The team at Singleton Hospital, Swansea has instead formulated a protocol using a total of 3 injections over an 8 week period for loading before applying the standard treat and extend (T&E) algorithm which consists of extensions in 4 week increments or contractions in 2 week increments dependent on the status of the macula.

Understanding the outcomes in this population was crucial for optimising treatment strategies and improving long-term visual outcomes. This study aims to contribute valuable insights to the growing body of evidence surrounding faricimab's effectiveness and safety, with implications for clinical practice and decision-making.

In the subsequent sections, we detail the methodology, results, and discussions that form the backbone of our investigation into faricimab treatment in treatment-naïve nAMD patients in Swansea, shedding light on the practical implications of this novel therapeutic approach.

Material and Methods

Study Design

This study is a single-centre retrospective analysis conducted to investigate the outcomes of a Treat and Extend (T&E) Farcimab algorithm for patients with neovascular AMD.

Data Collection

Patient Selection

The study included patients from Singleton Hospital, Swansea's medical retina unit who underwent treatment for choroidal neovascular membrane between December 2022 and October 2023. The inclusion criteria encompassed all patients diagnosed with neovascular AMD who had not previously received anti-VEGF treatment. Patients who were not treatment-naïve were excluded. No additional exclusion criteria were applied to better reflect real-world conditions.

Data Sources

The data were extracted from patient case notes and Optical Coherence Tomography (OCT) scans. The key parameters assessed included:

Best Corrected Visual Acuity, (BCVA, EDTRS letters)

Central Macular Thickness (CMT, µm)
Total Retinal Fluid (TRF)
Presence of Intraretinal Fluid (IRF) and Subretinal Fluid (SRF).

Diagnosis

Patients underwent a meticulous assessment involving a comprehensive review of medical history and thorough examination within the dedicated rapid access clinic for wet age-related macular degeneration. Standard diagnostic procedures, including visual acuity testing, Optical Coherence Tomography (OCT), and OCT-Angiography, were conducted to ascertain the presence of neovascular AMD. If the presence of nAMD was called into question a fluorescein angiogram was performed.

Injection Protocol

Following the establishment of a diagnosis for neovascular age-related macular degeneration (nAMD) patients were enrolled in the "treat and extend" injection algorithm for faricimab, as illustrated in Figure 1.

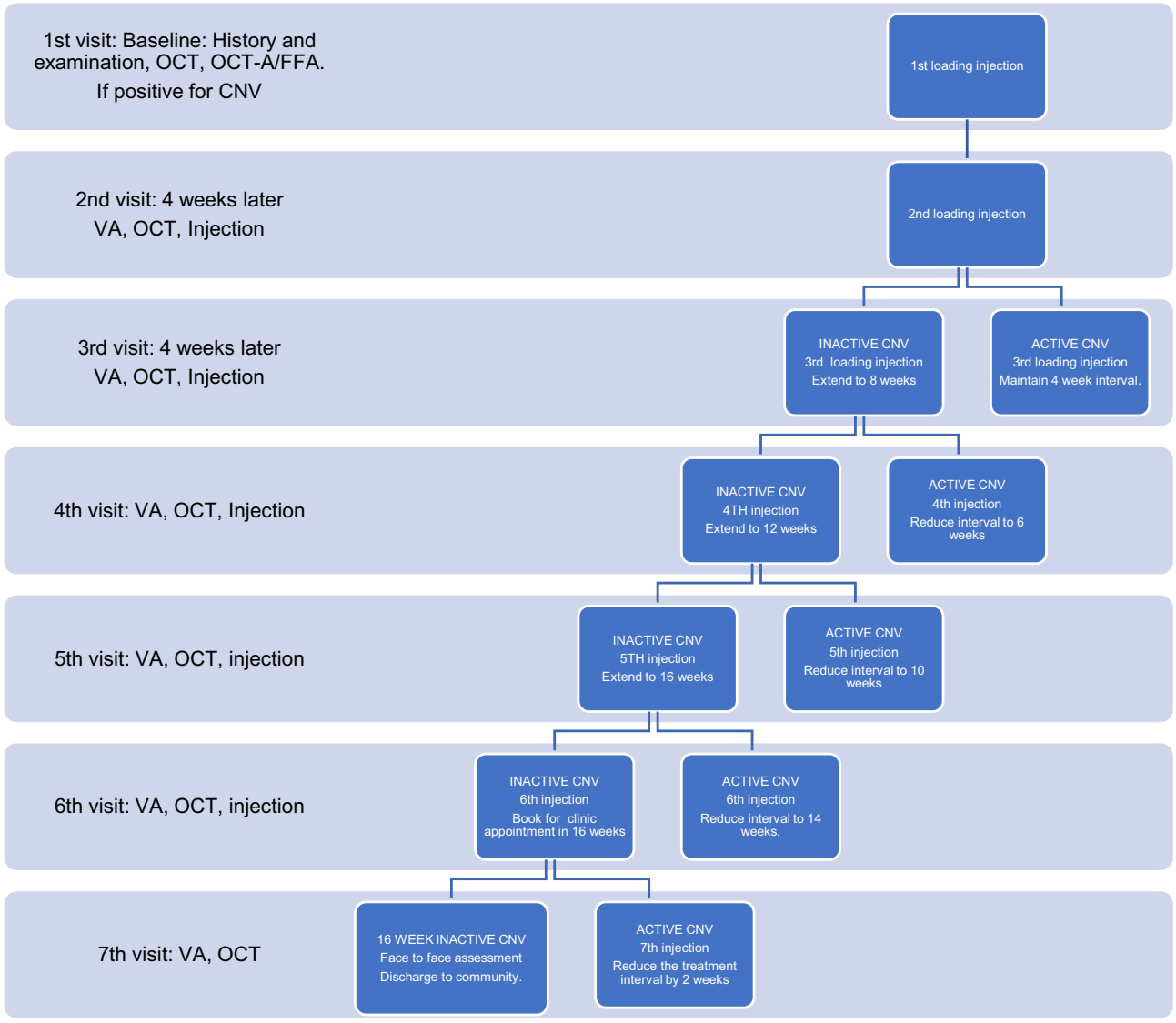

Figure 1 Treat and Extend algorithm and discharge guidelines for the use of Faricimab in neovascular age related macular degeneration n(AMD). Where ACTIVE CNV is defined by the presence of new or residual intraretinal and/or subretinal fluid and new haemorrhages, INACTIVE CNV is characterized by a dry macula, resolving old haemorrhage, and resolving intraretinal and subretinal fluid. Fluid that remains unchanged for 3 consecutive visits may be considered inactive and eligible for trial extension of the treatment interval.

Monitoring

Regular patient monitoring comprised assessments of Best-Corrected Visual Acuity (BCVA), OCT scans, and a meticulous review of case notes conducted during each visit.

Discharge

Upon receiving their 16-week injection, patients who demonstrated inactivity were subjected to a subsequent review after an additional 16 weeks. If this assessment confirmed sustained inactivity, patients were discharged to the community for ongoing follow-up.

Data Analysis

Descriptive statistics were used to summarise patient demographics, baseline characteristics, and treatment outcomes. Changes in BCVA, CMT, and the presence of IRF and SRF were analysed over the course of the study period. The number of injections and the treatment interval periods were reviewed as secondary outcomes. For VA and CMT, statistical significance were assessed comparing to baseline using paired *T* Test. Statistical analyses were performed using Excel.

Ethical Considerations

This retrospective study adhered to ethical guidelines, including patient confidentiality and data anonymisation. A joint decision, within the Research and Development (R&D) department, by the Joint Study Review Committee (JSRC) and the R&D director declared this exercise as "non-research" and therefore a R&D and NHS Research Ethics Committee (REC) application was not required.

This study complies with the Declaration of Helsinki.

Results

In this study, there were 66 eyes from 62 patients. Two patients (contributing a total of 3 eyes) died of natural causes during the loading dose phase and were excluded from analysis.

Baseline characters are shown in Table 1. 66 eyes with nAMD received three loading doses of Faricimab for disease control.

Figure 2A-E shows the change in VA, CMT, TRF, residual IRF and SRF over the course of 3 faricimab injections. After the first dose of faricimab the average BCVA improved by 0.05 LogMAR (+2.5 letters), the average CMT

Table 1 Baseline Demographic and Clinical Characteristics of Treatment-Naive nAMD Patients

Number of Eyes	66
Age (years, range)	77 ±10
Male:Female	46:54
Ethnicity	95.5% White/Welsh/British; 4.5% were other
Diagnosis	87.3% by OCTA, 5.6% by FFA/ICG and 7.0% OCT alone
Lesion type	60 eyes: Type 1 and Type 2
	6 eyes: Peripapillary CNV
Vision (LogMAR, letters)	0.53 ± 0.29, 26.5 letters
CMT (μm)	313.1 ± 76.6
Total fluid present (%)	100
IRF (%)	71.2
SRF (%)	86.4

Abbreviations: nAMD, neovascular age related macular degeneration; CMT, central macular thickness; IRF, intraretinal fluid; SRF, subretinal fluid; CNV, choroidal neovascular membrane; OCTA, optical coherence tomography angiography; FFA, Fundus fluorescein angiography; ICG, Indocyanine Green Angiography; OCT, optical coherence tomography.

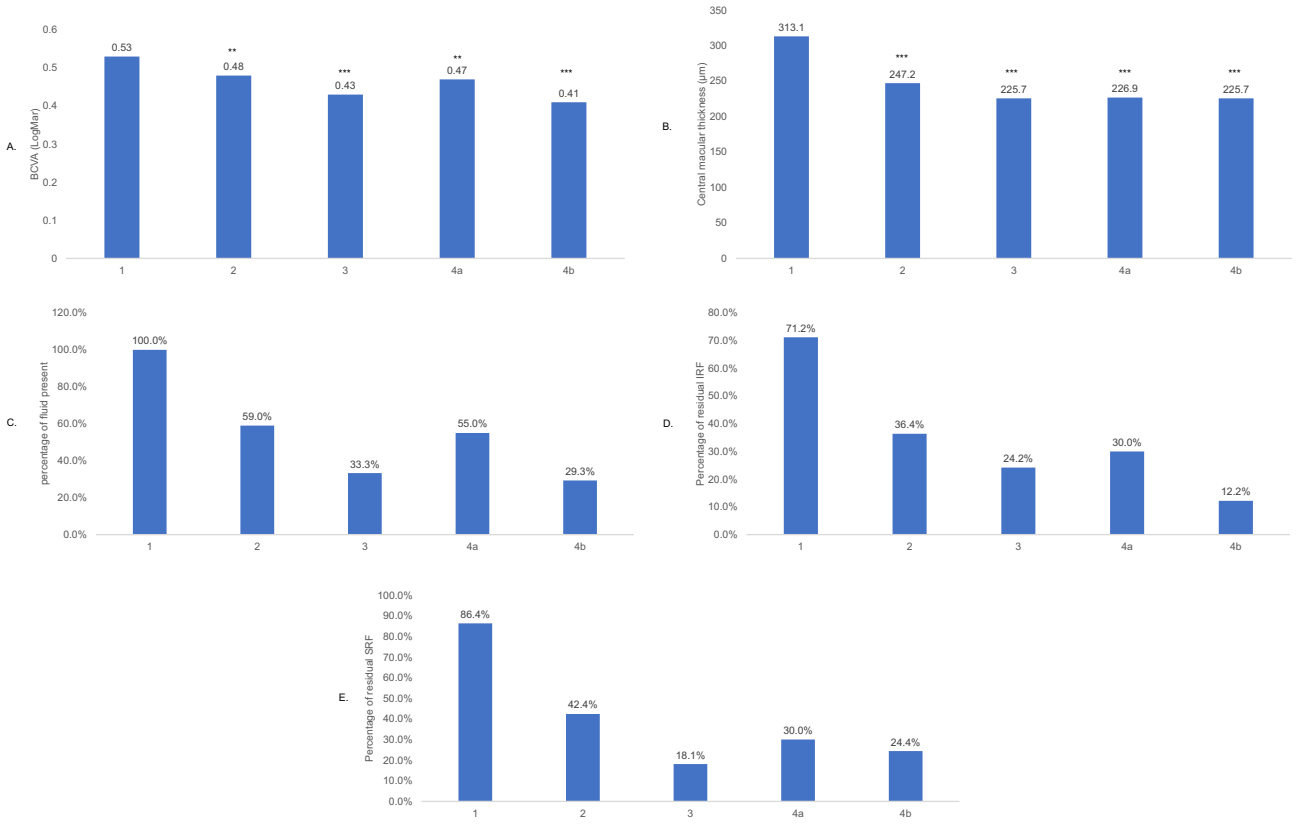

Figure 2 Efficacy of Faricimab over the course of 3 loading injections. (**A**) Change in the best corrected visual acuity (BCVA), (**B**) Change in the central macular thickness (CMT), (**C**) Change in the percentage of total retinal fluid (TRF) present, (**D**) Change in the intraretinal fluid (IRF) and (**E**) Change in the subretinal fluid (SRF). Timeline: 1, baseline week 0; 2, 4 weeks following the 1st loading injection at week 4; 3, 4 weeks following the 2nd loading injection at week 8; At the extension phase: 4a, 4 weeks following the 3rd loading injection at week 12; 4b, 8 weeks following the 3rd injection at week 16. ***p<0.001, **p<0.01 compared to baseline.

decreased by 65.9µm and 41% of patients were found to be inactive. After the 3rd loading injection, eyes were assigned into either a 4 week extension group (12 weeks from baseline) or an 8 week extension group (16 weeks from baseline) depending on their activity. For both BCVA and CMT, there was a statistically significant improvement (0.12 LogMar, +6 letters and −87.4µm) during loading which was maintained in the 8 week extension group while there was a smaller improvement from baseline (0.06 LogMar, +3 letters and 86.2µm) in the 4 week extension group, (Figure 2A and B). For the TRF, IRF and SRF groups (Figure 2C–E) there was a decrease in fluid during loading which increased in the 4 week group but was maintained in the 8 week group. The total retinal fluid decreased by 45% and 70.7%, leaving only 30% and 12.2% residual intraretinal fluid (IRF) and 30% and 24.4% residual subretinal fluid (SRF), respectively.

At week 8, when the patients received their third and final loading dose, the patients were assigned their treat and extend intervals based on their fluid status. (Figure 3). Figure 3A, illustrates the results of the first dosing interval extensions post disease control. 33% of eyes remained on a 4 week treatment interval, 3% were extended to 6 weeks (in error, according to the department's aflibercept pathway) and 64% were extended to 8 weeks. By the 4th injection post disease control, the percentage of patients with a 4 week interval decreased to 14% and the percentage with dosing intervals of ≥10 weeks was 42% (Figure 3B). By the 3rd stage of interval extension, the percentage of patients with a 4 week interval increased slightly to 16% but the percentage with dosing intervals of ≥10 weeks increased further to 55% (Figure 3C). Of particular note, 24% of patients achieved a 16 weeks dosing interval.

In total, 28.8% of eyes were able to extend out to 16 weeks during the period. 5% occurred at the 4th injection, 74% of which occurred by the 5th injection and a further 16% and 5% occurred by the 6th and 7th injections respectively.

For the 19 eyes who achieved a 16 week interval, 16, (84%) were neovascular AMD types 1 and 2 while 3 (16%) were peripapillary CNV. They had an average of 5.4 (Range 4–7, including injections at loading) injections. The BCVA at the 5th injection for those 14 eyes was 0.49 ± 0.42 LogMAR and the average CMT 211.8 ± 33.6µm. 4 eyes had

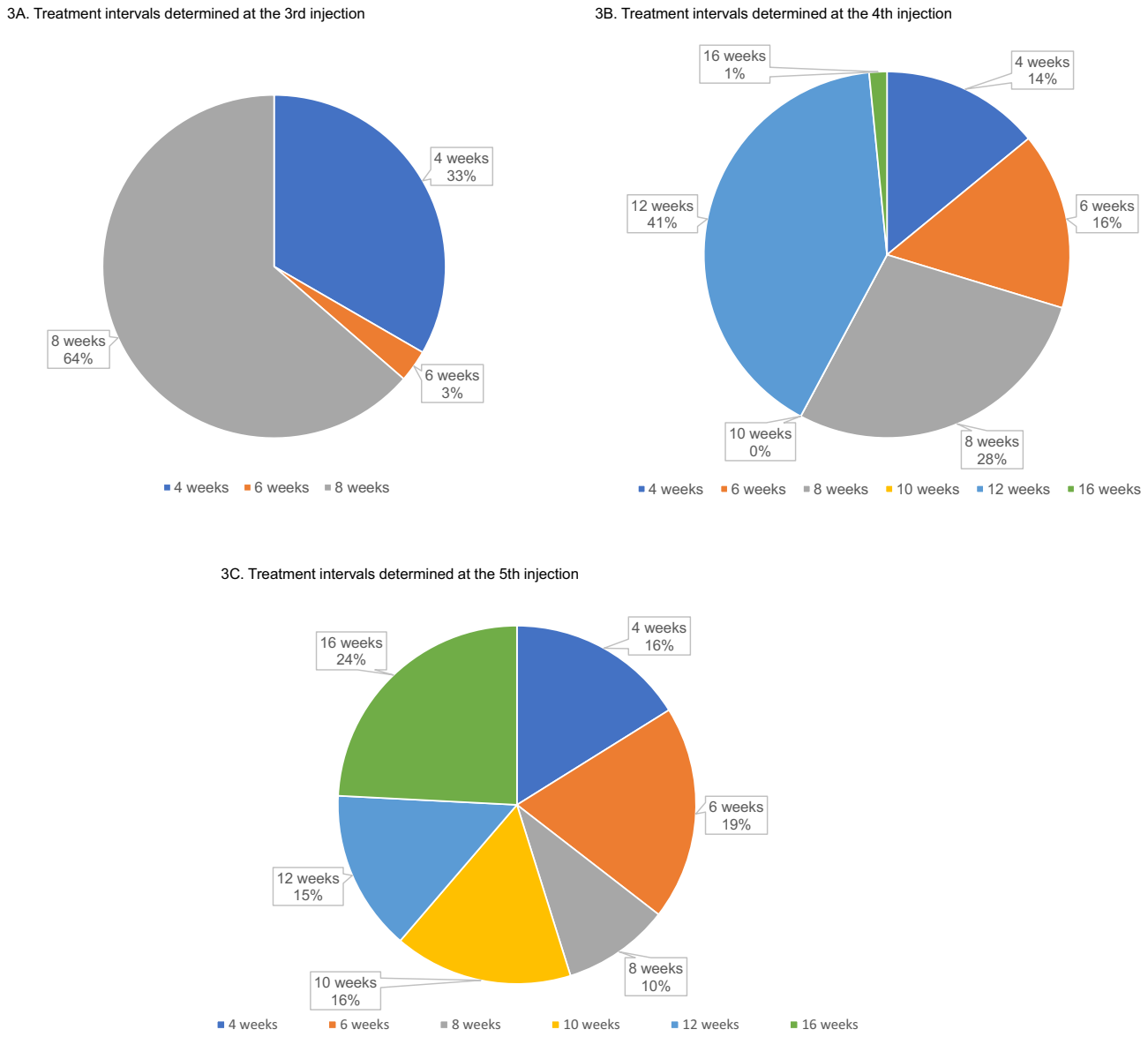

Figure 3 Pie charts illustrating the treatment intervals determined by the (**A**) third, (**B**) fourth and (**C**) fifth Faricimab injections. Represented by percentages.

a 16 week follow-up within the time period review where 3 continued to be inactive (dry). One patient was noted to have subretinal fluid and redefined as active/wet.

Finally, during the review period, the majority of eyes 24.2%, 30.3%, 21.2% received 5, 6 and 7 respectively to attain inactivity (Figure 4). While 1 patient (1.5%) needed as many as 11 injections. (see Figure 4) Of the two eyes recorded to have received 4 injections, one had its interval extended early to 16 weeks after the 4th injection, while the other did not attend its injection appointments. Additionally, one eye that received 3 injections was diagnosed and commenced treatment later than its fellow eye. The average number of injections with loading was 6.6 (3.6 injections without loading).

One patient experienced an adverse event after their seventh injection of Faricimab, presenting with vitritis and increased intraocular pressure. These issues were managed appropriately and reported via the Yellow Card scheme. Despite the adverse event, this patient was included in the subset that maintained a four-week treatment interval. There were no reported cases of retinal vasculitis or retinal occlusive vasculitis.

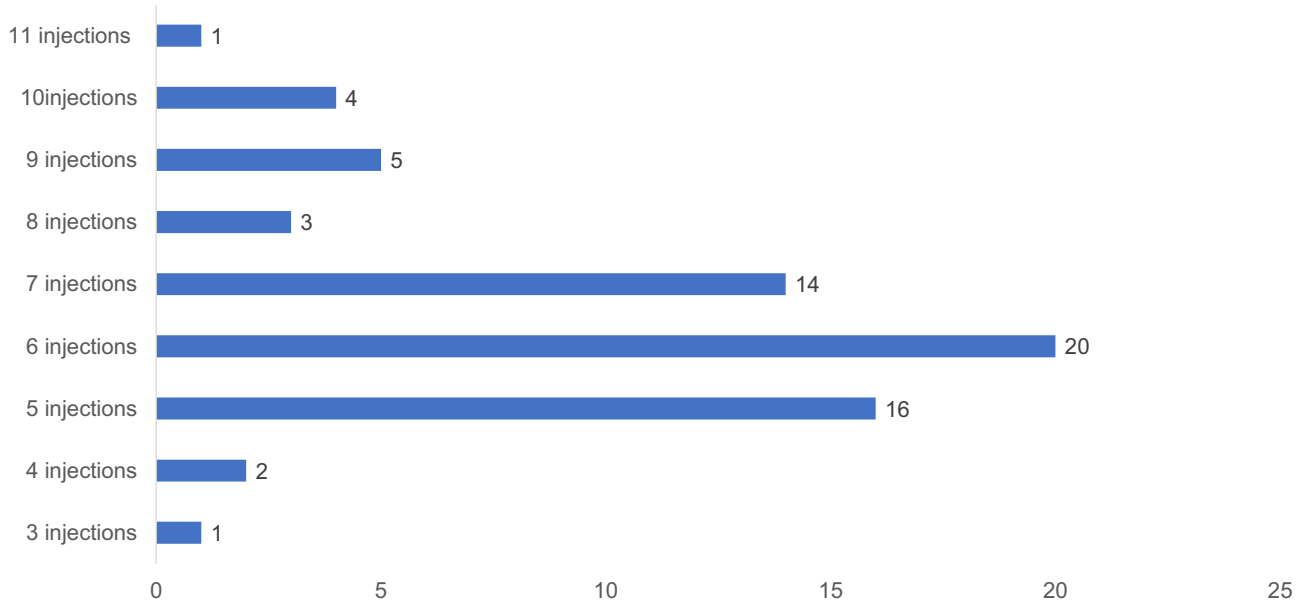

Figure 4 Graph depicting the total number and frequency of Faricimab injections received during the observed period.

Discussion

We retrospectively investigated the outcomes of 66 treatment-naive nAMD eyes injected with faricimab. Our initial data suggests that faricimab can provide adequate disease control (defined as fluid resolution) in treatment-naive nAMD patients and provide treatment extensions of up to 16 weeks.

Currently, anti-VEGF therapy is the standard of care for nAMD patients.[1] Data suggests that the additional inhibition of ANG2 may provide extra disease control (Regula et al 2016) and real-world evidence is emerging, suggesting that binding to ANG2 may improve disease control in nAMD patients.[5–18]

The data obtained with our naïve patients are comparable to those obtained in the Phase III trials TENAYA and LUCERNE.[19,20] We obtained similar changes in BCVA from baseline (5.8 and 6.6 letters respectively vs 6 letters). In addition, the decrease in CMT and decrease in SRF and IRF (28% vs 35%) were similar at week 8, 4 weeks after the second loading injection. A notable difference was observed in the percentage of patients able to achieve dosing intervals of more than 12 weeks and 16 weeks. In our study, fewer individuals reached these extended dosing intervals compared to the trial results. One potential reason is that our protocol utilised 3 loading injections, whereas the trial employed 4 loading injections. The additional loading dose in the trial may provide better disease control, enabling more patients to achieve longer dosing intervals. Furthermore, we implemented the option to consider both 2-week and 4-week extension intervals, which were not part of the trial protocol. This flexibility in dosing adjustments could influence the variability in dosing intervals observed among patients in our study compared to the trial. Nevertheless, by the 5th injection we achieved interval extensions of 39% >12 week and 24% at 16 weeks. Further, our study was able to identify those eyes that maintained a 4 week interval due to persistent activity while extending those eyes that responded well to the drug earlier. Of particular interest is the rate at which we achieved longer dosing intervals after 4 and 5 injections. This aligns with the rapid drying ability of faricimab, where 75% of nAMD patients achieved a dry retina after 2 injections.[21]

Our study is also comparable with emerging real-world studies. FARWIDE is the real world national UK Medisoft study.[22] In comparison to a recent report, after 5 injections, we observed a higher number of patients with dosing intervals <8 weeks (13% vs 35%) but had a higher percentage of patients with intervals ≥12 weeks (24% vs 39%).[23,24] Two Japanese studies, Mukai et al and Matsumoto, reported that 80% of eyes were dry at month 3, whereas in our study, the dryness rate was 45.5%.[23,24] In four studies involving treatment-naïve nAMD patients, including Mukai et al, Matsumoto, Cheng et al, and Stanga et al, all reported improvements in best-corrected visual acuity (BCVA) and improvements in retinal anatomy similar to our study findings.[7,10,23,24]

We compared the mean number of injections administered in our clinic over a similar period with other anti-VEGF agents, using a comparable protocol for treating nAMD patients. According to a 2020 audit, our average was 8.4 injections per year for aflibercept. This is consistent with findings by Jaggi et al, who reported an average of 8.1 ± 2.0 injections per year.[25] These results suggest that treating patients with faricimab (average 6.6 injections) in a real-world UK clinic, using a pathway with three four-weekly loading doses, is not only efficient in terms of capacity but also cost-effective. This approach facilitates quick drying of nAMD with fewer visits to the medical retina clinic and rapid extensions of treatment intervals. We believe that no other real-world data demonstrates such rapid extension of treatment in a treat-and-extend protocol, resulting in decreased total retinal fluid and stable visual outcomes.

Safety

The safety of any new medicine has been at the front of clinicians and patients concerns in the last 3–4 years.[26–31] The safety profile of Faricimab (total AEs, SAEs, ocular AEs, ocular AEs associated with anti VEGF therapy and number of patients with >1 IOI event) was shown to be comparable to aflibercept 2mg in TENAYA and LUCERNE.[31] Of particular interest, there were no cases of retinal vasculitis or retinal occlusive vasculitis. Moreover, real-world data have also suggested faricimab safety profile is acceptable.[32,33] In line with this, we only experienced 1 AE in our patient cohort.

Limitations

Limitations of this study include its retrospective nature, potential selection bias, limited racial and ethnic diversity, and reliance on available case notes and OCT data.

Conclusion

Faricimab should therefore be seen as a viable therapy in nAMD treatment-naive patients, and adhering to three loading doses as opposed to four does not impede a successful outcome.

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Disclosure

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