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The Efficacy and Safety of Faricimab for the Treatment of nAMD and DME: A Meta-Analysis

Liu L[1,2,3], Li G[1,2,3] and Chuan J[2,3]**

[1]Traffic Hospital of Sichuan Province, Chengdu, China

[2]Department of Pharmacy, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, China

[3]School of Medicine, University of Electronic Science and Technology of China, China

Abstract

Introduction: Faricimab is a novel bispecific antibody that simultaneously blocks Vascular Endothelial Growth Factor (VEGF) and Angiopoietin 2 (Ang-2), resulting in therapeutic effects in neovascular Age-related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME). However, the efficacy and safety of faricimab are not yet clear through the results of some single clinical trials. In this study, a meta-analysis of randomized controlled trials of faricimab was conducted to assess its efficacy and safety.

Methods: RCTs of faricimab were retrieved from PubMed, Embase, Cochrane library, Clinic trail. gov., up to April 1st, 2022. Change in Best Corrected Visual Acuity (BCVA), Central Sub-Field Thickness (CSFT), change in total area of Macular Neovascularization (MNV) about nAMD, and absence of Subretinal Fluid (SRF) in DME, two-step Early Treatment Diabetic Retinopathy Study-Diabetic Retinopathy Severity Scale (ETDRS-DRSS) improvement in DME, incidence of serious adverse events, ocular adverse events and serious ocular adverse events are extracted from RCTs. Data analysis was performed using Revman 5.4.1.

Results: Seven RCTs with 3,798 patients were finally included in this meta-analysis, four of which were related to nAMD and three to DME. Statistical results of faricimab treatment of nAMD, including change in BCVA, CSFT, and change in total area of MCV, confirmed that there was no statistical significance between faricimab groups and control groups (aflibercept, ranibizumab). Similarly, there was no significant difference in the safety indicators of faricimab in nAMD including adverse events, serious adverse events, ocular adverse events and serious ocular adverse events. For the pooled analysis of faricimab treatment in DME disease, changes in BCVA, CSFT absence of SRF, and two-step ETDRS-DRSS improvement were consistent with Aflibercept and Ranibizumab. And compared with control groups, the incidence of adverse events, serious adverse events, ocular adverse events were not statistically changed. However, faricimab induced higher CSFT reduction for DME compared with control agents (MD-26.34, 95% CI -36.47 to -16.22, P<0.00001). Meanwhile, faricimab caused more occurrence of serious ocular adverse events in DME than ranibizumab and aflibercept (MD 2.12, 95% CI 1.02 to 4.43, P=0.04).

Conclusion: The efficacy and safety of faricimab for the treatment of nAMD is similar to that of other anti-VEGF agents. Faricimab may cause more serious ocular adverse events in the treatment of DME, which needs to be focused on by ophthalmologists.

Keywords: Neovascular age-related macular degeneration; Faricimab; Efficacy; Safety; Meta-analysis

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Correspondence:
Gang Li, Department of Pharmacy, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, 610072, China
Junlan Chuan, Department of Pharmacy, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, 610072, China

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Introduction

Retinal neovascularization, especially Macular Neovascularization (MNV), is a major cause of irreversible blindness [1]. The most common diseases causing these two problems are Diabetic Retinopathy (DR), retinal vein occlusion and Age-related Macular Degeneration (AMD). DR and Diabetic Macular Edema (DME) are among the causes commonly seen of vision impairment due to the contemporary rise in the incidence of diabetes and the increase in visual impairment associated with DR [2]. Elevated blood glucose can cause disturbances in the retinal microvasculature, while damage to pericytes will alter capillary perfusion, thereby altering retinal blood regulation and leading to microaneurysm formation [3]. According to AMD's international classification and

grading system, it can be divided into dry AMD and wet AMD, which AMD is also called nAMD [4]. In industrialized countries, nAMD has become a major cause of irreversible vision loss in patients over the age of 65. Compared with dry AMD, the onset of nAMD is more acute and the outcome is more severe. From a pathophysiological perspective, pathological MNVs develop under the macula, leading to the accumulation of subretinal and intraretinal exudates, and fibrotic scars at an advanced stage [5]. Up-regulation of the gene product Vascular Endothelial Growth Factor (VEGF), Angiopoietin (Ang)-2 is essential for the sprouting of retinal, subretinal and choroidal neovascularization [1]. VEGF participates in the development of blood vessels by binding to its receptors, stimulating abnormal blood vessel growth and new blood vessels [6]. Anti-VEGF agents inhibit the activity of VEGF and prevent its biological effects by combining with VEGF, such as brolucizumab, aflibercept, ranibizumab, etc. [7]. However, drug resistance, non-response and relapse often occurred due to single target of anti-VEGF agents, prompting scientists to discover new targets. Proof-of-concept clinical trials have confirmed the truth of Tie2 as an important target in ocular neovascularization [3]. Tie2 is a tyrosine kinase receptor, mainly expressed on vascular endothelial cells, binds Ang to regulate angiogenesis. There are two types of Ang, among which Ang2 is a weak agonist. Ang2 competes with Ang1 for receptors and thus has an antagonistic effect [8]. Anti-Ang2 antibody abrogates endothelial instability caused by Ang and may normalize pathological ocular vascularization.

Faricimab, also known as RO6867461 or RG7716, is a bispecific antibody developed by Roche Company through CrossMAB technology and has been approved for marketing on March 28th, 2022 [9]. From the perspective of molecular structure, faricimab consists of an anti-VEGF-A antigen-binding fragment, an anti-Ang2 antigen-binding fragment and a modified fragment. It can bind to both VEGF-A and Angiopoietin 2 (Ang-2) *via* a single molecule, thus having therapeutic advantages [3]. At present, some of the latest phase III clinical studies (YOSEMITE, RHINE, TENAYA, LUCERNE) data have proved that faricimab has durable efficacy in the treatment of DME and nAMD [10,11]. When injected intraocularly at intervals of 16 weeks, faricimab still demonstrated non-inferior visual gain and similar adverse event rates to aflibercept. However, the small sample sizes of these individual studies and the constraints of many environmental conditions make the findings potentially biased. In response to these problems, we intend to conduct a meta-analysis of clinical studies related to faricimab with existing results to evaluate its effectiveness and safety.

Methods

This study followed the terms of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). And the title, abstract, background, methods, results, discussion, conclusions and other information included in this paper conform to its specification. At the same time, the flow chart also clearly described the process of including literature, and the number and reasons of excluded literature at each step. All RCTs with available results from Clinicaltrail.gov., PubMed, Embase, Cochrane library before April 1st, 2022 were included in the analysis, regardless of language.

Search strategy

The four databases were searched using keywords, and randomized controlled trial was used as the conditional restriction so as to obtain the retrieved articles initially. Keywords are faricimab, RO6867461, RG7716; databases include Clinicaltrail.gov., PubMed, Embase, Cochrane library.

Study selection

There are several criteria used to screen retrieved studies. First, participants in the trial should be patients with DME or nAMD. In addition, the study must be RCTs which include an experimental cohort of faricimab and at least one control group. Finally, the efficacy indicators of faricimab for the treatment of nAMD including changes in BCVA, CSFT, and MCV's total area; the efficacy indicators for the treatment of DME including changes in BCVA, CSFT, absence of SRF, two-step ETDRS-DRSS improvement; and the safety indicators of both for the number of occurrences of adverse events, serious adverse events, ocular adverse events, and serious ocular adverse events are necessary. But there are no restrictions on injection doses, dosing intervals and durations, control drugs, etc. Results of primary and secondary outcome were merged or split in case of multi-publication studies. The inclusion and exclusion criteria developed in this meta-analysis above reflect the principle of PICOS. And it clearly defines populations, interventions, comparators, outcomes, and study designs.

Data extraction and quality assessment

Studies initially screened from the database were further reviewed by two investigators separately after excluding duplicate studies. The review content includes title, abstract and a final full-text check to determine whether the article meets the inclusion criteria. If two researchers had controversy during the review process, the third investigator adjudicated on the disputes. The study name, region, date, total population, course of treatment, baseline characteristics, efficacy and safety endpoints in the RCTs were recorded in an excel sheet by two researchers independently. And a third investigator was responsible for resolving any arisen disagreements. Investigators were unaware of the authors, institutions, and journals of the studies when extracting data. Bias analysis was performed using Revman 5.4 software to assess the quality of the studies. Two researchers evaluated each study item by item respectively, and disagreements were determined by the third one.

Statistical analysis

In this study, continuous variables mainly include changes in BCVA, CSFT, and MNV area. Binary variables mainly include ocular adverse events, adverse events, serious adverse events, serious ocular adverse events, absence of SRF, and two-step ETDRS-DRSS improvement. For continuous variables, we pooled data on changes from baseline over time, and final results were presented as Mean Difference (MD) and 95% Confidence Interval (CI). However, for dichotomous variables, we aggregated the number of patients, and finally showed the data with Odds Ratio (OR) and 95% CI. If more than one faricimab cohort was encountered, data for efficacy and safety measures were combined across multiple cohorts. Heterogeneity was evaluated using Q and I^2 values obtained from Revman software analysis. Random effects model was applied under circumstance of moderate and high heterogeneity ($P<0.1$, $50\% < I^2 < 75\%$) ($P<0.1$, $I^2 > 75\%$); Fixed effects model was used for statistics in case of low heterogeneity ($P>0.1$, $I^2 < 50\%$). Moreover, statistical significance was indicated when the P value was less than 0.05.

Results

Study selection

A total of 100 studies were initially retrieved from the database, including 28 duplicates, 21 reviews, 13 conference editorials, 18

Table 1: Characteristics of the included 7 RCTs.

Research name	Year	Region	Trial type	NCT	Phase	Total participants	Intervention	Subjects	Primary endpoints
BOULEVARD	2020	United States, 60 study locations	RCT	NCT02699450	2	229	Faricimab	Patients with diabetic macular oedema	c,d
AVENUE	2020	United States, 52 study locations	RCT	NCT02484690	2	273	Faricimab	Patients with nAMD	c,d
STAIRWAY	2021	United States, 25 study locations	RCT	NCT03038880	2	76	Faricimab	Patients with nAMD	c,d
TENAYA[a]	2022	United States, Canada etc., 163 study locations	RCT	NCT03823287	3	671	Faricimab	Patients with nAMD	c,d
LUCERNE[a]	2022	United States, Argentina etc.,144 study locations	RCT	NCT03823300	3	658	Faricimab	Patients with nAMD	c,d
YOSEMITE[b]	2022	United States, Austria etc.,186 study locations	RCT	NCT03622580	3	940	Faricimab	Patients with diabetic macular oedema	c,d
RHINE[b]	2022	United States, Argentina etc., 195 study locations	RCT	NCT03622593	3	951	Faricimab	Patients with diabetic macular oedema	c,d

[a]TENAYA and LUCERNE experimental data from the article Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): Two randomized, double-masked, phase 3, non-inferiority trialsSafety and pharmacokinetics of RTH258 in subjects with age-related macular degeneration

[b]YOSEMITE and RHINE experimental data from the article Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomized, double-masked, phase 3 trials

[c]Best Corrected Visual Acuity (BCVA) change from baseline by Visit

[d]The incidence of ocular adverse events

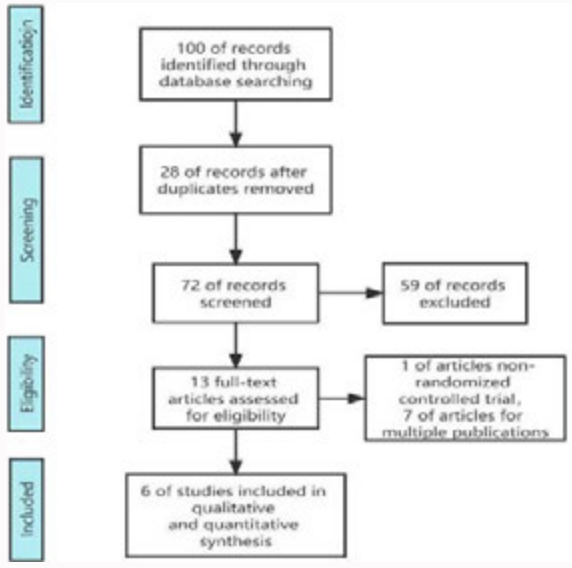

Figure 1: PRISMA flow diagram of eligible studies.

inconclusive studies, 7 irrelevant articles, 7 multiple publications, and 1 non-RCT. The remaining 5 studies containing 7 RCTs were included, of which 4 RCTs were related to nAMD and 3 RCTs were related to DME (Figure 1).

Study characteristics

This meta-analysis included five articles containing seven RCTs, which were published between 2020 and 2022. The included RCTs consisted of three phase 2 studies and four phase 3 studies, involving 3798 participants altogether. 50.6% of the subjects were female. The basic features of the included RCTs are shown in Table 1. The baseline characteristics including BCVA and CSFT are shown in Table 2. The results of the risk-of-bias analysis showed that none of the 7 RCTs showed high risk. Unclear risk mainly focused on blinding of outcome assignments, other risk included incomplete data outcomes and assignment concealment and the remaining items were low risk (Figure 2).

Estimation of efficacy

Efficacy in treating nAMD: A pooled analysis of the changes in

Table 2: The baseline characteristics of subjects in 7 RCTs.

Study	Subgroup within study	Case, n	Male, n (%)	Age, mean (Standard Deviation)	BCVA Mean (Standard Deviation)	CSFT Mean (Standard Deviation)
BOULEVARD	A: Ranibizumab,0.3 mg,6 IVT	90	54 (60.0%)	62.3 (9.2)	61.51 (10.43)	489.01 (136.74)
	B: Faricimab,1.5 mg,6 IVT	55	20 (36.4%)	61.5 (7.7)	61.16 (11.12)	532.89 (162.72)
	C: Faricimab,6 mg,6 IVT	82	46 (56.1%)	60.8 (9.2)	59.48 (12.49)	485.31 (130.10)
AVENUE	A: Ranibizumab,0.5 mg,9 IVT	68	29 (42.6%)	76.4 (8.9)	55.2 (12.7)	495.7 (144.6)
	B: Faricimab,1.5 mg,9 IVT	46	14 (30.4%)	78.2 (8.9)	56.7 (11.1)	Not Provided
	C: Faricimab,6 mg, 9 IVT	39	12 (30.8%)	78.0 (9.1)	56.2 (12.2)	Not Provided
	D: Faricimab,6 mg, 6 IVT	46	12 (26.1%)	80.0 (8.0)	56.3 (11.5)	Not Provided
	E: Ranibizumab + Faricimab, 0.5 mg + 6 mg, 3+6 IVT	64	24 (37.5%)	79.2 (8.3)	55.7 (11.6)	Not Provided
STAIRWAY	Faricimab, 6 mg,7 IVT	24	11 (45.8%)	80.3 (7.23)	57.8 (10.46)	417.9 (84.28)
	Faricimab, 6 mg, 6-7 IVT	31	13 (41.9%)	77.7 (8.38)	60.4 (10.80)	382.2 (80.87)
	Ranibizumab 0.5 mg, 13 IVT	16	6 (37.5%)	77.3 (10.29)	55.3 (12.08)	443.1 (125.00)
TENAYA	Faricimab, 6 mg,7-10 IVT	334	143 (43%)	75.9 (8.6)	61.3 (12.5)	360.5 (124.1)
	Aflibercept, 2.0 mg, 9 IVT	337	126 (37%)	76.7 (8.8)	61.5 (12.9)	356.1 (107.0)
LUCERNE	Faricimab, 6 mg,7-10 IVT	331	128 (39%)	74.8 (8.4)	58.7 (14.0)	353.1 (120.1)
	Aflibercept, 2.0 mg, 9 IVT	327	139 (43%)	76.1 (8.6)	58.9 (13.3)	359.0 (131.1)
YOSEMITE	A: Faricimab, 6 mg, 15 IVT	315	187 (59%)	61.6 (9.5)	62.0 (9.9)	492·3 (135·8)
	B: Faricimab, 6 mg, 9 IVT	313	197 (63%)	62.8 (10.0)	61.9 (10.2)	485·8 (130·8)
	C: Aflibercept, 2 mg, 10 IVT	312	178 (57%)	62.2 (9.6)	62.2 (9.5)	484·5 (131·1)
RHINE	A: Faricimab, 6 mg, 15 IVT	317	194 (61%)	62.5 (10.1)	61.9 (10.1)	466.2 (119.4)
	B: Faricimab,6 mg, 9 IVT	319	199 (62%)	61.6 (10.1)	62.5 (9.3)	471.3 (127.0)
	C: Aflibercept, 2 mg, 10 IVT	315	186 (59%)	62.3 (10.1)	62.1 (9.4)	477.3 (129.4)

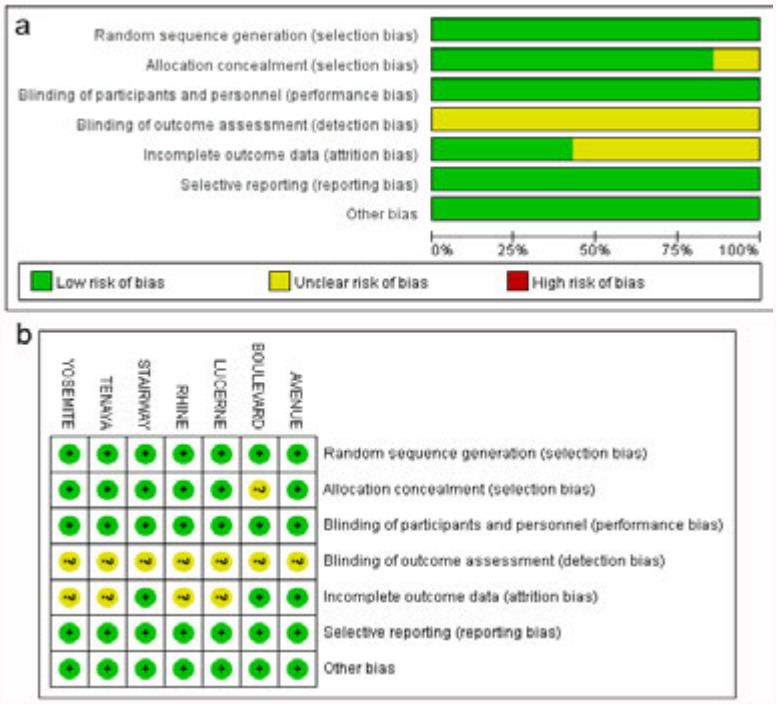

Figure 2: Risk of bias graph (a) and summary (b).

BCVA, CSFT, and MNV's total area was performed to indicate the effectiveness of faricimab in the treatment of nAMD. All four RCTs (AVENUE, STAIRWAY, TENAYA, LUCERNE) reported data on the changes of BCVA, CSFT, and MNV's total area from baseline to the indicated time points though with different time points for each RCT.

In each RCT, we selected the reported change values of BCVA CSFT, and MNV's total area from baseline to the maximum time point. In all of the 4 RCTs, the experimental group was treated with

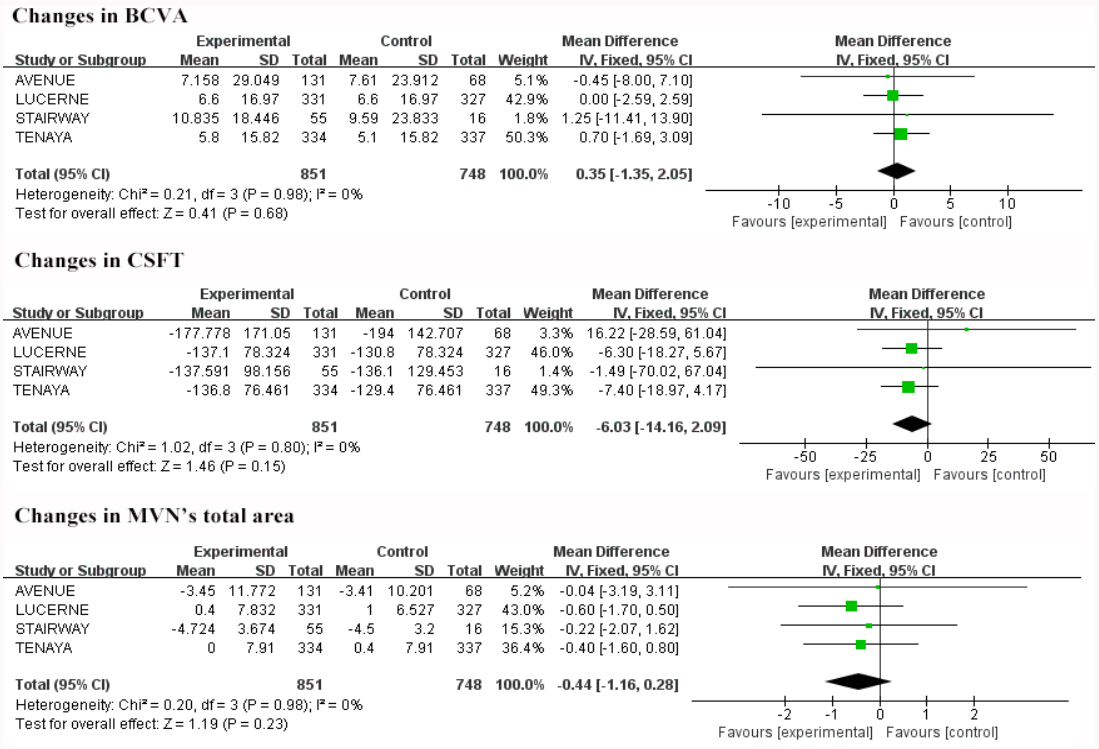

Figure 3: Comparison of the efficacy in nAMD treatment between faricimab and control group.

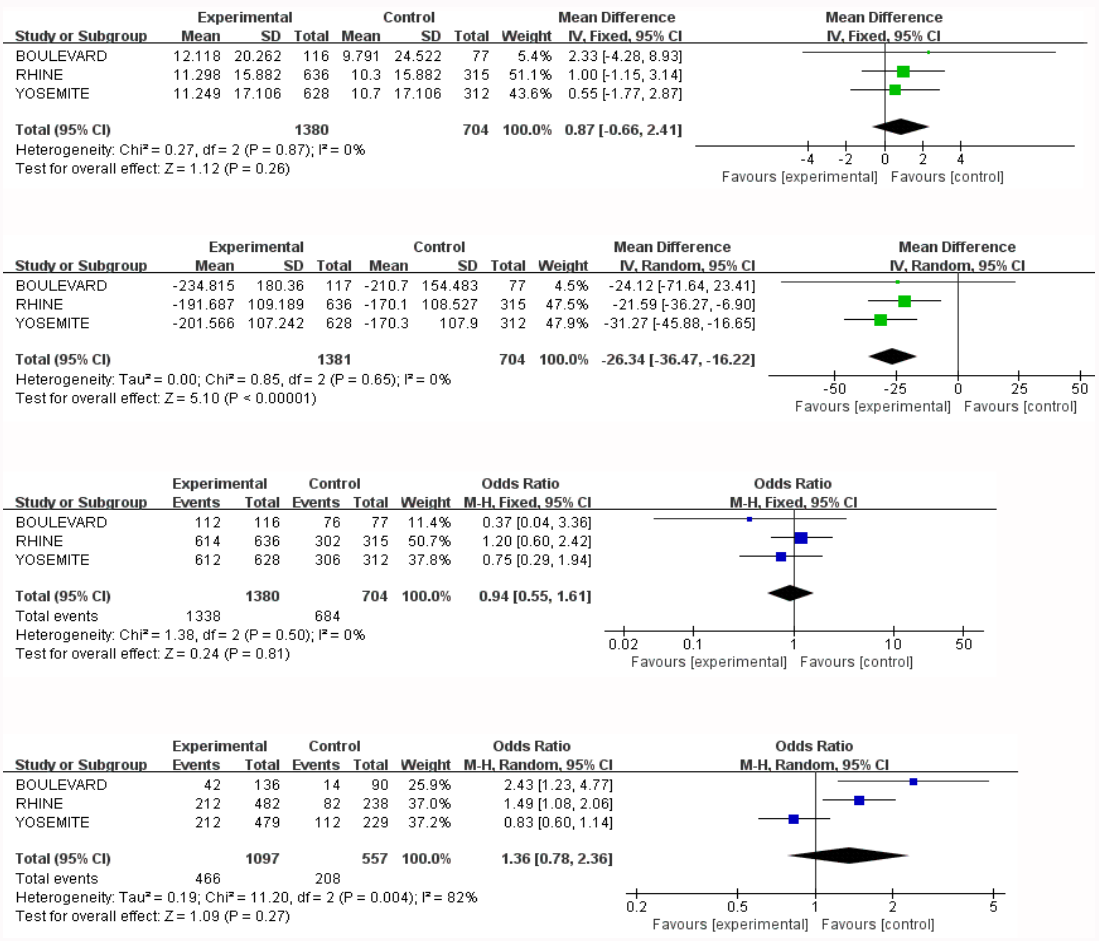

Figure 4: Comparison of the efficacy in DME treatment between faricimab and control group.

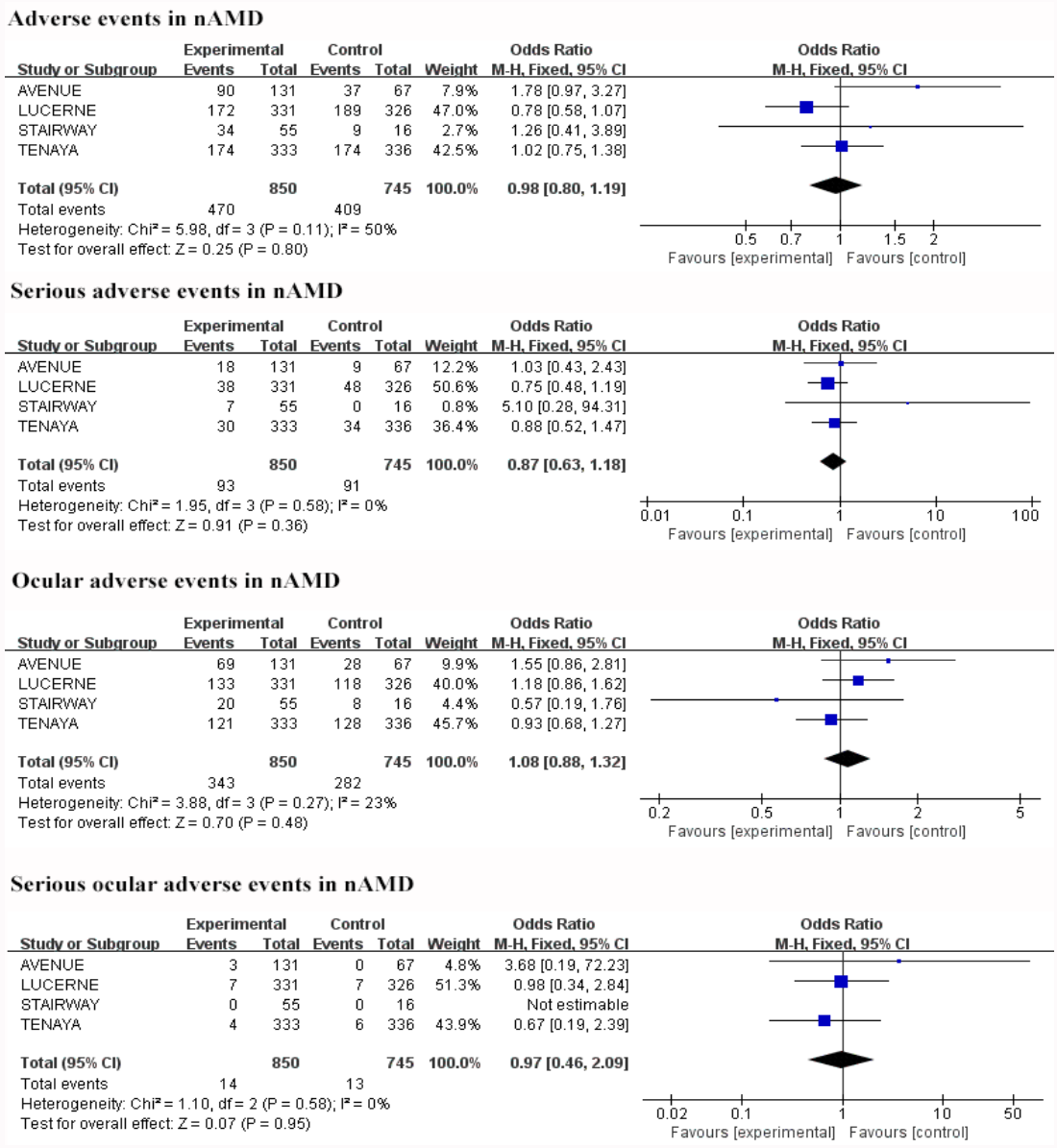

Figure 5: Analysis of safety profile of faricimab in nAMD treatment.

faricimab (1.5 mg, 6 mg), and the control group was treated with ranibizumab (0.5 mg) or aflibercept (2 mg), both of which were injected intraocularly. The analysis results showed that the change of BCVA was no statistical significance between faricimab and control drugs (MD 0.35, 95% CI -1.35 to 2.05, P=0.68) (Figure 3). This confirms that the effect of faricimab on BCVA change is non-inferior to that of ranibizumab and aflibercept. Likewise, changes in CSFT proved to be insignificant (MD -6.03, 95% CI -14.16 to 2.09, P=0.15) (Figure 3), and a fixed-effects model was employed with low heterogeneity (I^2=0%, P=0.8). MNV is one of the indicators representing disease progression in nAMD. A summary analysis of the change in total area of MNV showed non-statistical significance (MD -0.44, 95% CI -1.16 to 0.28, P=0.23) with low heterogeneity (I^2=0%, P=0.98) (Figure 3). It meant that faricimab was not inferior to ranibizumab and aflibercept in reducing area of MNV.

Efficacy in treating DME: Three RCTs (BOULEVARD, YOSEMITE, RHINE) reported efficacy data for faricimab in DME, including BCVA, changes in CSFT, absence of SRF, and two-step ETDRS-DRSS improvement. The experimental group received faricimab (1.5 mg, 6 mg), while the control group was administrated with Aflibercept 2 mg or Ranibizumab 0.3 mg. Likely, we selected the maximum time points of the changes in BCVA and CSFT in each study as data for inclusion in the analysis. The absence of SRF, and two-step ETDRS-DRSS mainly counts the number of occurrences in each group. There were no statistical differences between faricimab and control agents in BCVA changes (MD 0.87, 95% CI -0.66 to 2.41, P=0.26) (Figure 4). However, a pooled analysis of change in CSFT found that it was statistically significant compared to the control groups (MD-26.23, 95% CI -36.47 to -16.22, P<0.00001) (Figure 4), which demonstrated that faricimab group reduced CSFT more than control groups for treating DME, namely faricimab was superior to ranibizumab and aflibercept. Meanwhile, our meta-analysis results revealed that no statistically difference in occurrence of SRF absence (OR 0.94, 95% CI 0.55 to 1.61, P=0.81) (Figure 4) and two-step ETDRS-DRSS improvement (MD 1.36, 95% CI 0.78 to 2.36, P=0.27)

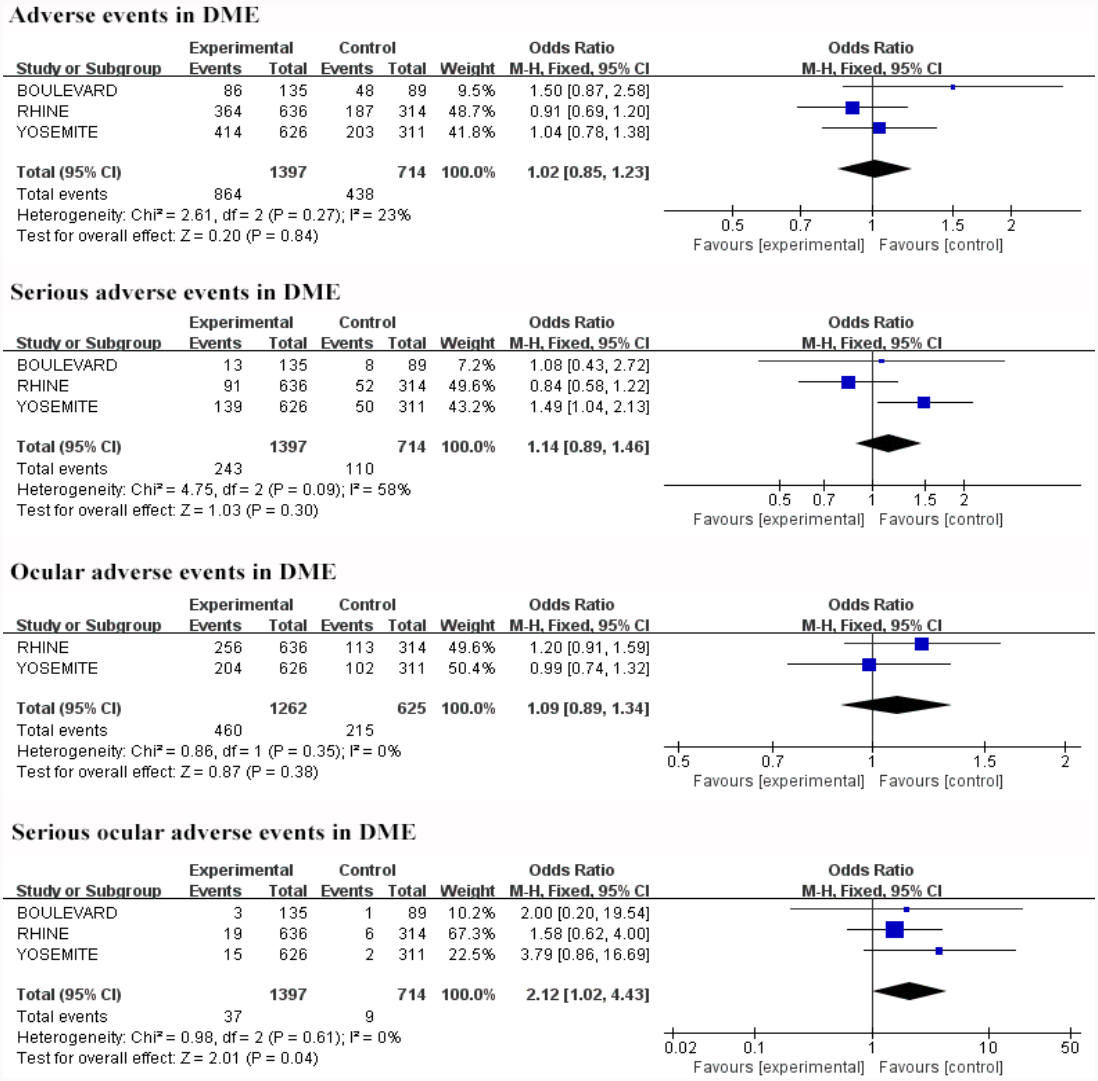

Figure 6: Analysis of safety profile of faricimab in DME treatment.

(Figure 4).

Evaluation of Safety

Safety in treating nAMD: Incidence of adverse events, serious adverse events, ocular adverse events, and serious ocular adverse events were selected as the safety indicators of faricimab in the treatment of nAMD. When collecting the number of patients with adverse events and serious adverse events in LUCERNE, TENAYA, RHINE, YOSEMITE, two investigators had different opinion. Finally, a third researcher resolved the differences and decided to use non-ocular adverse events and non-ocular serious adverse events as adverse events and serious adverse events, which improved the rigor of the article. All four RCTs (AVENUE, STAIRWAY, TENAYA, LUCERNE) were included in statistical analysis of the safety about faricimab treating nAMD.

Data processing results showed that the incidence of adverse events in faricimab group was similar to that in the control groups (OR 0, 98% CI 0.8 to 1.14, P=1.19) (Figure 5). Serious adverse events consisted of ear and labyrinth disorders, severe cardiac disorders, infections and infestations, nervous system disorders, neoplasms benign, malignant and unspecified (incl cysts and polyps), psychiatric disorders, injury, poisoning and procedural disorders. The meta-analysis showed that the incidence of serious adverse events caused by faricimab was similar to that caused by control agents (OR 0.87, 95% CI 0.63 to 1.18, P=0.36) (Figure 5), with low heterogeneity (I^2=0%, P=0.58).

Analysis of the incidence of ocular adverse events showed no apparent difference between faricimab and aflibercept, ranibizumab (OR 0.87, 95% CI 1.08 to 0.88, P=1.32) with low heterogeneity (I^2=23%, P=0.27) (Figure 5). Serious ocular adverse events including Glaucom, Keratic Precipitates, Macular hole, and Neovascular age-related disease, the incidence of which caused by faricimab was comparable to that caused by controls (OR 0.97, 95% CI 0.46 to 2.09, P=0.95) (Figure 5).

Safety in treating DME: The safety study of faricimab in DME also included the incidence of adverse events, serious adverse events, ocular adverse events, and serious ocular adverse events. All three RCTs (BOULEVARD, YOSEMITE, RHINE) reported data on adverse events, serious adverse events, and serious ocular adverse events; two RCTs (YOSEMITE, RHINE) reported data on ocular adverse events.

The pooled analysis results of the incidence of adverse events,

serious adverse events, and ocular adverse event revealed that faricimab was consistent with the other comparators and was not statistically significant (OR 1.02, 95% CI 0.85 to 1.23, P=0.84) (OR 1.14, 95% CI 0.89 to 1.48, P=0.3) (OR 1.09, 95% CI 0.89 to 1.34, P=0.38) (Figure 6). However, a meta-analysis of the incidence of serious ocular adverse events found a statistically significant difference between faricimab and the comparators (OR 2.14, 95% CI 1.02 to 4.43, P=0.04) (Figure 6). This suggested that more ocular adverse events may occur when faricimab is used in the treatment of DME.

Discussion

VEGF and Ang-2 are important genes regulating vascular angiogenesis, growth and maturation. VEGF can induce pathological MNV growth by binding VEGF receptors to trigger downstream signal and resulting vascular angiogenesis. Up-regulation of Ang-2 under pathological conditions can promote the effect of Ang-1 to boost vascular growth, cause vascular instability and increase the sensitivity of VEGF receptors [8]. Ang-2 and VEGF cooperates to lead vascular leakage, angiogenesis and inflammation, which has become a major main mechanism of retinal neovascular disease [12]. Currently, single anti-VEGF drugs commonly used to treat retinal neovascular mainly include brolucizumab, ranibizumab and aflibercept. Due to the singularity of the target, some patients do not have a complete response to anti-VEGF drugs. Some patients develop drug resistance and relapse. Moreover, the short interval between injections makes the patient's compliance not as high as it was expected [13].

Faricimab can block both the VEGF pathway and the Ang/Tie pathway. As a bispecific antibody, it undoubtedly opens up a new treatment idea for retinal neovascular diseases and overcomes the shortcomings of single therapeutic targets [14]. Phase I to III clinical trials [10,11,15-17] have confirmed that faricimab is effective in the treatment of nAMD and DME. However, due to the relatively small population of each clinical trial, different protocols, different control drugs, different types of diseases to be treated, different drug courses and doses, and different dosing intervals, it is impossible to obtain sufficient proof of efficacy and safety from individual RCTs. Therefore, we conducted a meta-analysis of the existing clinical research data on faricimab to overcome the above problems as much as possible and to obtain strong evidence of its safety and efficacy.

The findings of this study suggest that the changes in BCVA, CSFT, and MNV area were not statistically significant when faricimab was used in the treatment of nAMD, and its efficacy was non-inferior to aflibercept or ranibizumab. The statistical results of the four safety indicators of faricimab were also not different from those of the control group. It is proved that faricimab did not change its therapeutic efficacy and medication safety while prolonging the dosing interval. Slightly different, when faricimab was used in the treatment of DME, although the BCVA, SRF, two-step ETDRS-DRSS statistics were comparable to that of control agents, the CSFT decreased more, indicating that the effectiveness of faricimab increased. In terms of safety, attention should be paid to the incidence of serious ocular adverse events because the meta-analysis results of faricimab showed statistical significance. Nonetheless, this meta-analysis still has many restrictions. First, only 7 RCTs are included and our experimental sample is still relatively small, so our analysis outcomes may be different from the results of real-world applications. Secondly, four phase III experiments (YOSEMITE, RHINE, TENAYA, LUCERNE) only reported partial outcomes, which led to incomplete experimental data thus reducing the credibility of the results of this study. Finally, in the processing of data, due to the lack of source data for some items, we convert the existing data to obtain the consistent data between different researches and applied it in the analysis, which may cause some slight deviations in the final results. Despite the above deficiencies, this article is still the first article to evaluate faricimab with meta-analysis, which provided reference value for the efficacy and safety of faricimab.

Conclusion

Like aflibercept and ranibizumab, faricimab behaves similar in treating nAMD both in terms of efficacy and safety. When used in the treatment of DME, faricimab induced more CSFT reduction but caused higher risk of serious ocular adverse events. But its longer injection interval has better durability, and it may be used in the clinic as a better bispecific antibody drug for reducing disease burden in the future. More clinical trials are needed to provide evidence of its efficacy and safety.

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