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Intraocular Inflammation, Safety Events, and Outcomes After Intravitreal Injection of Ranibizumab, Aflibercept, Brolucizumab, Abicipar Pegol, and Faricimab for nAMD

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Abstract

Purpose: To compare the rates of intraocular inflammation (IOI) in patients with neovascular age-related macular degeneration (nAMD) after injection of intravitreal (IVT) antivascular endothelial growth factor drugs. **Methods:** This study included all phase 3 randomized clinical trials of patients with nAMD treated with ranibizumab, aflibercept, brolucizumab, abicipar pegol, or faricimab. The outcomes assessed were the incidence of IOI, retinal artery occlusion (RAO), retinal vasculitis and choroiditis, endophthalmitis, and serious systemic adverse events (AEs) as well as the change in visual acuity (VA) (Early Treatment Diabetic Retinopathy Study letters) and in central retinal thickness (CRT). **Results:** Abicipar pegol was associated with a higher incidence of IOI than aflibercept, ranibizumab, faricimab, and sham injections, while brolucizumab was associated with a higher rate of IOI than aflibercept, faricimab, and sham injections. Abicipar pegol was also associated with a higher rate of endophthalmitis than aflibercept. Significantly more retinal vasculitis and choroiditis was seen with abicipar pegol and brolucizumab than with ranibizumab and aflibercept, respectively, and RAOs occurred more frequently with abicipar pegol and brolucizumab than with ranibizumab and aflibercept, respectively. There were no differences in the change in VA among the drugs. Treatment with brolucizumab resulted in a greater change in CRT than with abicipar pegol, aflibercept, ranibizumab, and faricimab, while treatment with faricimab resulted in a greater change in CRT than aflibercept and ranibizumab. Faricimab was associated with fewer serious systemic AEs than aflibercept. **Conclusions:** Abicipar pegol and brolucizumab were associated with a higher incidence of ocular AEs in phase 3 randomized controlled trials. The potential benefits of these drugs should be weighed against the AEs.

Keywords

neovascular age-related macular degeneration, intravitreal anti-VEGF injection, intraocular inflammation, uveitis, occlusive vasculitis

Introduction

Approximately 5.9 to 7.9 million intravitreal (IVT) antivascular endothelial growth factor (anti-VEGF) injections are performed in the United States annually.[1–3] Multiple drug options exist for the treatment of neovascular age-related macular degeneration (nAMD). In 2015, aflibercept (Eylea; Regeneron) comprised 32% of injections and ranibizumab (Lucentis, Genentech/Roche) comprised 26% of injections.[1] Despite the widespread use of anti-VEGF injections for the treatment of nAMD, there is concern about the adverse inflammatory events associated with these medications.

Brolucizumab 6 mg (Beovu, Novartis) was approved by the US Food and Drug Administration (FDA) on October 8, 2019. Postmarketing surveillance found cases of severe vision loss from intraocular inflammation (IOI) and occlusive retinal vasculitis.[4–7] The American Society of Retina Specialists Research and Safety in Therapeutics Committee reported a 0.07% incidence of severe IOI and occlusive retinal vasculitis with vision loss.[5–7] As a result, some ophthalmologists called for a moratorium on its use.[8]

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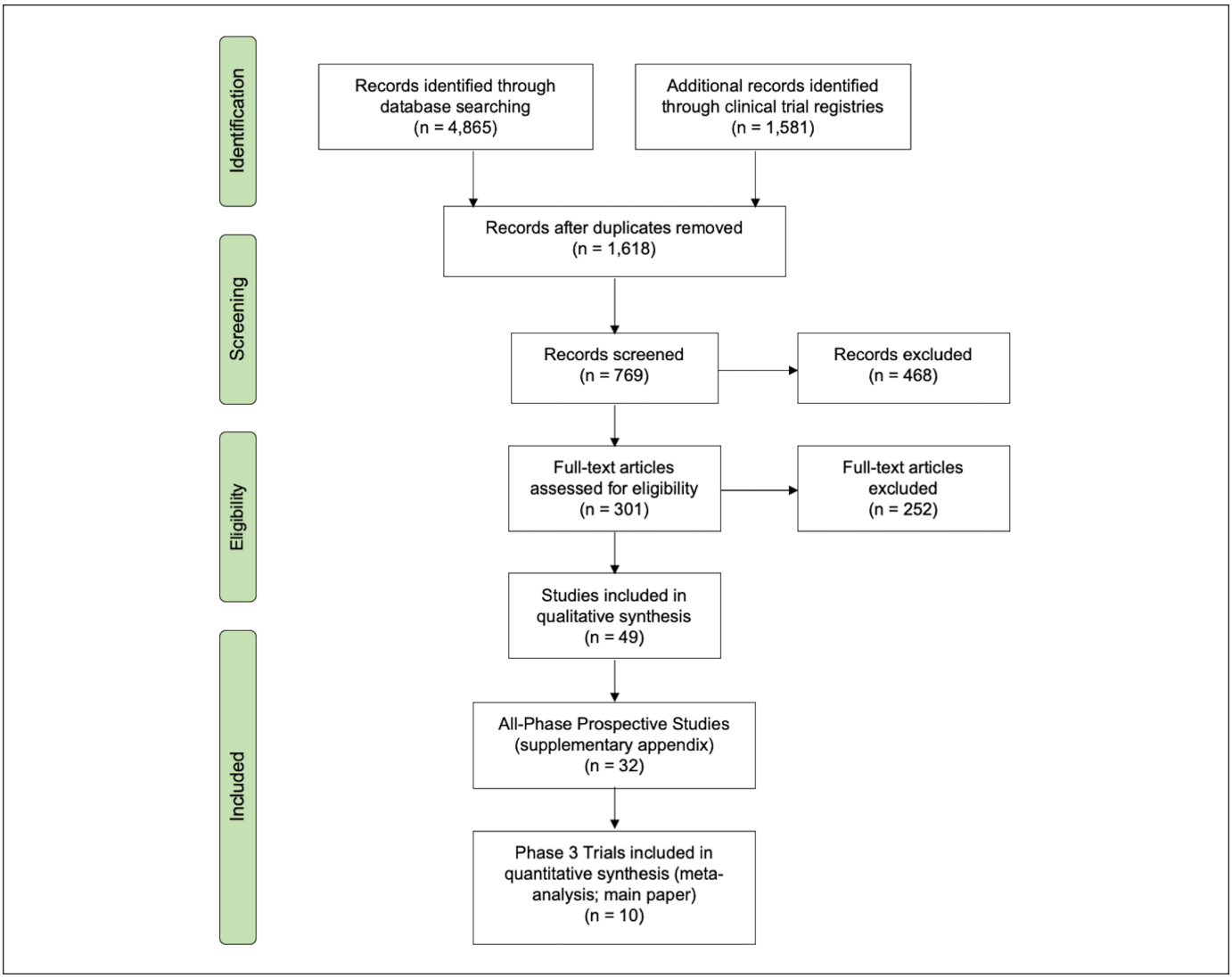

Figure 1. Study flow diagram of reports screened, included, and excluded.

Abicipar pegol (Allergan) failed to receive FDA approval in 2020 because of an unfavorable risk-to-benefit ratio, including a 15.4% incidence of IOI and a 1.7% incidence of severe vision loss. Improvements in manufacturing reduced the incidence of IOI to 8.9%.[9] On January 28, 2022, faricimab 6 mg (Vabysmo, Genentech/Roche) was approved by the FDA for nAMD.[10] Like the other medications, faricimab inhibits VEGF-A. It also neutralizes angiopoetin-2, reducing vascular permeability. The fragment crystallizable (Fc) domain was engineered to avoid binding with neonatal Fc and Fcγ receptors, decreasing faricimab's systemic half-life and theoretically reducing inflammation.[11,12]

Methods

This study was conducted between June 15, 2020, and March 1, 2022. PubMed, MEDLINE, PubMed Central, EMBASE, and ClinicalTrials.gov were searched for "neovascular age-related macular degeneration AND ranibizumab OR bevacizumab OR aflibercept OR brolucizumab OR abicipar OR faricimab". Institutional review board approval and informed consent were not required for this meta-analysis of published and publicly available randomized controlled trials with de-identified data. This study complied with the US Health Insurance Portability and Accountability Act of 1996 and conformed to the tenets of the Declaration of Helsinki.

Of 1618 potential trials identified, 769 were screened and 301 met the initial eligibility criteria and were carefully reviewed. From these 301 trials, 99 were included in the qualitative synthesis of this study. A quantitative network meta-analysis was performed on 10 phase 3 randomized controlled trials (Figure 1).[10,13–23] Bevacizumab was not included in our analysis because no studies focusing on this drug were phase 3 randomized controlled trials. The risk for bias was assessed (Table 1).

Table 1. Risk for Bias and Quality of Data on Ocular and Adverse Events from Phase 3 Clinical Trials for nAMD.

		Risk for Bias								
Clinical Trial	Drug	Random	Alloc	Part Mask	Mask Assess	IOI	Endoph	RVC	RAO	All SSAE
MARINA	Rani vs Sham	+	?	+	+	H	H	M	M	L
ANCHOR	Rani vs PDT	+	?	+	+	H	H	M	M	H
VIEW 1	Aflib vs Rani	+	+	+	+	H	H	L	L	H
VIEW 2	Aflib vs Rani	+	+	+	+	H	H	L	L	H
HAWK	Brolu vs Aflib	+	+	+	?	H	H	H	H	H
HARRIER	Brolu vs Aflib	+	+	+	?	H	H	H	H	H
CEDAR	Abic vs Rani	+	+	+	+	H	H	H	H	H
SEQUOIA	Abic vs Rani	+	+	+	+	H	H	H	H	H
TENAYA	Faric vs Aflib	+	?	+	?	H	H	H	M	H
LUCERNE	Faric vs Aflib	+	?	+	?	H	H	H	M	H
Overall quality grade	—	—	—	—	—	H	H	M	M	H

Abbreviations: Abic, abicipar pegol; Aflib, aflibercept; Alloc, allocation concealment (selection bias); Brolu, brolucizumab; Endoph, endophthalmitis; Faric, faricimab; H, high-quality data provided by the study; IOI, intraocular inflammation; L, low-quality or no data provided by the study; M, moderate-quality data provided by the study; Mask Assess, masking of outcome assessment, meaning the data analysts were masked (detection bias); nAMD, neovascular age-related macular degeneration; Part Mask, participant masking of both physicians and patients (performance bias); PDT, photodynamic therapy with verteporfin; Random, randomization (selection bias); Rani, ranibizumab; RAO, retinal artery occlusion; RVC, retinal vasculitis or choroiditis; SSAEs, serious systemic adverse events; +, performed by the trial to mitigate bias; ?, unclear whether performed by trial.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to assess the incidence of IOI, vasculitis, retinal artery occlusion (RAO), other ocular and systemic adverse events (AEs), and anatomic and functional outcomes after IVT injections of ranibizumab, aflibercept, brolucizumab, abicipar pegol, faricimab, and sham injections. Sham injections were performed by applying pressure to the eye at the typical injection site with the hub of a syringe but no needle. Data on sham injections were included when available.

Comprehensive data were abstracted, including demographics, treatment status, the baseline best-corrected visual acuity (BCVA) assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, the change in ETDRS letters, the baseline central retinal thickness (CRT) on optical coherence tomography, and the change in CRT, among other variables. The main outcome measure was the incidence of IOI, as defined by each study; IOI did not include infectious endophthalmitis. The incidence was calculated as the number of events per patient over the entire study period for which data could be obtained. Secondary ocular AEs included the incidence of endophthalmitis, retinal vasculitis or choroiditis, RAO, and all serious systemic AEs.

Randomized controlled trials and corresponding online supplemental data were carefully assessed for quality. A high-quality grade ("H") reflected high confidence in the comprehensiveness of the dataset for the particular outcome. A moderate-quality grade ("M") indicated an incomplete dataset or moderate confidence in the comprehensiveness of data. A low-quality grade ("L") was given if there were no available data or there was no mention of the particular outcome. All trials reported on IOI. If a trial reported on "all" or "serious" ocular AEs but did not specifically mention "endophthalmitis," "retinal vasculitis or choroiditis," or "retinal artery occlusion," these outcomes were included in the analysis for that trial, assigned a value of zero, and given a data-quality grade of "L."

Descriptive statistics were computed. Statistical analysis was performed using SPSS software (version 27, SPSS Inc) and R software (version 4.0.2, R Project for Statistical Computing). A Bayesian network meta-analysis was performed to compare the incidence of (1) IOI, (2) retinal vasculitis, (3) RAO, and (4) serious systemic AEs among all drugs and sham injections as well as (5) the change in BCVA and (6) the change in CRT. Measures of association were reported as risk ratios for outcomes 1 through 4 and treatment differences for outcomes 5 and 6, and 95% credible intervals (Bayesian CIs) were reported for each measure. Operationally, Bayesian estimation proceeds with Markov chain Monte Carlo sampling methods. Three chains of 20 000 iterations each were performed.[24] Given the inherent sampling in this algorithm, rank probabilities for each drug were computed and, based on clinical trial data, the relative safety and efficacy of each anti-VEGF agent were compared. All mean values are ± SD.

Results

Risk for Bias and Quality of the Data

Clinical trials and accompanying online supplemental data were assessed for the risk for bias and quality of data (Table 1). All trials were phase 3 randomized controlled trials; randomization mitigated selection bias and masking mitigated detection bias. The average quality grade of all data was moderate (Table 1).

Table 2. Ocular Adverse and Systemic Events and Outcomes for Phase 3 Clinical Trials for Neovascular AMD.

Parameter	Sham	Ranibizumab	Aflibercept	Brolucizumab	Abicipar	Faricimab
Patient characteristics						
Total number of patients (n)	236	1974	3217	1088	1251	665
Mean injections (n) per patient-year ± SD	12.0 ± 0	11.4 ± 1.9	9.8 ± 2.8	7.9 ± 0.1	6.0 ± 1.4	6.7 ± 0.1
Mean age (y) ± SD	77.0 ± 7.0	76.4 ± 8.4	76.1 ± 8.5	76.1 ± 8.7	76.1 ± 8.3	75.4 ± 8.5
Female, n (%)	159 (66.8)	1500 (57.3)	1842 (57.4)	625 (57.5)	698 (55.5)	394 (59.3)
White, n (%)	231 (97.1)	2343 (93.0)	2735 (85.1)	927 (85.2)	1029 (81.8)	581 (87.4)
Treatment-naïve, n (%)	236 (100)	2573 (100)	3210 (100)	1088 (100)	1251 (100)	665 (100)
Ocular adverse events, n (%)						
Intraocular inflammation	6 (2.5)	62 (3.1)	33 (1.0)	50 (4.6)	211 (16.9)	20 (3.0)
Endophthalmitis	0	16 (0.8)	9 (0.3)	7 (0.6)	17 (1.4)	5 (0.8)
Retinal vasculitis or choroiditis	0	0	0	36 (3.3)	29 (2.3)	1 (0.2)
Retinal artery occlusion	0	0	1 (0.03)	10 (0.92)	12 (0.96)	1 (0.15)
Systemic adverse events, n (%)						
All serious systemic adverse events	—	581 (47.6)	1431 (44.5)	399 (36.7)	514 (41.1)	223 (33.5)
Functional and anatomic outcomes						
Mean baseline ETDRS BCVA ± SD	53.6 ± 14.1	51.8 ± 16.7	56.6 ± 13.9	61.1 ± 13.3	56.6 ± 12.7	60.0 ± 13.3
Mean change in ETDRS letters ± SD	−13.8 ± 18.5	8.3 ± 15.3	7.1 ± 14.6	5.9 ± 14.6	6.9 ± 17.5	4.1 ± 15.6
Mean baseline CRT on OCT (μm) ± SD	—	348 ± 120	363 ± 135	468 ± 168	379 ± 125	357 ± 122
Mean change in CRT on OCT (μm) ± SD	—	−135 ± 104	−139 ± 109	−184 ± 130	−146 ± 98	−151 ± 62

Abbreviations: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography.

Total Intravitreal Injections and Study Drug

This analysis comprised 8574 patients treated with approximately 135 402 IVT injections for nAMD in 10 phase 3 randomized controlled trials. The mean (±SD) age of the patients was 76.16 ± 8.35 years, 86.1% were White, and 57.6% were women.[9,14–19,21,25] Two hundred thirty-six patients were given approximately 5664 sham injections in 1 trial, 1974 patients were treated with approximately 43 539 ranibizumab injections in 6 trials, 3217 patients were treated with approximately 48 643 aflibercept injections in 6 trials, 1088 patients were treated with approximately 15 896 brolucizumab injections in 2 trials, 1251 patients were treated with approximately 15 010 abicipar pegol injections in 2 trials, and 665 patients were treated with approximately 6650 faricimab injections in 2 trials (Table 2). Rates of ocular and systemic AEs were calculated (Table 2 and Supplemental Table 1). Figure 2 shows the network comparisons.

Intraocular Inflammation

There were 383 cases of IOI across all drugs and sham injections (incidence 4.5%). The incidence of IOI was as follows: aflibercept (1.0%), faricimab (3.0%), sham (2.5%), ranibizumab (3.1%), brolucizumab (4.6%), and abicipar pegol (16.9%). Aflibercept (risk ratio, 0.06; 95% CI, 0.01-0.29), ranibizumab (risk ratio, 0.07; 95% CI, 0.03-0.15), faricimab (risk ratio, 0.09; 95% CI, 0.02-0.47), and sham (risk ratio, 0.03; 95% CI, 0.01-0.09) were less associated with IOI than abicipar pegol. There was significantly less IOI associated with aflibercept (risk ratio, 0.23; 95% CI, 0.1-0.51), faricimab (risk ratio, 0.32; 95% CI, 0.1-0.93), or sham (risk ratio, 0.1; 95% CI, 0.02-0.54) than with brolucizumab, and the incidence of IOI was less associated with sham injections than with ranibizumab (risk ratio, 0.37; 95% CI, 0.13-0.92) (Figures 3A and 4, and Supplemental Table 2a). The quality of the data was high (Table 1).

Retinal Artery Occlusion

Across all phase 3 clinical trials, the incidence of RAO was as follows: sham injection (0%), ranibizumab (0%), aflibercept (0.03%), faricimab (0.15%), brolucizumab (0.92%), and abicipar pegol (0.96%). From the adjusted analysis, the incidence of RAO was significantly less associated with ranibizumab than with abicipar pegol (risk ratio, 0; 95% CI, 0-0.15) (Figures 3B and 4, and Supplemental Table 2b), and RAO was less associated with aflibercept than with brolucizumab (risk ratio, 0.12; 95% CI, 0.01-0.74). The quality of the data was moderate (Table 1).

Retinal Vasculitis or Choroiditis

The incidence of retinal vasculitis or choroiditis was as follows: sham injection (0%), ranibizumab (0%), aflibercept (0%), faricimab (0.2%), abicipar pegol (2.3%), and brolucizumab (3.3%). From the adjusted analysis, the incidence of retinal vasculitis or choroiditis was significantly less associated with ranibizumab than with abicipar pegol (risk ratio, 0; 95% CI, 0-0.02). In addition, retinal vasculitis or choroiditis was significantly less associated with aflibercept than with brolucizumab (risk ratio, 0; 95% CI, 0-0.03) (Figures 3C and 4, and Supplemental Table 2c). The quality of the data was moderate (Table 1).

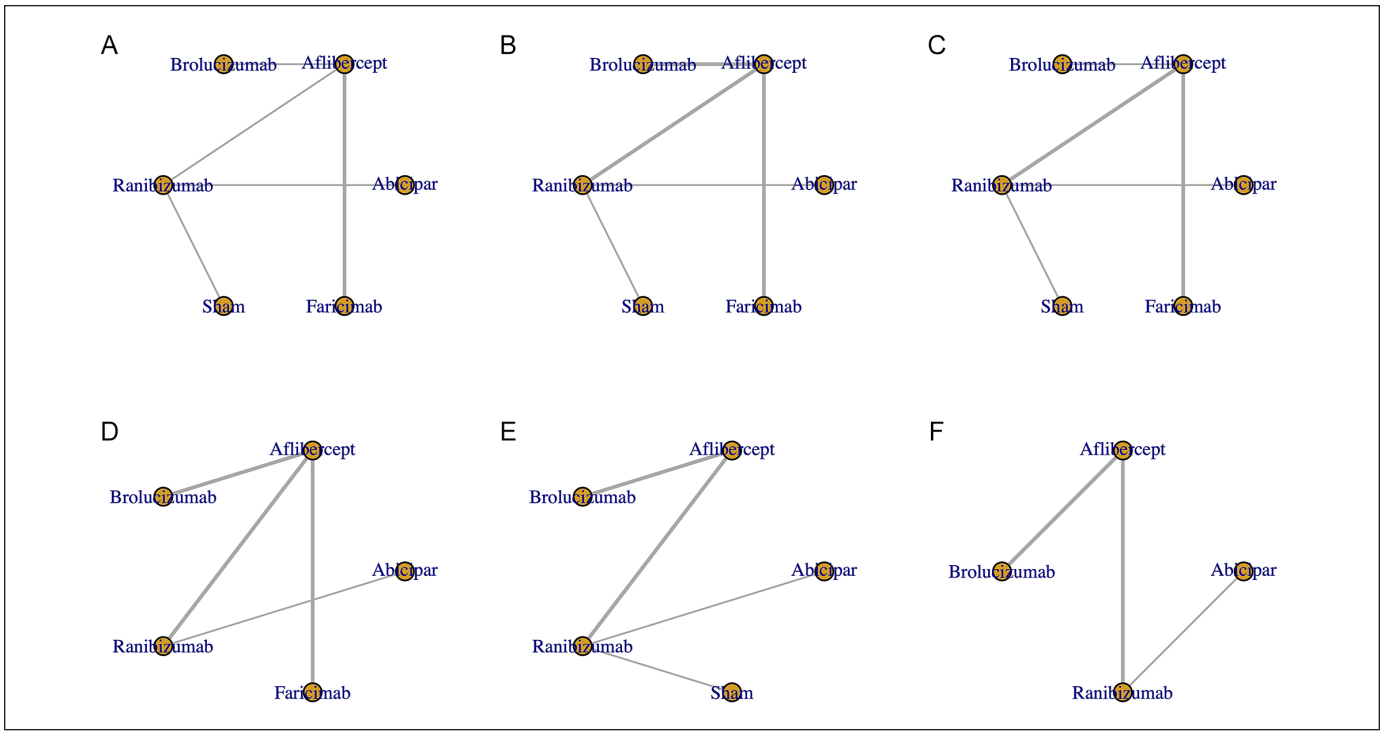

Figure 2. Visual representation of drug-study linkages. Network graphs show adverse events, including (A) intraocular inflammation, (B) retinal artery occlusion, (C) retinal vasculitis, and (D) serious systemic adverse events, as well as (E) visual acuity outcomes and (F) central retinal thickness outcomes. Each node (orange circle) represents 1 drug. The size of the node is proportional to the number of patients randomized to that drug. The lines represent direct comparisons; that is, when there is a line connecting 2 drugs, those 2 drugs have been directly compared with one another in a trial. The width of the line is proportional to the number of trials with direct comparisons between the 2 drugs. The total number of trials was 10. The maximum number of patients contributing to a given network was 8574.

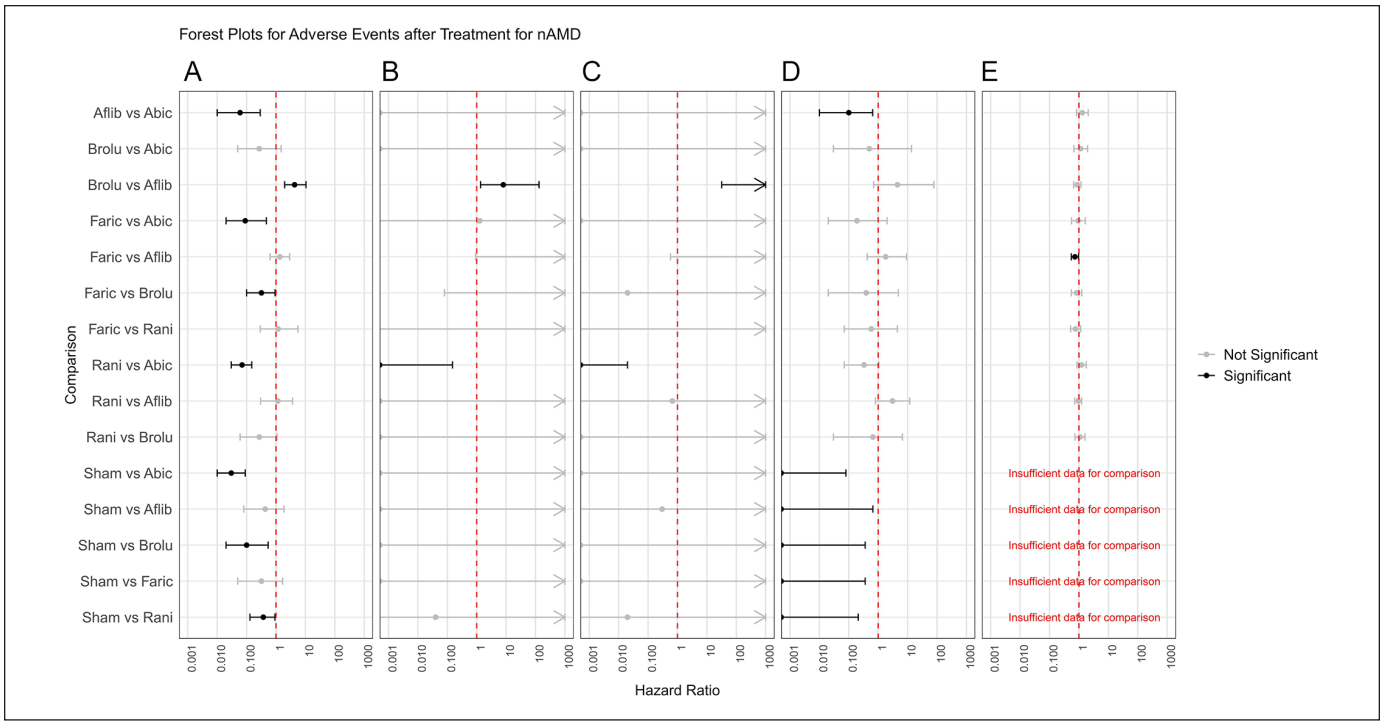

Figure 3. Network meta-analysis with forest plots for adverse events after treatment for nAMD. (A) Intraocular inflammation. (B) Retinal artery occlusion. (C) Retinal vasculitis. (D) Endophthalmitis. (E) Serious systemic adverse events.
Abbreviations: Abic, abicipar; Aflib, aflibercept; Brolu, brolucizumab; Faric, faricimab; nAMD, neovascular age-related macular degeneration; Rani, ranibizumab.

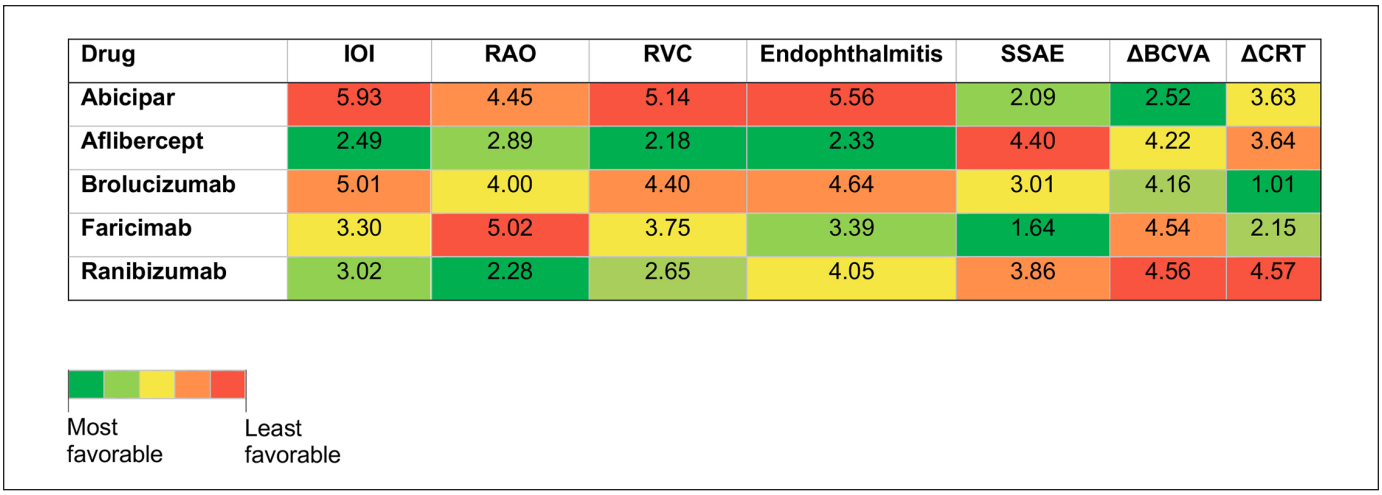

Figure 4. Ranking probabilities for each drug. (Figure available in color online.)
Abbreviations: ΔBCVA, change in best-corrected visual acuity; ΔCRT, change in central retinal thickness; IOI, intraocular inflammation; RAO, retinal artery occlusion; RVC, retinal vasculitis and choroiditis; SSAE, serious systemic adverse events.

Endophthalmitis

The incidence of endophthalmitis was as follows: sham injection (0%), faricimab (0.8%), abicipar pegol (1.4%), aflibercept (0.3%), ranibizumab (0.8%), and brolucizumab (0.6%). From the adjusted analysis, endophthalmitis was less associated with sham injections than with all the studied drugs as follows: abicipar pegol (risk ratio, 0; 95% CI, 0-0.08), aflibercept (risk ratio, 0; 95% CI, 0-0.66), brolucizumab (risk ratio, 0; 95% CI, 0-0.36), ranibizumab (risk ratio, 0; 95% CI, 0-0.21), and faricimab (risk ratio, 0; 95% CI, 0-0.36). In addition, endophthalmitis was less associated with aflibercept than with abicipar pegol (risk ratio, 0.1; 95% CI, 0.01-0.65) (Figures 3D and 4, and Supplemental Table 2d). The quality of the data was high (Table 1).

All Serious Systemic Adverse Events

From the adjusted analysis, there were significantly fewer serious systemic AEs associated with faricimab than with aflibercept (risk ratio, 0.73; 95% CI, 0.55-0.97) (Figures 3E and 4, and Supplemental Table 2e). The quality of the data was high (Table 1).

Visual Acuity

From the adjusted analysis, there was no significant difference in the baseline BCVA among the studies (mean ETDRS letters: sham 53.6 ± 14.1; ranibizumab 51.8 ± 16.7; aflibercept 56.6 ± 13.9; brolucizumab 61.1 ± 13.3; abicipar pegol 56.6 ± 12.7; faricimab 60.0 ± 13.0) ($P < .001$). No difference was found in VA gains among the 5 drugs. Patients treated with sham injections, however, lost almost 3 lines of VA (−13.8 ETDRS letters) and had worse outcomes than those treated with any drug (Figure 5A and Supplemental Table 3a).

Central Retinal Thickness Outcomes

From the adjusted analysis, patients treated with brolucizumab had a significantly larger mean baseline CRT than the other patients (ranibizumab 348 ± 120 μm; faricimab 357 ± 122 μm; aflibercept 363 ± 135 μm; abicipar pegol 379 ± 125 μm; brolucizumab 468 ± 168 μm) ($P < .001$). Patients treated with brolucizumab had significantly greater reductions in CRT than those treated with ranibizumab (mean difference, −39.14; 95% CI, −57.74 to −20.72), aflibercept (mean difference, −34.16; 95% CI, −48.01 to −20.73), abicipar pegol (mean difference, −34.98; 95% CI, −56.59 to −12.62), or faricimab (mean difference, −24.04, 95% CI; −40.59 to −8.12). Treatment with faricimab resulted in a greater reduction in CRT than aflibercept (mean difference, −10.1; 95% CI, −18.56 to −1.43) or ranibizumab (mean difference, −15.03; 95% CI, −30.26 to −0.03) (Figures 4 and 5B, and Supplemental Table 3b).

Ranking Probabilities

To elucidate the relative performance of each drug in terms of efficacy and safety, rank probabilities for various outcomes were calculated and are shown in Figure 4. These ranks are not akin to odds ratios or relative risks but rather provide a relative standing of each drug within a specific outcome. Lower ranks denote more favorable outcomes, and higher ranks indicate less favorable outcomes. For instance, abicipar pegol had higher ranks in intraocular AEs, indicating less favorable outcomes (5.93 for IOI; 4.45 for RAO; 5.14 for retinal vasculitis or choroiditis; 5.56 for endophthalmitis) but showed more favorable outcomes, with lower ranks in serious systemic AEs (2.09) and the change in BCVA (2.52) and a moderate ranking in the change in CRT (3.63).

When the ranks are closely clustered, as seen with faricimab's rank in change in BCVA (4.54) compared with ranibizumab's

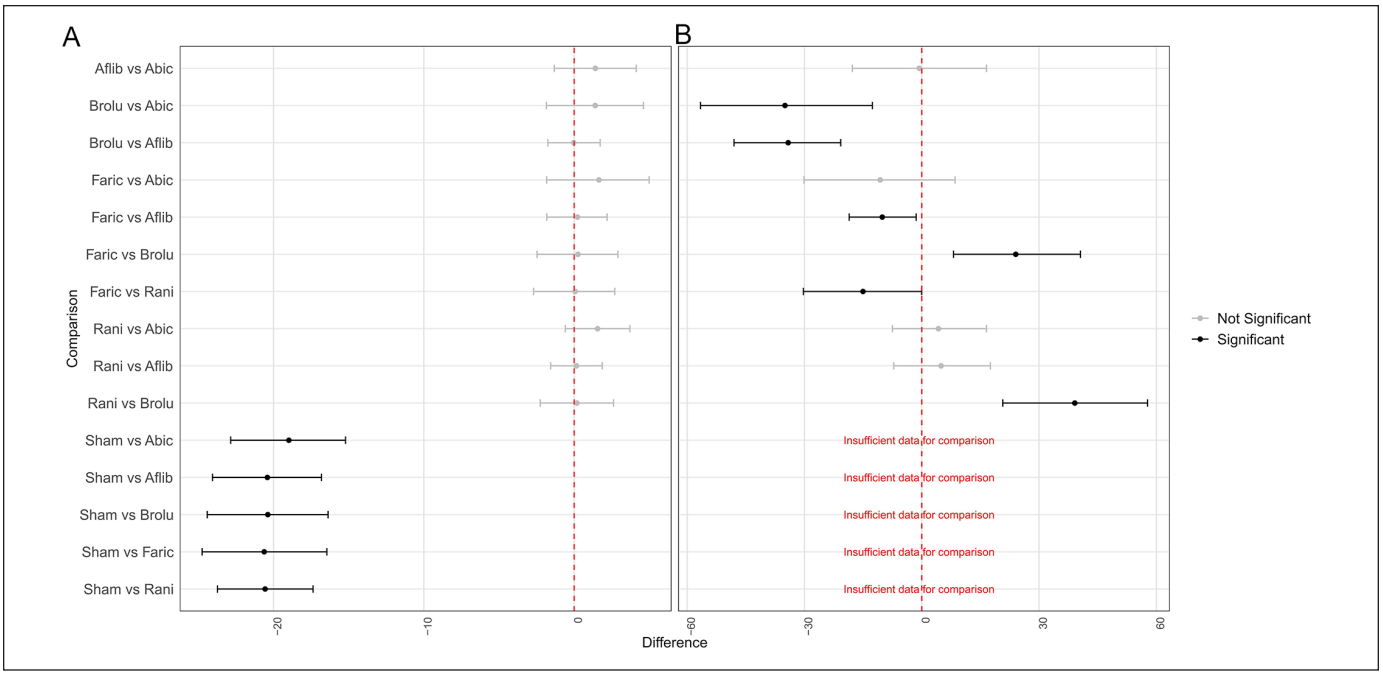

Figure 5. Network meta-analysis with forest plots for functional and anatomic outcomes after treatment for nAMD. (A) Change in best-corrected visual acuity measured by ETDRS letters. (B) Change in central retinal thickness on optical coherence tomography.
Abbreviations: Abic, abicipar; Aflib, aflibercept; Brolu, brolucizumab; ETDRS, Early Treatment Diabetic Retinopathy Study; Faric, faricimab; nAMD, neovascular age-related macular degeneration; Rani, ranibizumab.

rank (4.56), it suggests a similar level of effectiveness or safety between the drugs in that particular category. Conversely, a wider rank gap, such as between abicipar pegol's rank and aflibercept's rank in RAO (4.45 vs 2.89), indicates a more pronounced difference in their performance. In general, aflibercept had lower average ranks in RAO (2.89), retinal vasculitis or choroiditis (2.18), and endophthalmitis (2.33) but higher ranks for serious systemic AEs (4.40) and the change in BCVA (4.22). Brolucizumab had lower ranks in the change in CRT (1.01) but higher ranks in IOI (5.01), retinal vasculitis or choroiditis (4.40), and endophthalmitis (4.64). Faricimab's lowest rank was in serious systemic AEs (1.64), with higher ranks in RAO (5.02) and retinal vasculitis or choroiditis (3.75). Ranibizumab maintained low to moderate rankings in most ocular AEs but had higher ranks in the change in CRT (4.57) and the change in BCVA (4.56), reflecting its overall efficacy and safety profile.

Conclusions

This network meta-analysis showed significantly more cases of IOI associated with abicipar pegol than with aflibercept, ranibizumab, faricimab, or sham injections as well as more cases of IOI associated with brolucizumab than with aflibercept, faricimab, or sham injections. The rate of IOI in patients who received ranibizumab was higher than in those who received sham injections. Patients treated with abicipar pegol were also more likely to develop endophthalmitis than those treated with aflibercept. Patients treated with abicipar pegol had a significantly higher risk for retinal vasculitis or choroiditis than those treated with ranibizumab. Likewise, patients treated with brolucizumab had higher rates of retinal vasculitis than those treated with aflibercept. Finally, patients treated with abicipar pegol were more likely to develop RAO than patients treated with ranibizumab, and patients treated with brolucizumab had higher rates of RAO than those treated with aflibercept.

There were no differences among drugs in VA gained. Brolucizumab resulted in a greater reduction in CRT than the other drugs, and faricimab had a more favorable effect on CRT than aflibercept and ranibizumab. Faricimab was also associated with fewer serious systemic AEs than aflibercept. The findings in this analysis show the relative safety profiles and efficacy of the different anti-VEGF agents for patients with nAMD.

The rank probabilities allow clinicians to balance the overall benefits and risks of each drug (Figure 4). Although abicipar pegol was among the least favorable in most categories of intraocular AEs (IOI, RAO, retinal vasculitis or choroiditis, endophthalmitis), it was less associated with serious systemic AEs and had the best performance in terms of the change in VA. Aflibercept was less likely to be associated with RAO, retinal vasculitis or choroiditis, and endophthalmitis; however, it had a higher rank for serious systemic AEs and the change in BCVA, indicating a better safety profile but less efficacy in improving vision (the change in BCVA). Brolucizumab had a mixed performance, with lower ranks for the change in CRT, indicating that it might be particularly effective in reducing retinal thickness. However, it was more likely to cause adverse outcomes, as evidenced by higher rankings for IOI, retinal vasculitis or choroiditis, and endophthalmitis. Faricimab also had a

mixed profile, with its lowest rank in serious systemic AEs, suggesting a favorable systemic safety profile but with higher ranks in other categories such as RAO and retinal vasculitis or choroiditis. In general, ranibizumab had an average performance across most outcomes but had a high rank in the change in CRT, suggesting it may not be as efficacious for reducing retinal thickness.

There are several limitations to this analysis. One is the lack of occurrences for some AEs in several studies. When an AE occurred, a zero count limited the ability to draw comparisons between some drugs, leading to very small (~0) or very large (~∞) risk ratios and extremely wide CIs. Thus, for some AEs and pairwise drug comparisons, the CIs for artificially high-risk or low-risk ratios should be recorded as complete uncertainty; this phenomenon has been previously described.[26]

Furthermore, the lack of standardization in grading AEs can make the various clinical trials difficult to compare. For instance, although the definition of IOI is very similar between the different studies, there is some variation in the grading criteria. In the MARINA and ANCHOR trials, anterior chamber cell was determined using the definition proposed by Hogan et al,[27] while the CEDAR and SEQUIOA trials rely on the SUN criteria.[14,15,17,27,28]

Another challenge is the diagnostic uncertainty related to cases of endophthalmitis. Because approximately 30% to 40% of cases are culture negative, it can be difficult to determine whether a patient experienced a true intraocular bacterial infection or sterile inflammation related to the administered drug (IOI).[29,30] Of the patients in the CEDAR and SEQUOIA trials who had cultures obtained, 9 had negative cultures, suggesting that some cases classified as endophthalmitis may have been drug-induced sterile IOI.[17]

Despite the limitations in the current study, there was a clear trend toward abicipar pegol and brolucizumab being associated with a greater number of ocular AEs. The potential reasons these medications may induce ocular inflammation include changes in the drug product manufacturing, inherent drug immunogenicity, and patient-specific factors.[31]

Alterations to drugs during manufacturing may increase the risk for IOI. Abicipar pegol and brolucizumab, which are produced by *Escherichia coli*, have a greater risk for contamination by endotoxins than biologics created through other processes. Early studies of abicipar pegol found a 16% rate of IOI, which was attributed to contamination from *E coli*.[32] Changes in the manufacturing process resulted in a decrease in the IOI rate to 8.9% in the phase 2 MAPLE study.[9] Our analysis included results from the original formulation of abicipar pegol, as used in the phase 3 CEDAR and SEQUOIA trials, which might explain the higher rates of IOI, retinal vasculitis and choroiditis, and RAO associated with this medication.[33]

The size of the molecule may contribute to its immunogenicity. As a result of their smaller size, brolucizumab (26 kDa) and abicipar pegol (34 kDa) have enhanced diffusion through the retina and choroid compared with aflibercept (115 kDa). This enhanced diffusion may explain the comparatively higher rates of vasculitis associated with these drugs,[34,35] which can interact more readily with the eyes' immune cells, potentially causing a type IV cell–mediated hypersensitivity reaction.[5,36,37] Furthermore, the smaller molecular weight of brolucizumab allows for a single injection to deliver a molar dose 12 times and 22 times higher than aflibercept and ranibizumab, respectively.[38] This larger dose may increase this drug's interaction with the eyes' immune cells.

The structure of the biologic may also contribute to its propensity to induce IOI. A root cause analysis of ocular AEs found that brolucizumab's immunogenicity is likely related to its similarity to bacterial proteins, the formation of non-native immunogenic compounds after prolonged incubation in the eye, and the presence of non-natural surfaces, factors that increase the likelihood of anti-brolucizumab antibody formation.[39] Immune complexes that form between anti-brolucizumab antibodies, brolucizumab, and VEGF may subsequently trigger platelet aggregation and cytokine release, leading to vascular occlusive events and IOI.[39]

In contrast to previous studies, the current analysis did not find an increased risk for IOI with biologics containing an Fc fragment. Fc receptors are located on almost all cell types within the eye, and the Fc component of antibodies plays an important role in modulating immune responses.[40] IVT Fc fragment injection induces immune cell infiltration into the retina and vitreous, causing damage to retinal cells.[41,42] Aflibercept contains an Fc region, while faricimab has a modified Fc component. Ranibizumab, brolucizumab, and abicipar pegol all lack an Fc region. In this analysis, abicipar pegol and brolucizumab, both of which lack an Fc region, were associated with higher rates of vasculitis, choroiditis, RAO, and IOI. It seems that the Fc component of antibodies may not have as much of an effect on IOI as previously thought.

Antidrug antibodies also confer a risk for IOI by triggering a type III hypersensitivity reaction.[36,43–46] In the ANCHOR, HAWK, and HARRIER trials, patients with antidrug antibodies experienced higher rates of IOI.[7,14,20] Clinical trials report the presence of antidrug antibodies in treatment-naïve patients.[13,15,21,47] These likely form as a result of previous exposure to homologous proteins.[47] In the HAWK and HARRIER trials, 36% to 52% of patients had preexisting antibodies, which increased to 53% to 67% after exposure to brolucizumab.[7] An analysis of antibodies in patients who experienced inflammatory events after brolucizumab injections did not find a specific antibody isotype, epitope, subclass, or binding affinity that was predictive of inflammatory potential.[47] Understanding which factors affect antibody formation could identify patients at higher risk and allow for a patient-centered approach to the management of nAMD.[48,49]

This study examined 5 IVT agents used to treat nAMD and the reported rates of AEs of inflammation. Reduced safety profiles were found with abicipar pegol and brolucizumab. Rigorously investigating IOI and safety signals from clinical trials and postmarketing data is essential to help patients with nAMD and physicians better understand the risks and benefits involved in their treatment.

Authors' Note

Drs. Stevanovic and Koulisis contributed equally as co-first authors to the manuscript.

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Ethical Approval

Institutional review board approval and informed consent were not required for this meta-analysis of published and publicly available randomized clinical trials with de-identified data. The collection and evaluation of all protected patient health information were performed in a US Health Insurance Portability and Accountability Act–compliant manner and conformed to the tenets of the Declaration of Helsinki.

Informed Consent

Informed consent was not required for this meta-analysis of published and publicly available randomized controlled trials with de-identified data.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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Supplemental Material

Supplemental material is available online with this article.

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