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Comparative efficacy and safety of Faricimab with other intravitreal anti-vascular endothelial growth factor in the treatment of neovascular age--related macular degeneration – A systematic review and meta-analysis

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ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of visual impairment in patients age >50 years, with an estimated 200 million people affected worldwide. The neovascular subtype of AMD (nAMD) has been associated with worse vision outcomes. At present, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is the standard treatment modality for nAMD. Faricimab (Immunoglobulin G1-derived bispecific antibody) is a newer anti-VEGF directed against VEGF-A and angiopoietin-2 used for the treatment of Neovascular AMD. This systematic review was to evaluate the efficacy and safety of Faricimab and compare it with other intravitreal anti-VEGF in the treatment of neovascular AMD. PubMed and Google Scholar were systematically searched until October 2024. The meta-analysis included all published randomized controlled trials that investigated the efficacy and safety of Faricimab over other intravitreal anti-VEGF agents in adults >50 years with neovascular nAMD. Data extraction was guided by a predetermined checklist. Using RevMan 5 software, mean visual, anatomical, and functional outcomes were pooled from the selected studies. The fixed-effect model was used to assess and compare the effectiveness of Faricimab with other intravitreal anti-VEGF therapy. Data analyses were performed in November 2024. The primary outcome was the assessment of the safety and efficacy of Faricimab in the treatment of nAMD. The secondary outcome was to compare the Faricimab (intervention) group with other intravitreal anti-VEGF (control) groups. The initial search yielded 57 records of which 48 articles underwent full-text evaluation, which identified six articles and a total of 4454 patients (intervention group-2226 and control group 2228) were included in the study. The findings were in favor of Faricimab with respect to best corrected visual acuity (BCVA), central subfield thickness (CST), and choroidal neovascularization (CNV) when compared to other intravitreal anti-VEGF. The pooled MD for BCVA between Faricimab and Aflibercept or Ranibizumab was 0.20 (95% CI: 0.14–0.26). In the case of CST, it was −0.16 (95%CI–0.10–0.22) and CNV it was 0.26 (95% CI: 0.32–0.20) Heterogeneity was found in all outcomes and was statistically significant with the P<0.00001. This systematic review and meta-analysis demonstrated that Faricimab showed a comparable efficacy and safety outcome benefits with a reduction in the frequency of injections compared with other intravitreal anti-VEGF drugs, representing a valuable treatment option for nAMD.

Key words: Neovascular age-related macular degeneration; Faricimab; Intravitreal anti-vascular endothelial growth factor; Best corrected visual acuity; Aflibercept; Ranibizumab; Choroidal neovascularization; Central subfoveal thickness

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INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is one of the primary causes of blindness globally, with global prevalence estimated to increase from 196 million in 2020 to 288 million in 2040 due to the aging population.[1] Despite studies suggesting that antioxidant vitamin and mineral supplements may slow the growth of age-related macular degeneration (AMD), the development of nAMD is often inevitable.[2] In recent years, there have been major advancements in the treatment of nAMD, particularly anti-vascular endothelial growth factor (anti-VEGF). Ranibizumab, Aflibercept, and Brolucizumab are some examples of anti-VEGF Medications.[3] Despite their efficacy and safety, due to their multiple injections, several monitoring visits, and recurrent diagnostic tests continue to be major issues.

Faricimab (Roche/Genentech, Switzerland) is a novel anti-VEGF drug that blocks both angiopoietin-2 (Ang-2) and VEGF-A.[4] Ang-2 production causes inflammation and vascular leakage, which leads to neovascularization.[5] Faricimab blocks VEGF and Ang-2 signaling concurrently, resulting in improved vascular stability and less retinal inflammation than other anti-VEGF[3] monotherapies.

Further, Faricimab is purported to have the capacity for dosing intervals up to 16 weeks in many patients, which may reduce the treatment burden placed on patients.[6] This meta-analysis aimed to comprehensively consolidate clinical trial data to determine the comparative efficacy and safety outcomes of newer bispecific anti-VEGF/Ang2 inhibition with Faricimab relative to other anti-VEGF therapies in nAMD.

Aims and objectives

To evaluate the efficacy and safety of Faricimab and compare it with other intravitreal anti-VEGF in the treatment of neovascular AMD.

MATERIALS AND METHODS

This study protocol was prospectively registered with PROSPERO and conducted with the requirements of the reporting rules in the "preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines"[7] and strictly complied with its specifications. Since this work is a systematic review, the heterogeneity was present within the acceptable range, meta-analysis was performed.

Eligibility

Inclusion criteria

1. Adult patients with nAMD more than 50 years of age
2. Intravitreal Faricimab as monotherapy
3. Outcome indicators: Best corrected visual acuity, Anatomical outcome
4. Double-blinded, randomized controlled trials (RCT).

Exclusion criteria

1. Case–control, cross-sectional, and observational studies
2. Randomized, double-blind studies with incomplete data
3. Studies evaluating non-anti-VEGF therapy (steroid, photodynamic therapy)
4. Studies evaluating causes and differential diagnosis other than nAMD.

Search strategy

The electronic retrieval methods were used for the literature retrieval. A complete and systematic review of studies until 2024 was carried out, utilizing a combination of Medical Subject Headings, controlled vocabulary, and keywords from multiple databases such as PubMed and Google Scholar. The keywords selected were "Neovascular AMD," "Faricimab," "Intravitreal anti-VEGF," "Aflibercept," and "Randomized control trial." In addition, a manual search of the reference list of primary trials from the selected topics was performed, and relevant articles were included in the review and analysis.

Study selection

To select studies, the search results were entered into Rayyan,[8] an online systematic review tool. The selection of the studies was done by a two-step screening procedure. The literature search was carried out by two independent writers (R.K., N.P.), who also assessed each study's title, abstract, and keywords. Two authors, R.K. and N.P., independently screened the abstract and full text to choose the articles that met our review's qualifying criteria. Any conflicts or discordances that arose during the selection process were resolved either by consensus or consultation with the third author (R.M). If differences emerged between reviewers, the fourth and fifth, reviewers (P.N, J.F.M,) moderated a conversation to reach a consensus.

Data extraction and management

The relevant study features for the review were collected from the included studies independently by the first and coauthor based on the outcome measure. A predetermined checklist was used to extract data, which included the first author's last name, published year, total sample size, gender, study design, duration of intervention, participant age, adults over 50 years with nAMD, type of intervention (Faricimab or other intravitreal anti-VEGF), efficacy, safety, and outcome (visual, anatomical, functional) of Faricimab.

The first author (R.K) entered the collected data into the software Review Manager (RevMan_5.3).[9] The second

author (N.P) double-checked the data input for accuracy by comparing the data presented in the review.

Outcome measure for the study

The primary outcome was an assessment for the efficacy and safety of Faricimab in the treatment of nAMD. Secondary outcome was the comparison of effectiveness and outcome of Faricimab (intervention) with other intravitreal anti-VEGF agents (control).

Quality assessment

The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[10] was used to assess the risk of bias of the selected articles and the quality review process was monitored. Each study was categorized as follows: "low-risk," "some concerns," or "high-risk" of bias [Summarized in Figures 7and 8].

Statistical analysis

An extensive qualitative analysis was performed. RevMan_5.3.[7] was used to do the quantitative meta-analysis on binomial data. When studies reported numerous arms in a single trial, only the relevant arms were considered for analysis. Due to the heterogeneity among studies, a logistic-normal-random-effect model was used. The 95% confidence interval (CI) was calculated for both study-specific and general pooled prevalence. The I^2 statistic was employed to analyze heterogeneity. Significant heterogeneity was defined as a $P<0.05$ or an $I^2>50\%$ among the trials.

Subgroup analysis was used to evaluate the study heterogeneity and potential confounding. Forest plots were used to graphically represent study-specific and pooled estimates for both combined and subgroup analyses. Sensitivity analyses were used to measure the reliability of the meta-analysis estimates.

RESULTS

Study selection and characteristics

A total of 48 studies were initially retrieved following the removal of duplicates. On screening, 19 studies were deemed irrelevant to our review. The remaining 29 were assessed for eligibility. Out of those, six studies[11-16] met the inclusion criteria and were ultimately included for the qualitative and quantitative analyses (Tables 1-3). Figure 1 illustrates the PRISMA flowchart for the study selection.

When using Cochrane risk-of-bias tool, two studies had a low risk of bias and two studies had some concerns. The major limitation was the small sample size in the two studies. Baseline characteristics were found to be similar in both intervention and control groups in all studies.

Table 1: Characteristics of study population

First authors	Year of publication	Journal	Study setting	Study design	Blinding	Study period	Study population	Sampling strategy
Heier JS-Tenaya	2022	Lancet	Hospital	Randomized controlled clinical trial	Double-blind	Not mentioned	Adults	Randomization
Heier JS-Luc	2022	Lancet	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization
Koizumi H-2 year (J)	2024	Graefes Arch clinical and experimental ophthalmology	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization
Koizumi H-2 year (G)	2024	Graefes Arch clinical and experimental ophthalmology	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization
Mori R-1 year (J)	2024	Jpn J ophthalmology	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization
Mori R-1 year (G)	2024	Jpn J ophthalmology	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization
Arshad M Khanani	2024	Jama Ophthal	Hospital	Randomized controlled trail, single dose, parallel-group trials	Double-blind	Not mentioned	Adults	Randomization
Arshad M Khanani	2024	Jama Ophthal	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization
Jayashree Sahni	2020	Jama Ophthal	Hospital	Randomized controlled trial	Double-blind	Not mentioned	Adults	Randomization

Table 2: Characteristics of study population

First authors	Intervention group	Type of comparator	Type of analysis (PP/ITT)	Intervention (mean and SD or median [IQR])	Control (mean and SD or median [IQR])	Intervention	Control
Heier JS-Tenaya	Faricimab	Aflibercept	ITT	75.9 (8.6)	76.7 (8.8)	334	337
Heier JS-LUC	Faricimab	Aflibercept	ITT	74.8 (8.4)	76.1 (8.6)	331	327
Koizumi H-2 year (J)	Faricimab	Aflibercept	ITT	24.7 (5.3)	24. I (5.1)	66	67
Koizumi H-2 year (G)	Faricimab	Aflibercept	ITT	72.8 (7.4)	77.1 (8.0)	665	664
Mori R-1 year (J)	Faricimab	Aflibercept	ITT	72.1 (7.5)	71.8 (9.5)	66	67
Mori R-1 year (G)	Faricimab	Aflibercept	ITT	75.4 (8.5)	76.4 (8.7)	665	664
Arshad M Khanani	Faricimab	Ranibizumab	PP	80.3 (7.23)	77.3 (10.29)	24	16
Arshad M Khanani	Faricimab	Ranibizumab	PP	77.7 (8.38)	77.3 (10.29)	31	16
Jayashree Sahni	Faricimab	Ranibizumab	PP	80.0 (8.0)	76.4 (8.9)	46	68

IQR: Interquartile range

Table 3 : Characteristics of study population

First Author	BCVA	CST	CNV	BCVA	CST	CNV	Intervention	Control
Heier JS-TENAYA	61.3 (12.5)	360.5 (124.1)	4.7 (1.2)	61.5 (12.9)	356.1 (107.0)	4.5 (1.8)	858	812
Heier JS-LUC	58.7 (14.0)	351.1 (120.1)	4.7 (1.3)	58.9 (13.3)	359.0 (131.1)	4.3 (1.0)	812	846
Koizumi H-2 year (J)	7.1	355.6 (102)	13.3 (0.52)	58 (7.2)	326 (102)	12.2 (0.52)	320	248
Koizumi H-2 year (G)	4.4	4	5.9 (2.9)	58.4 (12.1)	5.2	4.6 (1.02)	111	99
Mori R-1 year (J)	59.1 (13.1)	354.1	3.2 (0.82)	59.9 (13.2)	335.8	4.1 (1.06)	158	102
Mori R-1 year (G)	60.0 (13.3)	356.8	7.1 (3.2)	60.2 (13.1)	357.5	7.1 (2.8)	1897	1863
Arshad M Khanani	57.8 (10.5)	417.9 (84.3)	7.1 (3.9)	55.3 (12.1)	443.1 (125.0)	7.3 (2.9)	9	8
Arshad M Khanani	60.4 (10.8)	382.2 (80.9)	5.9 (3.8)	55.3 (12.1)	443.1 (125.0)	7.3 (2.9)	11	8
Jayashree sahni	56.3 (11.5)	464.4 (110.6)	7.5 (4.4)	55.2 (12.7)	437.8 (122.4)	7.3 (3.8)	27	28

BCVA: Best corrected visual acuity, CST: Central subfield thickness, CNV: Choroidal neovascularization

Characteristics of the study population

From all six studies included, a total of 2,228 patients were in the intervention group and 2,226 patients were in the control group. The mean age for the overall RCT included in this study ranged from 50 to 70 years.[11,14,17,18] All the studies used Faricimab for the intervention group and other intravitreal anti-VEGF (Aflibercept or Ranibizumab) for the control group. The duration of the intervention ranged from 18 weeks to 2 years.

Methodological quality of the included studies

Final review of six included studies was all double-blinded, RCT with Faricimab as intervention and other intravitreal anti-VEGF (Aflibercept or Ranibizumab) as control and done in adults more than 50 years. These articles were published between 2020 and 2024 and done in the hospital setting.

Effectiveness of Faricimab on AMD

A meta-analysis of six eligible RCT studies involving 2228 subjects received Faricimab and 2226 controls who received other intravitreal anti-VEGF (Aflibercept or Ranibizumab). The fixed model effects showed a pooled mean difference (MD) between the intervention and control. The pooled standard MD for the age distribution between Faricimab and Aflibercept or Ranibizumab was −0.19 (95% CI: −0.13–0.25) (Figure 2).

Heterogeneity was found recording the use of Faricimab for nAMD among the studies included in the analysis. (I^2: 92% respectively) the overall effect of age distribution between Faricimab and Aflibercept or Ranibizumab was statistically significant with P<0.00001.

Sub-group analysis

We performed a subgroup analysis to assess the heterogeneity and difference in the effect of Faricimab across the other intravitreal anti-VEGF agents (Figures 4-6).

Efficacy analysis

BCVA

A total of 4454 subjects from 6 RCTs were pooled to estimate nAMD of BCVA. All six studies included in the analysis assessed the BCVA through ETDRS letters. The intravitreal Faricimab group showed uniformity in maintenance or improvement in the BCVA compared with other intravitreal anti-VEGF group. The pooled standard MD for the BCVA between Faricimab and Aflibercept or Ranibizumab was 0.20 (95% CI: 0.14–0.26) (Figure 3).

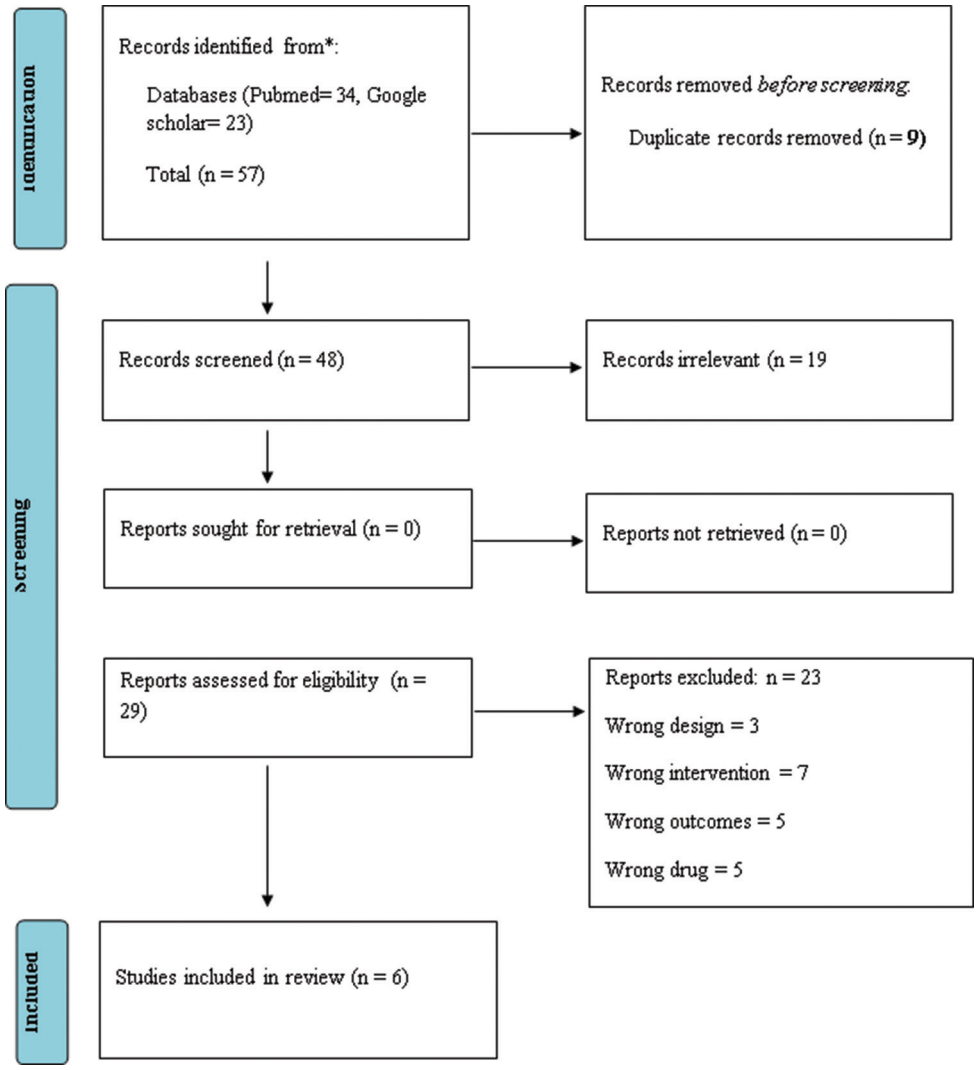

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram of the study selection process

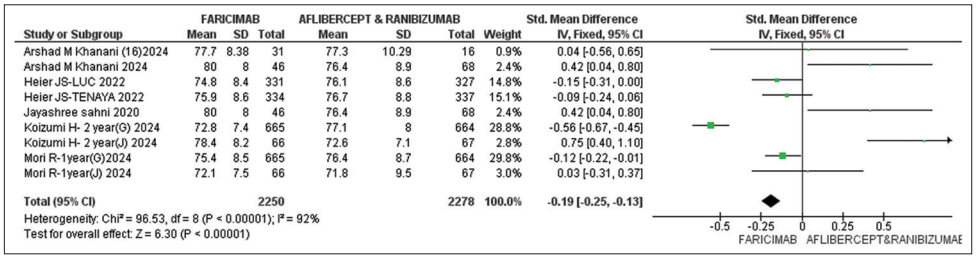

Figure 2: Comparison of age distribution between Faricimab and other intravitreal anti-VEGF. nAMD: Neovascular age-related macular degeneration, VEGF: Vascular endothelial growth factor, CI: Confidence interval

Heterogeneity was found recording the use of Faricimab for nAMD among the studies included in the analysis. ($I^{2:}$ 93% respectively) the overall effect of BCVA between Faricimab and Aflibercept or Ranibizumab was statistically significant with P<0.00001.

CST

A total of 4454 subjects from 6 RCTs were pooled to estimate nAMD of CST. All the six studies included in the analysis assessed the CST. The intravitreal Faricimab group showed a change in the spectral-domain optical coherence tomography measured central subfield thickness when compared with other intravitreal anti-VEGF group. The pooled standard MD for the CST between Faricimab and Aflibercept or Ranibizumab was −0.16 (95% CI: −0.10–0.22) (Figure 4).

Heterogeneity was found recording the use of Faricimab for nAMD among the studies included in the analysis.

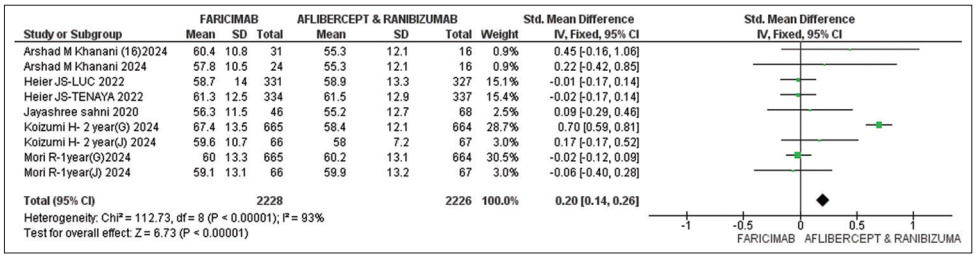

Figure 3: Comparison of BCVA between Faricimab and other intravitreal anti-VEGF. BCVA: Best corrected visual acuity, CI: Confidence interval, VEGF: Vascular endothelial growth factor

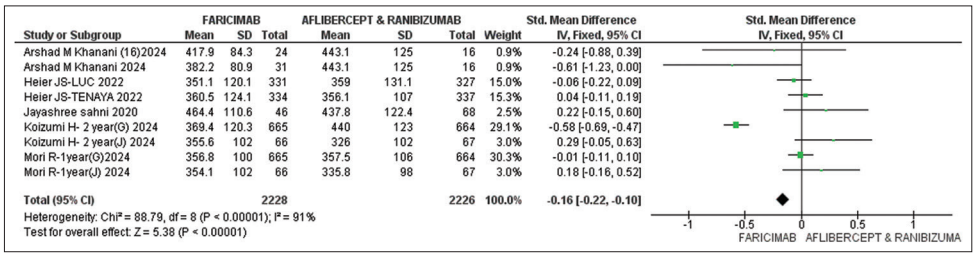

Figure 4: Comparison of CST between Faricimab and other intravitreal anti-VEGF. CST: Central subfield thickness, CI: Confidence interval

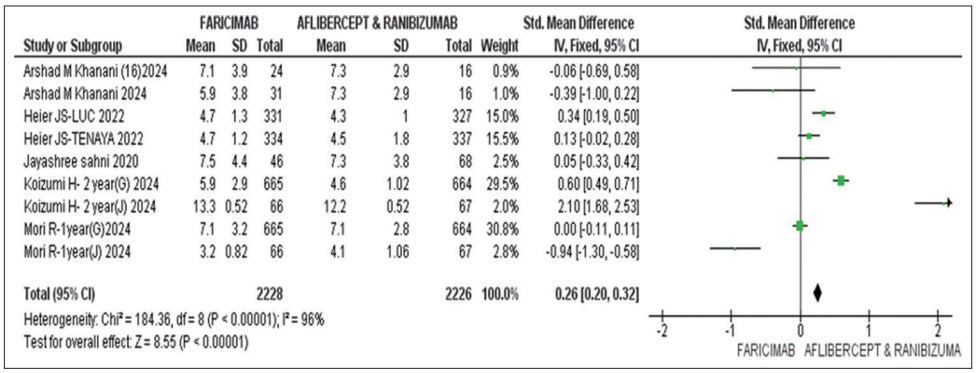

Figure 5: Comparison of CNV between Faricimab and other intravitreal anti-VEGF. CNV: Choroidal neovascularization, VEGF: Vascular endothelial growth factor, nAMD: Neovascular age-related macular degeneration, CI: Confidence interval

(I^2: 91% respectively) the overall effect of CST between Faricimab and Aflibercept or Ranibizumab was statistically significant with P<0.00001.

CNV

A total of 4454 subjects from 6 RCTs were pooled to estimate nAMD of CNV. All six studies included in the analysis assessed the CNV. The intravitreal Faricimab group showed the change from baseline in total area of CNV lesion and total area of CNV leakage at the end of the study when compared with other intravitreal anti-VEGF group. The pooled standard MD for the CNV between Faricimab and Aflibercept or Ranibizumab was 0.26 (95% CI: 0.32–0.20) (Figure 5).

Heterogeneity was found recording the use of Faricimab for nAMD among the studies included in the analysis. (I^2: 96% respectively) the overall effect of CNV between Faricimab and Aflibercept or Ranibizumab was statistically significant with P<0.00001.

Adverse effects

Key ocular and non-ocular adverse events as reported by the study investigator summarized in Figure 6. Overall, Faricimab was well tolerated as evidenced by a low incidence of adverse events. The MD of ocular adverse events was comparable between treatment groups 0.70 (95% CI: 0.79–0.61). Common non-ocular adverse events were generally similar with no safety concerns and occurred at similar rates in both treatment groups.

DISCUSSION

This current systematic review and meta-analysis provide a comprehensive evaluation of nAMD therapy, including data from six RCTs.[11-16] This study included 2228 patients with a focus on efficacy, safety, and frequency of injection of Faricimab comparing with other anti-VEGF. The result suggested that Faricimab is equivalent to other anti-VEGF medications considering BCVA. The findings are consistent

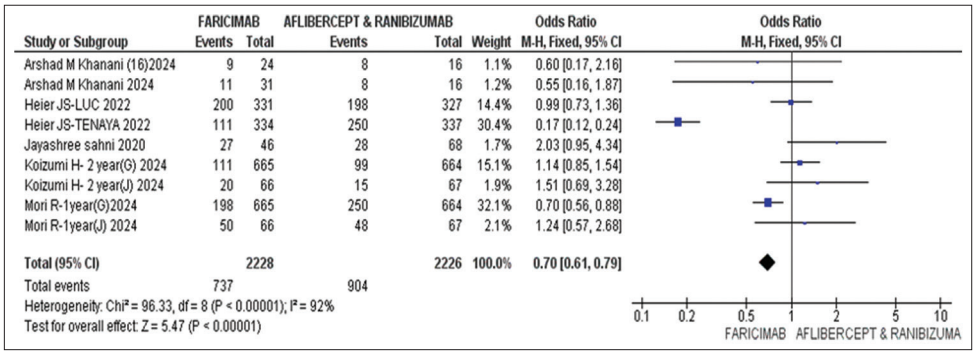

Figure 6: Comparison of adverse effects between Faricimab and other intravitreal anti-VEGF. CI: Confidence interval, VEGF: Vascular endothelial growth factor

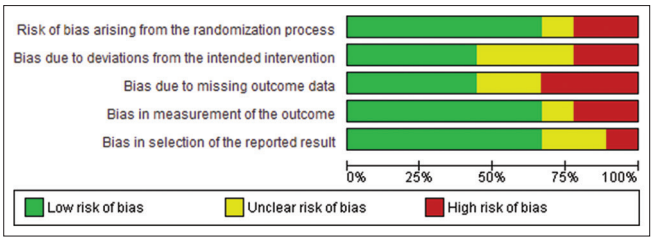

Figure 7: Risk of bias graph

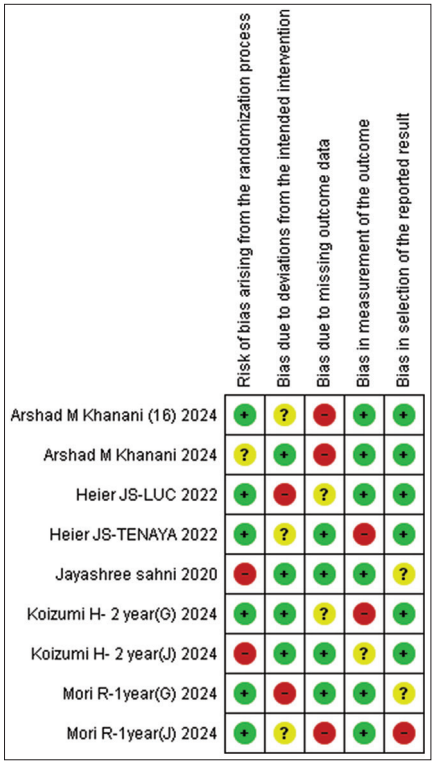

Figure 8: Risk of bias summary

across all six studies. In terms of anatomical outcomes, this study found that Faricimab performed well. Moreover, Faricimab had an adequate safety profile when compared to other anti-VEGF therapies. This analysis covered various treatment strategies, and data for the treatment- naïve population, providing clinicians with comprehensive evidence to guide nAMD management.

The BCVA evaluation revealed that Faricimab is equivalent to other anti-VEGFs in terms of vision maintenance or improvement, with the exception of the AVENUE phase II trial, where Faricimab did not meet its superiority over Ranibizumab, but gain in visual acuity seen in STAIRWAY.[17] Rapid BCVA gain and stable maintanence of visionsupports Faricimab and Aflibercept in TENAYA and LUCERNE.[18] However, Phase III and other trials proved visual gain with Faricimab. This finding is consistent with previous studies done by Samacá D et al.[19]

Our analyses for anatomic outcomes were in favor of Faricimab when compared with other anti-VEGF including an increased probability of post-treatment retinal free-fluid. Similarly, sensitivity analysis for CST showed a favorable significant effect of Faricimab. When compared to other anti-VEGF drugs, Faricimab reduced CST more significantly. CST reduction does not always correspond with improvements in visual acuity; yet, CST reduction should be evaluated in clinical practice due to its importance in assessing disease control.

In terms of safety outcomes, Faricimab had an acceptable safety profile, with a comparable risk of ocular events to other anti-VEGF agents. On the other hand, it had statistically significant lower SOAEs than other anti-VEGF medicines, implying a superior safety profile.

Our study proved that Faricimab improved visual and structural outcomes despite fewer injections, highlighting its long-term efficacy. This is comparable to all the RCTs done before. Overall, we demonstrated that the patients who received Faricimab for nAMD, in all six studies included in this meta-analysis have better outcomes when compared with the use of other intravitreal anti-VEGF agents.

Limitations of the study

Despite a thorough review of our meta-analysis, we identified certain limitations in our study. First, the number of injections, sample size, and follow-up regimes varied between the selected RCT studies. Second, the assessment did not include newer anti-VEGF therapies such as Brolucizumab.

CONCLUSION

The results of our meta-analysis show that Faricimab showed a comparable clinical benefit in efficacy for BCVA with decreasing CST and decreased leakage area and also it significantly reduces the number of injections when compared with other intravitreal anti-VEGF agents. In terms of safety, Faricimab was similar to other anti-VEGF agents in the absence of statistical difference in the risk of ocular adverse events. Faricimab thus represents a valuable therapeutic option for people with nAMD. Although our meta-analysis offered an evidence-based study of Faricimab for nAMD, further large, long-term follow-up RCT studies are needed to determine the optimum therapeutic approach.

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