ORIGINAL RESEARCH

Efficacy, Safety, and Treatment Burden of Aflibercept 2 mg and Ranibizumab in Retinal Vein Occlusion: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: This systematic review and meta-analysis aimed to provide an updated evidence base for clinical decision-making by comparing the efficacy and safety of aflibercept 2 mg and ranibizumab in treating retinal vein occlusion (RVO).

Methods: A systematic search was conducted using eight databases up to December 2021. Randomized controlled trials (RCTs) and real-world studies (RWSs) comparing aflibercept and ranibizumab in patients with RVO were evaluated. The primary outcomes assessed were efficacy, number of injections administered, and adverse events.

Results: Three RCTs (424 patients) and 11 RWSs (1415 patients) were included. For central RVO (CRVO), RCTs demonstrated a comparable efficacy, whereas RWSs showed that mean changes from baseline in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were significantly greater with aflibercept compared to ranibizumab; the number of injections of aflibercept was fewer than that of ranibizumab in RCTs, but similar in RWSs. For branch RVO (BRVO), no statistically significant difference in efficacy between the two drugs in RCTs/RWSs was observed, with fewer injections of aflibercept at 12 months in RWSs. The safety profiles of both drugs were similar for both CRVO and BRVO.

Conclusions: For CRVO, aflibercept had similar efficacy and safety profile but with fewer injections versus ranibizumab in RCTs; RWSs showed greater BCVA improvement and CRT reduction with aflibercept than ranibizumab. For BRVO, RCTs showed similar in efficacy, safety, and injection numbers for both drugs, while RWSs demonstrated that aflibercept required fewer injections at 12 months of follow-up. Overall, this study provides updated evidence for clinical decision-making in the treatment of RVO.

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Key Summary Points

Anti-vascular endothelial growth factor therapy has become the standard of care for retinal vein occlusion (RVO) treatment. Aflibercept and ranibizumab are commonly used drugs, but there is still no clear evidence of their comparative effectiveness.

We conducted a systematic review and meta-analysis of both randomized controlled trials and real-world studies to provide an updated evidence base for clinical decision-making by comparing the efficacy and safety of aflibercept 2 mg and ranibizumab in RVO.

The results demonstrated that both aflibercept 2 mg and ranibizumab are effective in improving visual function for patients with central RVO, with aflibercept requiring fewer treatment injections on average. Real-world studies showed that the mean changes in best-corrected visual acuity and central retinal thickness from baseline were greater with aflibercept, compared to ranibizumab. For patients with branch RVO, there was no significant difference in efficacy or safety between aflibercept and ranibizumab, but aflibercept required fewer treatment injections at 12 months in a real-world setting.

These findings provide valuable information for clinical decision-making in the treatment of RVO. More high-quality clinical studies should be conducted to elucidate the optimal treatment strategies for patients with RVO.

INTRODUCTION

Retinal vein occlusion (RVO) is a common, sight-threatening retinal vascular disorder [1], and is thought to be the result of thrombotic events, external compression, or vessel wall pathology [2]. RVOs can be divided into two main categories based on the site of obstruction: central RVO (CRVO) and branch RVO (BRVO) [3]. Research indicates that CRVO is caused by a combination of risk factors, including advanced age, hyperlipidemia, and hypertension [4]. The pathogenesis of BRVO is believed to involve both retinal vein compression by the corresponding retinal arteriole and damage to the vessel wall, resulting in thrombus formation [5]. CRVO and BRVO share similar clinical manifestations, with CRVO affecting a larger area [6]. The prevalence of CRVO is estimated to be 0.80 per 1000 persons, indicating that approximately 2.5 million adults are affected by CRVO globally [4, 7]. The prevalence of BRVO is estimated at 4.40 per 1000 persons, indicating that approximately 13.75 million adults are affected by BRVO globally [4, 7]. RVO can be classified as ischemic or non-ischemic types based on the degree of capillary non-perfusion, and such distinction is important for clinical management as ischemic RVO has a poorer visual outcome than non-ischemic RVO and requires more effective treatment [8].

Due to the severity and rising prevalence of RVO, effective and widely available treatments are necessary [4]. RVO is characterized by an increase in vascular endothelial growth factor (VEGF), which is a homodimeric protein that stimulates vascular endothelial cell growth and induces vascular permeability [9]. The increase in VEGF is a result of hypoxia caused by the occlusion and its sequelae. VEGF plays a crucial role in the pathophysiology process of retinal disease [10] and its levels were found to be elevated in the ocular fluids of patients with CRVO [11]. As a result, macular edema is a common pathological feature that leads to visual impairment in patients with RVO. Anti-VEGF therapy has become the standard of care for RVO treatment, as it has been proven to inhibit vascular leakage and effectively improve and

maintain vision. According to the latest EUR-ETINA guidelines, aflibercept and ranibizumab treatment have been accepted as the gold standard for treating macular edema secondary to RVO [12]. While other treatments such as grid laser photocoagulation for BRVO and pan-retinal photocoagulation for both CRVO and BRVO, as well as intravitreal corticosteroids, have also been used for this condition, the use of corticosteroids is associated with an increased risk of cataract progression and intraocular pressure elevation [13–15]. Compared to corticosteroids and photocoagulation, anti-VEGF therapy not only reduces these risks but also results in better visual acuity improvement. Several studies and systematic reviews have indicated that anti-VEGF therapy is superior in terms of safety and efficacy compared to corticosteroid and photocoagulation treatments [13–15]. Furthermore, the destructive nature of laser photocoagulation and the risk of laser scars remain concerns [16].

This study focuses solely on first-line treatment options and excludes other treatments such as corticosteroids. As first-line treatment, anti-VEGF drugs can be classified as anti-VEGF aptamer, antibodies to VEGF, antibody fragments to VEGF, and fusion proteins which consist of VEGF receptor(s) and Fc fragment of immunoglobulin, etc. [17, 18]. Aflibercept and ranibizumab are typical and representative drugs that are of clinical interest. Patients with ischemic RVO were included in in all three phase III clinical trials of aflibercept, and the proportion of patients ranged from 8% to 20% [19–21]. In contrast, almost all patients with ischemic RVO were excluded in the study of ranibizumab. Therefore, at the level of study design, studies investigating aflibercept included a more comprehensive patient population and better represents the real world. Previous head-to-head randomised controlled trials (RCTs) that compared aflibercept and ranibizumab are limited. Although relevant meta-analyses have provided indirect comparative results [2, 4, 5, 14], the conclusions remain unclear. Based on previous studies, there is no statistically significant difference between aflibercept and ranibizumab in vision improvement, although aflibercept may have a slight advantage over ranibizumab because it has been shown that fewer injections are required [4, 14]. In subsequent years, several relevant RCTs have been published [6, 7, 19, 22, 23], thus prompting this systematic evaluation study to be conducted to provide an updated evidence base for clinical decision-making, by comparing the efficacy and safety profile of aflibercept and ranibizumab in the treatment of RVO.

METHODS

This systemic literature review (SLR) and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA 2020) extension statement [24]. The protocol for this review has been registered in the PROSPERO database (CRD42022361445).

Search Strategy

Systematic search was conducted using PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Database, China Science and Technology Journal Database (VIP), and China Biology Medicine (CBM) Database up to December 2021. There were no restrictions on date, time, or literature design. This review uses a combination of subject words and free words. Our search strategies are reported in detail (Supplementary Materials Appendix 1).

Eligibility Criteria

RCTs and non-randomized controlled studies fulfilling the following criteria were included:

(1) adult patients (aged ≥ 18 years) with RVO;
(2) aflibercept monotherapy versus ranibizumab monotherapy. If combined with other drugs, administration of this in both groups should be consistent.

Studies were excluded if:

(1) they were not written in Chinese or English;
(2) follow-up was less than 6 months after full loading doses;

(3) they only had abstracts without full text.

For studies with multiple references, we included the most complete data available.

Outcome Measures

The primary outcomes included the mean change from baseline in best-corrected visual acuity (BCVA), the proportion of patients with complete resolution of macular edema, adverse events (AEs), and the number of injections administered. The secondary outcomes included the proportion of patients who gained at least 15 letters BCVA from baseline to a pre-defined follow-up time point, those who gained at least ten letters, mean change from baseline in central retinal thickness (CRT, μm), quality of life score and cost of treatment. Supplementary Materials Appendix 2 provides further details and explanations of these outcomes.

Study Selection

Two evaluators independently examined the search findings to recognize every potentially relevant reference, using titles and abstracts or full texts if requisite. Any discrepancy encountered during the sifting procedure was reconciled through deliberation and, if necessary, with the intervention of a third party. The procedure of study selection was presented in the PRISMA flow diagram (Fig. 1).

Data Extraction

Data extraction was independently performed by two reviewers using a specifically designed data extraction form. Any ambiguities in extraction were resolved by discussion with assistance from a third party if necessary. The extracted data included general study characteristics (including first author, publication year, contact information, study center involved, sample size); patient characteristics (including gender, age, baseline visual acuity, baseline CRT, RVO duration, etc.); intervention characteristics (including name, dose,

frequency, drug combination); outcome definitions, timepoint of follow-up, and results data.

Assessment of Risk of Bias

The quality of the RCTs was assessed utilizing the Cochrane Risk of Bias tool [25], encompassing sequence generation, allocation concealment, masking of participants and personnel, outcome evaluation concealment, absent result data, and selective result articulation. A bias risk chart and a bias risk summary were subsequently generated, with green, yellow, and red suggesting low risk, unclear risk, and high risk, respectively. In the presence of any discrepancies, we sought resolution through dialogue with intervention from an external third party when deemed appropriate.

The quality of the included non-randomized controlled studies was assessed using the Newcastle–Ottawa Scale (NOS) [26], including three main categories of eight items: selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that no study subjects already had the disease under review at the start of this study); comparability (of the exposed and non-exposed cohorts [design and analysis phases]); and outcome (assessment of outcomes, whether follow-up was sufficiently long for the disease studied, and completeness of follow-up). Disagreements were resolved through discussion, with third-party assistance if necessary.

Data Analysis

Data was synthesized with a random-effects model considering the clinical and methodological heterogeneity and analyzed using Rev-Man version 5.4 (Review Manager software, Cochrane Collaboration, 2020). For dichotomous results, we computed risk ratios (RRs) along with their 95% confidence intervals (CIs). For continuous results, we calculated mean differences (MDs) accompanied by their 95% CIs. Prior to initiating the meta-analysis, a comprehensive discussion concerning clinical and methodological heterogeneity took place. A
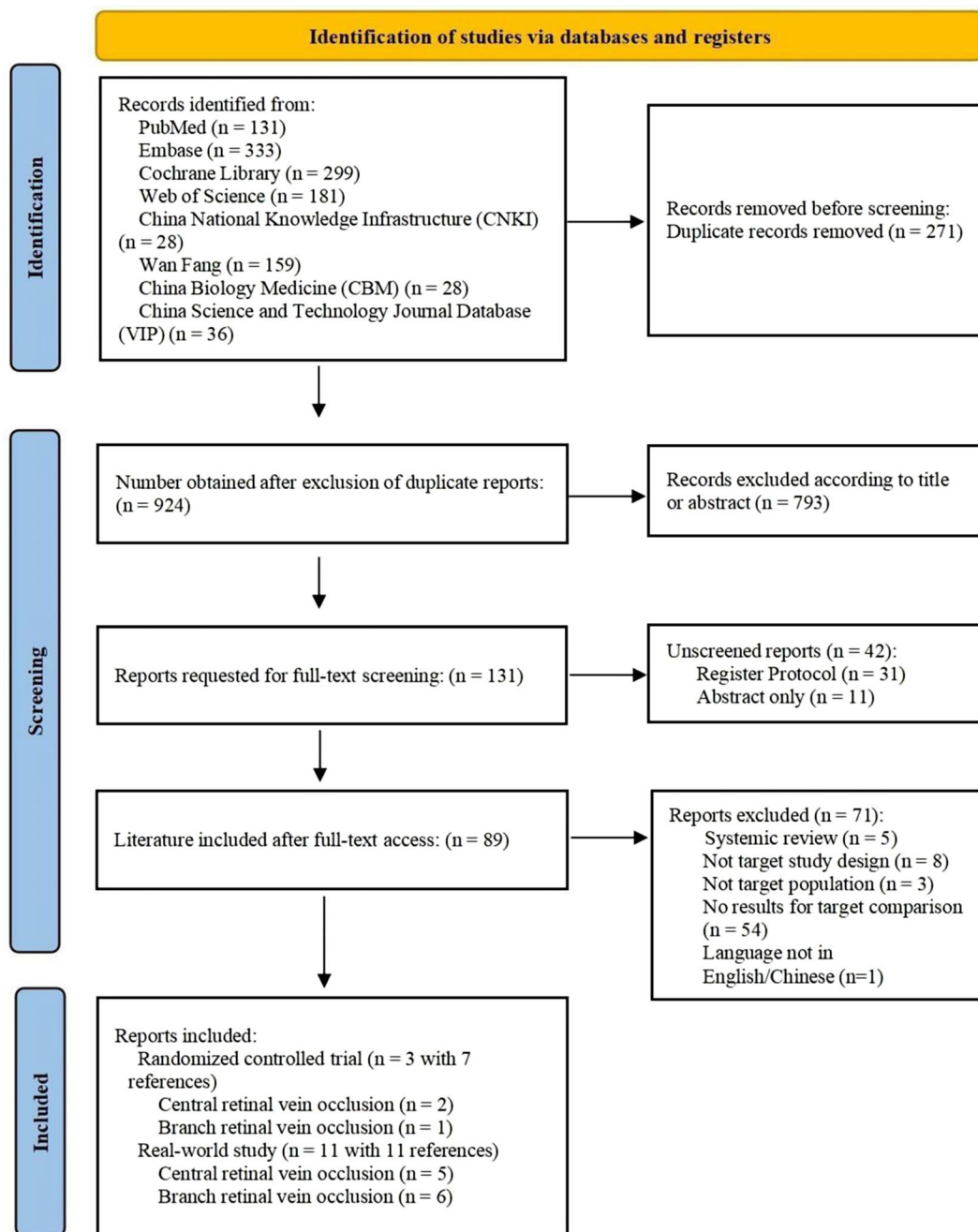
Fig. 1 PRISMA flow diagram

detailed narrative of the outcome date was provided in case meta-analyses were deemed unsuitable.

We defined $I^2 \geq 50\%$ with a statistically significant χ^2 test result ($P < 0.1$) as evidence of substantial levels of heterogeneity, where I^2 measures the proportion of variation that is due to between-study heterogeneity rather than due to chance [27]. Results of statistical heterogeneity were discussed. We analyzed the outcome of RCTs and non-randomized controlled studies to determine whether the difference was statistically significant between aflibercept and ranibizumab. The data obtained from using

different measurement standards for the same outcome indicator were transformed and standardized (Supplementary Materials Appendix 2). Sensitivity analyses were conducted with and without transformed and standardized data to ensure the robustness of the conclusions.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection

The initial search of electronic databases yielded 1195 references, from which 131 records were selected based on the examination of titles and abstracts. Finally, three RCTs with 424 patients and 11 real-world studies (RWSs) with 1415 patients were included (Fig. 1). Refer to Supplementary Materials Table S1 for the reasons for excluding or awaiting.

Study Characteristics

For CRVO, two RCTs [28, 29] with 352 patients from Sweden and England were used. The average age of these patients ranged from 68.7 to 70.1 years, and their baseline BCVA letters ranged from 45.9 to 54.1. There were five RWSs [1, 30–33], with patients from Sweden, England, Turkey, Greece, the USA, Switzerland, Australia, and France. Patients were treatment-naïve at baseline and the total sample size was 722, including groups ranging from 34 to 291 in number. One RWS [32] reported the median age as being 74 and 76 years in the two groups, respectively, and another four trials [1, 30, 31, 33] reported that the average age ranged from 61.2 to 73 years. Four RWSs [1, 30, 31, 33] reported that the average baseline of BCVA letters ranged from 28 to 65.3. In one study, only non-ischemic cases were included [1]. The other two studies did not report the

type of ischemia in patients [28, 32]. Other studies involved a mixed population of patients with ischemic or non-ischemic CRVO [29–31, 33] (Supplementary Materials Table S2).

For BRVO, one RCT [34] which included 70 treatment-naïve patients from Abu Dhabi reported that the average age ranged from 54.8 to 55.8 years and the average baseline of BCVA letters ranged from 56 to 59. Six RWSs [35–40] with a total of 693 patients (including the first treatment group [35–37, 39, 40] and the non-first treatment group [38]) from Israel, the UK, Australia, and Turkey had sample sizes ranging from 42 to 319. One RWS [39] reported the median age as being 74 years, and the median baseline of BCVA letters was 60. The other five RWSs [35–38, 40] reported that the mean age ranged from 62 to 71 years and that the average baseline of BCVA letters ranged from 56.9 to 67.5. Three studies exclusively included non-ischemic cases [34, 36, 40]. One study did not report the ischemic type of the patients [39], while the remaining studies involved a mixed population of patients with ischemic or non-ischemic BRVO [35, 37, 38] (Supplementary Materials Table S3).

This study also reported the intervention characteristics of CRVO and BRVO (Supplementary Materials Table S4, Table S5). Aflibercept was administered with a treatment dose of 2 mg/0.05 ml in all included studies, except for two studies that did not report the dose. Ranibizumab was administered with a treatment dose of 0.5 mg/0.05 ml in most studies, with only one study reporting a dose of 1.25 mg. Three studies administered either aflibercept or ranibizumab followed by moxifloxacin or ofloxacin eye drops to all patients. All other studies reported monotherapy treatment (Supplementary Materials Table S4, Table S5). Details of inclusion/exclusion criteria for each included study are provided in Supplementary Materials Table S6.

Risk of Bias in Included Studies

All the RCTs included in this study adequately reported random sequence generation and allocation concealment. Masking of the

outcome measurers was ensured in all studies, all outcomes predefined in the protocol were reported and no other risks were found. We rated some RCTs (33.3%) as risk unclear because these studies did not provide any information about masking. Some RCTs (33.3%) were rated as high risk because the loss of follow-up rate was more than 20%, or the loss between groups was unbalanced or unknown (Supplementary Materials Table S7 and Figure S1).

The NOS results for RWSs indicated that, in the category of selection, one study [1] received a score of 3, with the exception of a score of zero in the item of selection of the non-exposed cohort, and other studies got a score of 4; in the category of comparability, all studies received a score of 1; in the category of outcome, three studies [30, 38, 39] received a score of 2, with the exception of a score of zero in the item of completeness of follow-up and other studies received a score of 3. Seven studies [31–33, 35–37, 40] received a total score of 8, while four studies [1, 30, 38, 39] received a score of 7. All included studies were of high quality (Supplementary Materials Table S8 and Table S9). The key baseline characteristics, including age, BCVA score, CRT, and underlying health condition, were well balanced between the two compared groups, and known confounders were generally adequately controlled in most of these RWSs.

Change from Baseline in BCVA Letters

For studies about CRVO, two RCTs [28, 29] reported a change from baseline in BCVA letters at 18 months and 23 months, respectively. Regarding the meta-analysis, there was no significant difference between the two drugs ($n = 352$, MD 2.31, 95% CI -1.51 to 6.14, $P = 0.24$), and the individual results from both studies also showed no statistically significant difference (Supplementary Materials Figure S2). Three RWSs [1, 30, 33] reported a change from baseline in BCVA letters at 6 months and 12 months, respectively. The results for the two RWSs [1, 33] with BCVA change measured at 6 months showed a numerical trend of higher improvement for aflibercept compared with

ranibizumab, but the difference was not statistically significant ($n = 84$, MD 5.09, 95% CI -16.19 to 26.37, $P = 0.64$) (Fig. 2), similar to the subgroup of patients with non-ischemic CRVO (Supplementary Materials Table S10). The results based on one study [30] with 12-month outcome showed a significant improvement in vision of BCVA letters ($n = 296$, MD 6.80, 95% CI 1.18–12.42, $P = 0.02$) (Fig. 2).

For studies of BRVO, one RCT [34] reported that there was no difference between the two groups in terms of the change from baseline in BCVA letter results. We have provided a descriptive summary of the outcome data (Supplementary Materials Table S11). Six RWSs [35–40] reported changes from baseline in BCVA letters at 6 months, 9 months and 12 months, respectively; results showed that there was no statistical significance between aflibercept and ranibizumab (6 months: $n = 105$, MD 1.43, 95% CI -0.96 to 3.82, $P = 0.24$ [36, 40]; 9 months: $n = 105$, MD 0.73, 95% CI -1.54 to 3.00, $P = 0.53$ [36, 40]; 12 months: $n = 696$, MD 0.96, 95% CI -0.77 to 2.70, $P = 0.28$ [35–40]) (Supplementary Materials Figure S3). Results were similar to the subgroup of patients with non-ischemic BRVO (Supplementary Materials Table S10).

Proportions of Patients with Complete Resolution of Macular Edema

For CRVO, one RWS [31] reported the proportion of patients with complete resolution of macular edema at 6 months, 12 months, and 18 months, respectively. The results showed that there was no statistically significant difference between aflibercept and ranibizumab (6 months: $n = 62$, RR 0.95, 95% CI 0.52–1.76, $P = 0.88$; 12 months: $n = 62$, RR 0.89, 95% CI 0.56–1.44, $P = 0.65$; 18 months: $n = 62$, RR 0.86, 95% CI 0.50–1.48, $P = 0.58$) (Fig. 3).

For BRVO, one RWS [37] reported the proportion of patients with complete resolution of macular edema at 12 months. There was no statistically significant difference observed between the two groups (Supplementary Materials Table S12).
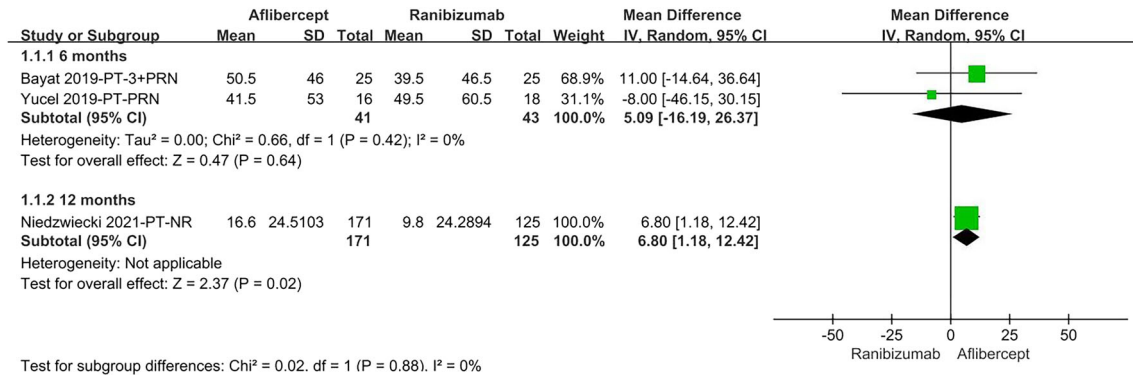
Fig. 2 Meta-analysis of aflibercept versus ranibizumab for CRVO of RWSs: change from baseline in BCVA letters. *BCVA* best-corrected visual acuity, *CI* confidence interval, *CRVO* central retinal vein occlusion, *NR* not reported, *PRN* pro re nata, *PT* primary treatment, *RWSs* real-world studies, *SD* standard deviation

Adverse Events

For CRVO studies, two RCTs [28, 29] reported serious AEs and ocular AEs, respectively. The safety profiles of the two drugs were similar (Supplementary Materials Figure S4). Two RWSs [1, 33] reported cataract development and elevated intraocular pressure; the proportions of patients with these AEs were comparable for the two drugs (Supplementary Materials Figure S5). In the two RCTs [28, 29], no inflammation (IOI) was reported, and in one RWS [31], no endophthalmitis events were reported.

Three RWSs [38–40] reported AEs in BRVO studies, but the difference was not significant (Supplementary Materials Table S13, Figure S6).

One RWS [35] reported one case of endophthalmitis but did not specify in which group.

The Number of Injections Administered

For studies on CRVO, two RCTs [28, 29] reported the number of injections at 6 months, 12 months, 18 months, and 23 months. The results showed that the number of injections was significantly lower in the aflibercept group compared with the ranibizumab group (6 months: $n = 352$, MD $- 0.35$, 95% CI $- 0.50$ to $- 0.21$, $P < 0.00001$ [28, 29]; 12 months: $n = 352$, MD $- 1.42$, 95% CI $- 2.27$ to $- 0.58$, $P = 0.0010$ [28, 29]; 18 months: $n = 43$, MD $- 3.50$, 95% CI $- 5.51$ to $- 1.49$, $P = 0.0007$ [28]; 23 months: $n = 309$, MD $- 1.80$, 95% CI
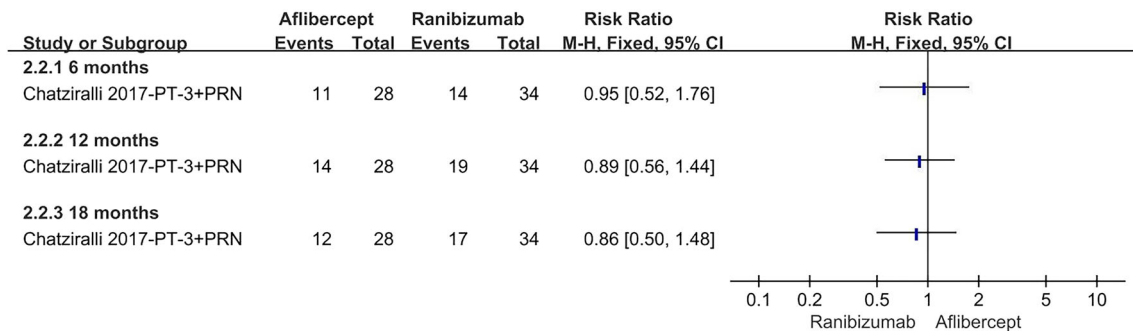

Fig. 3 Results of aflibercept versus ranibizumab for CRVO of RWSs: proportions of patients with complete resolution of macular edema. *CI* confidence interval, *CRVO* central retinal vein occlusion, *PRN* pro re nata, *PT* primary treatment, *RWSs* real-world studies

− 2.93 to − 0.67, *P* = 0.002 [29]) (Fig. 4). Five RWSs [1, 30–33] reported the number of injections at 6 months, 12 months, and 18 months, respectively. The results of the meta-analysis showed that there was no statistically significant difference between the two groups (6 months: *n* = 382, MD − 0.09, 95% CI − 0.49 to 0.32, *P* = 0.67 [1, 30, 33]; 12 months: *n* = 581, MD 0.30, 95% CI − 0.27 to 0.87, *P* = 0.30 [30, 32]; 18 months: *n* = 62, MD − 0.70, 95% CI − 1.56 to 0.16, *P* = 0.11 [31]) (Supplementary Materials Figure S7).

For BRVO studies, three RWSs [36, 37, 40] reported the number of injections of aflibercept and ranibizumab. The results from one RWS [36] with 6-month outcome showed a fewer number of injections of aflibercept compared with ranibizumab, but the difference was not statistically significant (*n* = 63, MD − 0.20, 95% CI − 0.47 to 0.07, *P* = 0.15); and the results based on two RWSs [37, 40] with 12-month outcome showed a fewer number of injections of aflibercept compared with ranibizumab, with a statistically significant difference (*n* = 104,

MD − 0.59, 95% CI − 0.96 to − 0.22, *P* = 0.002) (Fig. 5). One RWS [35] only reports the median and interquartile range of each group of data, without reporting the follow-up period; one RCT [34] reported the number of injections at 12 months, and there was no statistical difference between the two groups (Supplementary Materials Table S14, Table S15).

Change from Baseline in CRT

For CRVO studies, two RCTs [28, 29] reported the change from baseline in CRT at 18 months and 23 months, respectively. The evidence is insufficient to show a statistically significant difference between aflibercept and ranibizumab (*n* = 352, MD 22.64, 95% CI − 28.84 to 74.12, *P* = 0.39), and the individual results from both studies also showed no statistically significant difference (Supplementary Materials Figure S8). Three RWSs [1, 30, 33] reported the change from baseline in CRT at 6 months and 12 months, respectively; the results of the meta-analysis based on two RWSs [1, 33] with
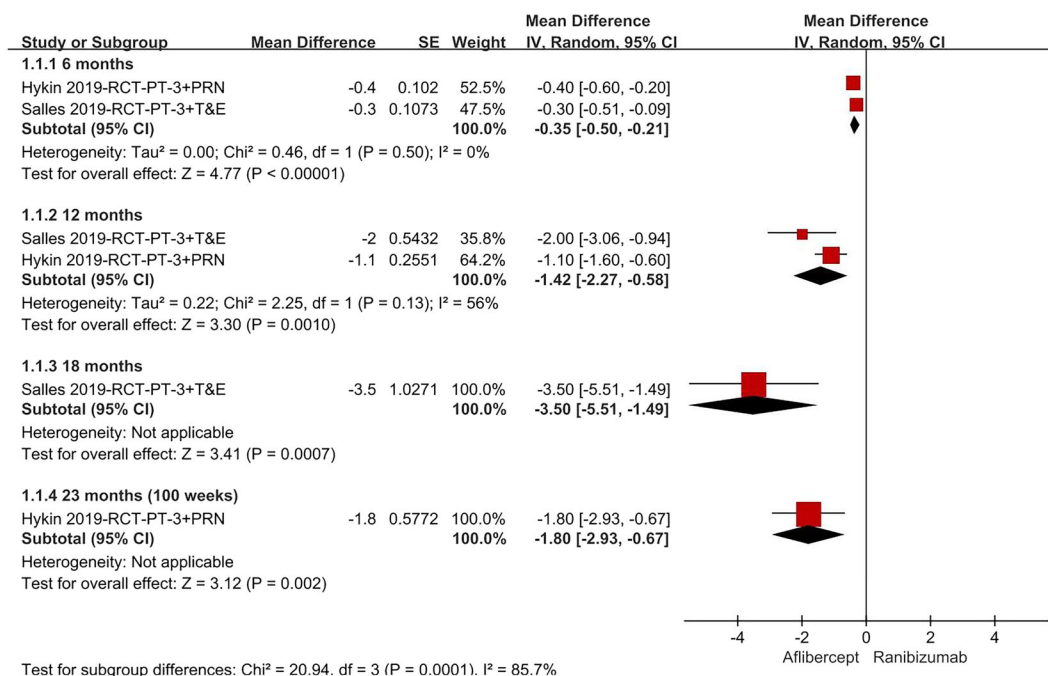

Fig. 4 Meta-analysis of aflibercept versus ranibizumab for CRVO of RCTs: the number of injections. *CI* confidence interval, *CRVO* central retinal vein occlusion, *PRN* pro re

nata, *PT* primary treatment, *RCTs* randomized controlled trials, *SE* standard error, *T&E* treat and extend
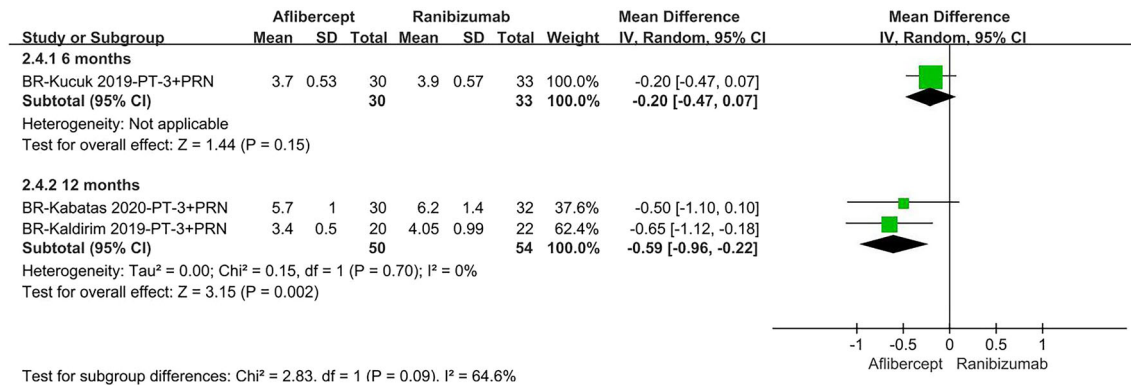
Fig. 5 Meta-analysis of aflibercept versus ranibizumab for BRVO of RWSs: the number of injections. *BRVO* branch retinal vein occlusion, *CI* confidence interval, *PRN* pro re nata, *PT* primary treatment, *RWSs* real-world studies, *SD* standard deviation

6-month outcome showed that aflibercept had a greater effect than ranibizumab, but the difference was not statistically significant ($n = 84$, MD -50.34, 95% CI -130.46 to 29.79, $P = 0.22$) (Supplementary Materials Figure S9), similar to the subgroup of patients with non-ischemic CRVO (Supplementary Materials Table S10); the result based on one RWS [30] with 12-month outcome showed a statistically significant improvement in CRT reduction between aflibercept and ranibizumab ($n = 296$, MD -52.00, 95% CI -94.15 to -9.85, $P = 0.02$) (Supplementary Materials Figure S9).

For BRVO studies, five RWSs [35–38, 40] reported the change from baseline in CRT; the results of meta-analysis showed that there was no statistically significant difference between aflibercept and ranibizumab (6 months: $n = 105$, MD -16.78, 95% CI -45.21 to 11.66, $P = 0.25$ [36, 40]; 9 months: $n = 105$, MD -7.47, 95% CI -37.80 to 22.87, $P = 0.63$ [40]; 12 months: $n = 516$, MD -7.76, 95% CI -18.54 to 3.02, $P = 0.16$ [35–38, 40]) (Supplementary Materials Figure S10), similar to the subgroup of patients with non-ischemic BRVO (Supplementary Materials Table S10).

The Proportion of Patients Who Gained At Least 15 or 10 Letters in BCVA

For CRVO studies, two RCTs [28, 29] and two RWSs [1, 31] reported the proportion of patients who gained at least 15 letters, whereas one RCT [29] and one RWS [31] reported the proportion of patients who gained at least ten letters in BCVA at different time points, respectively. The results showed no statistically significant difference between aflibercept and ranibizumab (Supplementary Materials Figures S11–S14).

Sensitivity Analysis

The results of the sensitivity analysis on the change from baseline in CRT and BCVA letters, and the number of injections, were similar to the main results (Supplementary Materials Figures S15–S25).

DISCUSSION

This systematic review summarized the results of three RCTs involving 424 patients and 11 RWSs involving 1415 patients. Both aflibercept and ranibizumab are anti-VEGF agents that improve visual acuity by reducing retinal edema through VEGF inhibition. In RCTs of CRVO, both drugs demonstrated similar efficacy, whereas in RWSs, aflibercept demonstrated greater improvement in BCVA and reduction in CRT compared to ranibizumab at 6 months with a numerical trend, and with statistically significant difference presenting at 12 months. This inconsistency could be attributed to differences in baseline characteristics, disease severity, and treatment regimens between real-

world clinical practice and RCTs. However, this inconsistency was not observed in patients with BRVO (i.e., no statistically significant differences in efficacy in both RCTs and RWSs), which might be related to the clinical symptoms of BRVO being relatively mild and the "ceiling effect" of drug treatment, which reduces the differences in drug efficacy. There were no statistically significant differences between the two drugs in other outcomes, such as the proportion of patients with complete resolution of retinal edema in RCTs and RWSs. In both RCTs of CRVO and RWSs of BRVO studies, aflibercept showed fewer injections than that for ranibizumab. This could be related to the pharmacokinetics properties of aflibercept and its affinity for binding to VEGF [41]. It is important to note that for these in RCTs of CRVO, although same treatment regimen was pre-defined (e.g., treat-and-extend [T&E] or pro-re-nata [PRN]) per the RCT protocol for both treatment groups, the actual number of injections would still be flexible due to the difference in the treatment needs for each patient under T&E or PRN. This could potentially result in statistical differences in the number of injections. The safety profiles of the two drugs were similar in both CRVO and BRVO in RCTs and RWSs. Quality of life score and cost were not reported.

Previous studies have conducted indirect comparisons of aflibercept and ranibizumab through meta-analysis, specifically in terms of the proportion of patients who gained at least 15 letters in BCVA. One network meta-analysis study [4] measured this outcome at 12 months and indicated that there was no statistically significant difference between aflibercept and ranibizumab (RR 1.45, 95% CI 0.21–9.28). In this study, the results of meta-analysis about the same outcome measured at 18 months and 23 months showed that there was no statistically significant difference between aflibercept and ranibizumab (RR 1.12, 95% CI 0.91–1.38). In terms of the change from baseline in BCVA at 6 months, the network meta-analysis study [4] reported that there was no statistically significant difference between the two groups (MD 4.04, 95% CI − 11.09 to 21.23), and another network meta-analysis study [5] demonstrated

that there was no statistically significant difference between aflibercept and ranibizumab (MD − 3.33, 95% CI − 8.55 to 1.90). In this study, where the above outcome was measured at 18 months and 23 months, the meta-analysis showed that there was no statistically significant difference between aflibercept and ranibizumab (MD 2.31, 95% CI − 1.51 to 6.14). To sum up, the results of the current study are consistent with those of previous studies.

This study is the first SLR and meta-analysis that evaluates the evidence of the comparison between aflibercept and ranibizumab in patients with BRVO and CRVO, with comprehensive data from both RCTs and RWSs. Multiple outcomes, including efficacy, safety, and the number of injections administered, were summarized. The protocol was detailed, and the search was comprehensive. If necessary, manual retrieval of information was incorporated. Two researchers screened the large sample of records independently, referring to a third-party researcher where consensus could not be reached. The robustness of the findings was confirmed by sensitivity analysis.

This study also has several limitations that should be considered. The number of RCTs available is small and their quality varies, which may affect the validity of the study results, but the consistent results from sensitivity analysis can help to mitigate this limitation. It should be noted that a risk of bias of publishing may exist because all included studies were written in English or Chinese exclusively, and the inclusion of only published studies and the lack of grey literature may limit the comprehensiveness of the analysis. Furthermore, the included studies did not report outcome measures such as retinal artery and vein blood flow and vessel diameter, as well as treatment cost and patient quality of life scores, which may limit the overall assessment of treatment efficacy and safety. In addressing clinical concerns regarding the necessity to switch to alternative therapeutic strategies, the current literature appears to be limited. We identified only one study [39] that provided comparative data on this matter. This study reported on a cohort of 35 eyes that continued treatment with ranibizumab and 77 eyes that switched from ranibizumab to

aflibercept. The outcomes measured were the average number of injections and the proportion of patients without macular edema at follow-up intervals of 3, 6, 12, and 24 months. The scarcity of similar studies limits our ability to draw broader conclusions. In addition, although RWSs were included, the current evidence base is still limited, and the analysis may not be sufficiently powered to conduct comprehensive subgroup analysis due to the lack of adequate data for differentiating between patients with ischemic and non-ischemic RVO, or comparison for outcomes measured at certain time points. The evaluation of heterogeneity might also be impeded. When analyzing results based on RWSs, it is important to note that although the baseline key characteristics were balanced in most studies, results may still be affected by unobserved confounders and should be interpreted cautiously. Future studies should focus on exploring new treatment regimens for anti-VEGF therapies, such as aflibercept 8 mg, and should also consider specific populations, such as patients with ischemic RVO.

CONCLUSIONS

The results based on the meta-analysis demonstrated that in RCTs of patients with CRVO, both aflibercept 2 mg and ranibizumab demonstrated comparable efficacy in improving visual function. Aflibercept exhibited a safety profile similar to that of ranibizumab. On average, aflibercept required fewer treatment injections than ranibizumab, thereby reducing the treatment burden. RWSs showed that aflibercept demonstrated greater improvement in BCVA and reduction in CRT compared to ranibizumab. Aflibercept and ranibizumab had similar AE rates, and the number of treatment injections required for both drugs was similar at 6, 12, and 18 months of follow-up. For patients with BRVO, RCTs showed that there was no significant difference in efficacy between aflibercept and ranibizumab. Both drugs showed a comparable safety profile without any severe ocular or systemic AEs. In terms of treatment burden, there was no significant difference in the number of treatment injections required between aflibercept and ranibizumab. In RWSs, there was no significant difference in efficacy between aflibercept and ranibizumab, and the incidence of AEs was similar between the two groups without any statistically significant difference. At 12 months of follow-up, aflibercept required fewer treatment injections than ranibizumab. These findings provide updated evidence for clinical decision-making in the treatment of RVO.

Data Availability. All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of Interest. Fang Qi and Zhan Zhao are employees Shanghai Daotian Evidence-based Technology Co., Ltd, Shanghai, China. Zhe Xu is an employee of Bayer Healthcare Company Ltd., Beijing, China. Jing Wu, Xiaoning He and Hong Yan declare that they have no competing interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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