

Antivascular endothelial growth factor for macular oedema secondary to retinal vein occlusion: a systematic review and meta-analysis

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ABSTRACT

Purpose To evaluate the efficacy and safety of antivascular endothelial growth factor (anti-VEGF) agents in treating macular oedema due to retinal vein occlusion (RVO-ME).

Methods Studies of randomised controlled trials were searched in PubMed, EMBASE, Cochrane databases and ClinicalTrials.gov registry. RevMan V.5.4 software and GRADE were used to synthesise the data and validate the evidence, respectively.

Results Seventeen studies were included in this meta-analysis. The anti-VEGF agents showed significant better mean best-corrected visual acuity (BCVA) improvement, more patients with ≥ 15 Early Treatment in Diabetic Retinopathy Study (ETDRS) letters gained and fewer patients with ≥ 15 ETDRS letters lost, more effectiveness at reducing central retinal thickness (CRT) and improving the quality of life than sham and steroids both at 6 and 12 months. Compared with laser, the anti-VEGF agents showed significant BCVA improvement and more effectiveness at CRT both at 6 and 12 months. The proportion of eyes gaining ≥ 15 ETDRS letters was greater in the anti-VEGF group at 6 months. The anti-VEGF and other three groups reported similar levels of non-ocular serious adverse events (SAEs). The incidence of eye pain was significantly higher in the anti-VEGF group than in the sham group. There was a significant increase in the incidence of ocular AEs and conjunctival haemorrhage in the anti-VEGF group compared with the laser group. The incidence of elevated intraocular pressure and cataract was significantly higher in the steroid group than in the anti-VEGF group.

Conclusions This meta-analysis suggested that treatment of ME secondary to RVO with anti-VEGF improves visual and anatomical outcomes compared with other treatments. Thus, anti-VEGF treatment is the first choice for treating patients with ME secondary to RVO.

INTRODUCTION

Retinal vein occlusion (RVO) is a heterogeneous disease, in which the thrombus is formed the retinal venous system, resulting in the obstruction of venous return from the retinal circulation.¹ The classification of RVO depends on the site of occlusion: branch RVO (BRVO) and central RVO (CRVO).² Both

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several systematic reviews have compared the efficacy and safety between antivascular endothelial growth factor (anti-VEGF) agents and non-anti-VEGF treatments but mainly focused on one anti-VEGF agent.

WHAT THIS STUDY ADDS

⇒ A large number of trials conducted in varied anti-VEGF agents have been included. We compared the efficacy of anti-VEGF agents in the branch retinal vein occlusion and central retinal vein occlusion subgroups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For some comparisons, the number of trials included was few, and outcomes reported were few.

CRVO and BRVO can be further classified into non-ischaemic subtype and ischaemic subtype based on the amount of retinal capillary perfusion. BRVO typically occurs at an arteriovenous intersection, whereas CRVO at or near the lamina cribrosa of the optic nerve. Both BRVO and CRVO share the same characteristic signs on fundus evaluation such as vein dilatation, haemorrhages, oedema and vascular stasis.³ But the ischaemic index in CRVO is much higher than that in BRVO and the retinal ischaemia in CRVO was more severe than that in BRVO.⁴ BRVO is more common than CRVO, but less visually damaging, than CRVO. The worldwide prevalence of BRVO is estimated at 0.4% and CRVO at around 0.08% with equal distribution between men and women and increased risk with older age.⁵ In most patients with RVO, macular oedema (ME) is the predominant cause of visual loss in the acute and chronic stages.⁶

Laser photocoagulation, intravitreal steroids and antivascular endothelial growth factor (anti-VEGF) agents all have demonstrated

therapeutic benefits in eyes with ME secondary to RVO (RVO-ME).^{7–11} Laser photocoagulation has been the primary RVO treatment for the past several decades. Intravitreal steroids (eg, triamcinolone and dexamethasone) have also been therapeutic options. Anti-VEGF agents have been considered the first-line treatment for RVO-ME. Ranibizumab and aflibercept were approved by the Food and Drug Administration of the United States (FDA) and the European Medicines Agency (EMA) for the treatment of RVO-ME. Bevacizumab has not yet been approved by FDA and EMA for ocular indications but is widely used as an off-label treatment for RVO-ME owing to its cost-effectiveness. Conbercept, a recombinant fusion protein with high affinity to all VEGF isoforms and placental growth factor,¹² was developed, approved and widely used for RVO-ME in China. However, all the methods have their limitations. Laser therapy is easy to cause iatrogenic injury of the retina. Intravitreal steroids are associated with the risk of glaucoma and cataract formation. Anti-VEGF agents need repeated injections to achieve a stable effect, which have the risk of infection and related injection complications.

Several systematic reviews have compared the efficacy and safety between the anti-VEGF agents and other treatments, but the clinical results are inconsistent and controversial.^{13–15} The previous meta-analysis of clinical trials that examined treating RVO with anti-VEGF agents have mainly focused on one anti-VEGF agent. To date, there have been few systematic reviews involving a direct comparison of anti-VEGF agents to other treatments including intravitreal steroids and laser for treating ME secondary to BRVO and CRVO. Given that the most common anti-VEGF agents all have the same therapeutic mechanism, data from studies with each of these agents can be combined into one group to expand the sample size. Therefore, our meta-analysis was conducted to quantify the main efficacy outcomes and adverse effects of anti-VEGF agents and non-anti-VEGF treatment strategies for treating RVO-ME by combining data from randomised controlled trials (RCTs). We compared the efficacies at different follow-up periods and also compared the efficacies of anti-VEGF treatment and other treatments in the BRVO and CRVO subgroups. We hope that our findings will aid treating ophthalmologists in choosing the best treatment options for their patients with RVO.

METHODS

Protocol register

This protocol of systematic review and meta-analysis has been drafted under the guidance of the Preferred Reporting Items for Systematic reviews and Meta-Analysis. In addition, it has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) on 20 December 2021 (Registration number: CRD42022298899).

Search strategy

A systematic literature search including PubMed, Embase, Cochrane databases and ClinicalTrials was conducted from inception to 6 January 2022, with no language restrictions. Previous systematic reviews were also reviewed to identify additional eligible studies. We used the MeSH term ‘retinal vein occlusion’ and the words ‘*RVO’, ‘*VEGF*’, ‘bevacizumab’, ‘Avastin’, ‘ranibizumab’, ‘Lucentis’, ‘aflibercept’, ‘Eylea’, ‘Zaltrap’, ‘conbercept’, ‘Brolucizumab’, ‘Beovu’, ‘triamcinolone’, ‘implant’, ‘dexamethasone’ and ‘Ozurdex’.

Inclusion and exclusion criteria

Eligible studies had to meet the following criteria: (1) the study population had RVO-ME; (2) the treatment arms were anti-VEGF agents monotherapies and non-anti-VEGF treatments including laser, intravitreal steroids, placebo or other treatments; (3) the main outcomes were the mean change in best-corrected visual acuity (BCVA) from baseline, the proportion of patients gaining or losing at least 15 letters from baseline, and mean change in central retinal thickness (CRT) from baseline; (4) studies were designed as RCTs; (5) duration of follow-up was ≥ 6 months; (6) studies gathered from ClinicalTrials.gov had a ‘completed’ status and their results were posted; (7) for overlapping patients, only studies with updated and complete information were selected.

The exclusion criteria were as follows: (1) most patients in the trial were previously treated with other treatments; (2) treatments were switched to other treatments in the trial during follow-up; (3) non-English language.

Data extraction and bias assessment

Two investigators (SX and ZS) independently screened the titles and abstracts of the searched studies. Full-text articles were evaluated for eligibility according to the inclusion criteria. Disagreements were resolved by discussion with the senior pharmacist. An excel sheet was used to compile baseline characteristics, drug regimes, key outcomes and any notes that could bias the results. Incomplete and missing values were requested by email from the corresponding authors of the articles or were calculated using the available information. When data were missing from a publication or ClinicalTrials.gov, we contacted investigators by email with a request to provide data for this review. The GRADE profiler was used to assess the quality of outcomes. The Cochrane Collaboration’s tool was used to assess the risk of bias in each study based on the Cochrane Handbook.

Outcomes of interest

The main outcomes were (1) improvement in BCVA (letters) at 6 and 12 months, (2) the proportion of patients who gained at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or 3 lines at 6 and 12 months, (3) the proportion of patients who lost at least 15 ETDRS letters or three lines at 6 and 12 months, (4) decrease in CRT (micrometres, μm) from baseline

to 6 and 12 months, (5) change in score of the Vision Functioning Questionnaire-25 (VFQ-25) at 6 and 12 months and (6) safety endpoints included ocular or systemic adverse outcomes during the study period. In RCTs, visual acuity (VA) was frequently quantified and reported as ETDRS letter score. When the Logarithm of the Minimum Angle of Resolution (logMAR) or Snellen chart scores was used to measure VA outcome, the score was converted to approximate ETDRS letter scores using the method proposed by Gregori *et al*¹⁶ in order to be included in quantitative analysis.

$$\log\text{MAR} = -1 \times \log(\text{Snellen fraction})$$

$$\text{Approximate ETDRS letter scores} = 85 + 50 \times \log(\text{Snellen fraction})$$

Statistical analysis

RevMan V.5.4 was used for the meta-analysis. The different types of RVO were not distinguished during the main quantitative synthesis. The differences in efficacy between BRVO and CRVO were analysed in the subgroup analysis. The risk ratios (RR) and mean differences (MD) were used to calculate the dichotomous data and continuous variable data with 95% CIs, respectively.¹⁰ Heterogeneity between studies was assessed by I^2 statistic, and $I^2 > 50\%$ was regarded as high heterogeneity. The meta-analysis was carried out under the random-effects model if $I^2 > 50\%$, otherwise under the fixed effects. P-values < 0.05 were considered statistically significant.

RESULTS

Search results

The selection process of studies included in this meta-analysis is illustrated in figure 1. About 1121 studies were identified (PubMed=346, Embase=405, Cochrane

Library=335 and Clinicaltrials.gov.=35) up to 6 January 2022. Five hundred and twenty-six duplicate records were eliminated and 595 potentially eligible studies were identified by reading their titles and abstracts. On reading the titles and abstracts, we further eliminated 5 animal studies, 312 reviews or conference abstracts or letters, 74 case reports, 46 non-RCT studies and 27 non-ME secondary to RVO. After reading the full text of the remaining 131 articles, 110 records were excluded due to various reasons. Seventeen studies with 21 reports were further included in the quantitative synthesis.

Study characteristics

Characteristics of included studies are summarised in table 1. Twenty-one reports of 17 studies including a total of 2649 patients suffering from RVO-ME were included in this meta-analysis. The 17 included studies were all RCTs, in which 9 studies were associated with BRVO (1438 patients, 54.28%) and the remaining 8 studies were associated with CRVO (1211 patients, 45.72%). In most trials, patients received the monthly injection of anti-VEGF agents for the first 3–6 months^{17–33} for once at baseline in four RCTs,^{34–37} then followed by monthly pro re nata (PRN or as needed) regimen in the extension phase. The follow-up duration varied from 1 to 12 months, and all the included RCTs had completed 6 months of the studies in each treatment arm at least.

Risk of bias in included studies

The risk of bias assessment is presented in figure 2. One study (Russo³⁵) was judged to be at high risk of selection bias because patients were assigned based on even or odd numbers of their retina clinic chart number. Five studies showed unclear levels of selection bias with no information given about random sequence generation or allocation concealment. We deemed eight studies to be high risk for performance bias and due to failure to mask investigators and participants. Five studies were judged to be at high risk of detection bias because the outcome assessors were not masked. Three studies were judged as high risk for attrition bias. Forty-two participants did not complete the study in the Ozurdex arm compared with only 14 in the ranibizumab arm in the study of Bandello *et al*²¹. In BRIGHTER²⁹, there were 13% loss of participants from ‘laser only’ group at 6 months. The ranibizumab arm showed 91.3% follow-up at 6 months, which was higher than the 84.7% in the dexamethasone arm in COMRADE-B²². For other biases, six studies were with a small sample size and five studies received pharmaceutical company funding: BRIGHTER²⁹, COMRADE-B²² 2018, Bandello *et al*²¹, VIBRANT²³ and RABAMES²⁸.

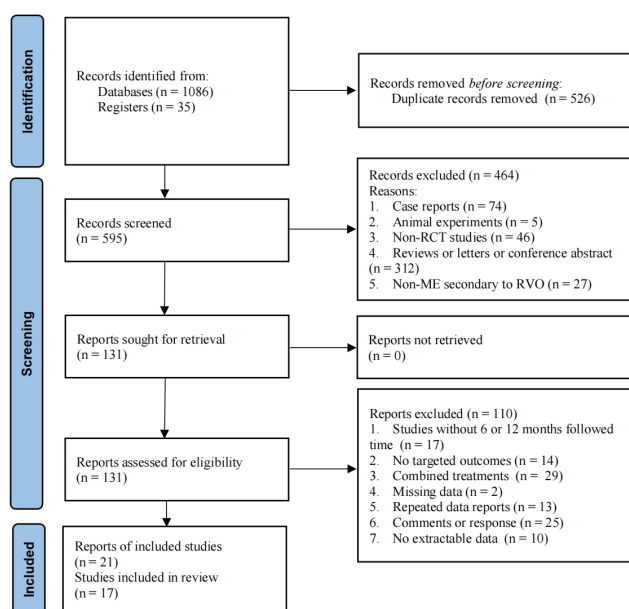


Figure 1 Flow diagram of study selection process. ME, macular oedema; RCT, randomised controlled trial.



Table 1 Study characteristics of the 17 included RCTs

Study, year	Country	Treatment arms (eyes, n)	Treatment regimen	Age (years)	Gender, male, n (%)	BCVA at baseline (letters, n)	CRT at baseline (µm)	Follow-up (months)
BRVO								
Bandello <i>et al</i> , 2018 ²¹	42 sites in France, Germany, Israel, Italy, Spain and the UK	IVR: 153	0.5 mg on day 1 and monthly for 5 months, then PRN	65.5±12.0	87 (56.9)	59.2±10.9	544±168	12
		DEX: 154	0.7 mg on day 1 and month 5, PRN at month 10 or 11	68.4±10.6	92 (59.7)	56.6±10.9	547±163	
VIBRANT, 2014 ²³	56 locations in USA, Canada and Japan	IVA: 91	2 mg monthly to week 20, then 2 mg 8 weekly, rescue laser PRN at week 36	67.0±10.4	44 (48.4)	58.6±11.4	558.9±185.9	6
		Laser: 92	Grid laser at baseline, from week 24 IVA 2 mg monthly for 3 months, then 8 weekly with rescue laser PRN at week 36	63.9±11.4	54 (60)	57.7±11.3	553.5±188.1	
COMRADE-B, 2018 ²²	74 sites across Germany, Great Britain, the Czech Republic, Poland and Hungary	IVR: 126	0.5 mg monthly for 3 months until stable VA and then PRN	65.7±10.9	50 (39.7)	–	–	6
		DEX: 118	0.7 mg single dose and then PRN	65.6±10.0	61 (51.7)	–	–	
BLOSSOM, 2020 ¹⁷	33 centres in China and Far East	IVR: 190	0.5 mg monthly until stable VA, then PRN	57.0±10.1	89 (46.8)	57.3±11.0	517.9±179.4	6, 12
BRIGHTER, 2016 ²⁹	82 centres in 17 countries worldwide	Sham: 93	Sham injections up to month 5 and 0.5 mg IVR PRN from month 6	56.8±10.0	55 (59.1)	57.5±13.1	539.3±219.6	
		IVR: 183	0.5 mg monthly (minimum three injections) until stable VA and then PRN	64.7±10.34	93 (50.8)	59.5±11.77	–	6
Miao Zhao <i>et al</i> , 2020 ³⁶	China	Laser: 92	Laser with minimum 4 months interval, IVR 0.5 mg PRN from month 6	67.7±9.67	37 (40.2)	56.5±14.13	–	
		IVC: 36	0.5 mg followed PRN	61.86±10.63	20 (55.56)	43.36±19.09	539.86±174.80	12
RABAMES, 2015 ²⁸	Germany	IVTA: 17	1 mg followed PRN	63.41±7.37	10 (58.82)	43.36±19.09	512.47±123.87	
		IVR: 10	0.5 mg monthly for three injections	64.2±8.6	4 (40)	–	584.2±250.9	6
Russo, 2009 ³⁵	Italy	Laser: 10	Grid laser at day 0 and an optional second laser at visit 6 (day 54–58)	68.8±9.5	5 (50)	–	570.6±158.1	
		IVR: 15	1.25 mg at baseline and then PRN	64.6±6.2	12 (80)	41.5±8	690±120	6, 12
		Laser: 15	Grid laser at baseline, then PRN after 3 months	65.2±6.5	11 (73.3)	40.5±6.5	650±140	

Continued

Table 1 Continued

Study, year	Country	Treatment arms (eyes, n)	Treatment regimen	Age (years)	Gender, male, n (%)	BCVA at baseline (letters, n)	CRT at baseline (μm)	Follow-up (months)
Higashiyama <i>et al</i> , 2013 ³⁷	Japan	IVB: 21 IVTA: 22	1.25 mg at baseline then PRN after 3 months 4 mg at baseline then PRN after 3 months	66.5 \pm 9.4 70.4 \pm 9.3	11 (50) 6 (28.6)	- -	- -	12
CRVO								
COPERNICUS, 2012, 2013 ^{18, 25}	70 sites in USA, Canada, Colombia, India and Israel	IVA: 115 Sham: 74	2 mg monthly for six injections then PRN monthly for six doses, then 2 mg IVA PRN	65.5 \pm 13.5 67.5 \pm 14.3	69 (61) 38 (52)	50.7 \pm 13.9 48.9 \pm 14.4	661.7 \pm 237.4 672.4 \pm 245.3	6, 12
CRUISE, 2010, 2011 ^{19, 26}	95 sites in USA	IVR: 262 Sham: 130	0.5 mg or 0.3 mg monthly for six doses then PRN monthly injection for six injections, then IVR 0.5 mg if met prespecified criteria	68.7 \pm 12.0 65.4 \pm 13.1	151 (57.6) 72 (55.4)	47.7 \pm 14.7 49.2 \pm 14.7	684.3 \pm 247.3 687.0 \pm 237.6	6, 12
COMRADE-C, 2016 ²⁷	66 sites in Germany, Great Britain, Poland and Hungary	IVR: 124 DEX: 119	0.5 mg for 3 consecutive monthly then PRN 0.7 mg at baseline	65.3 \pm 11.4 66.9 \pm 12.4	72 (58.1) 73 (61.3)	51.7 \pm 16.5 51.5 \pm 15.6	723.8 \pm 245.9 705.2 \pm 231.1	6
GALILEO, 2013, 2014 ^{20, 24}	63 sites in Europe and Asia Pacific	IVA: 106 Sham: 71	2 mg every 4 weeks for six doses and then PRN Sham injections monthly for 52 weeks	59.9 \pm 12.4 63.8 \pm 13.3	58 (56.3) 37 (54.4)	53.6 \pm 15.8 50.9 \pm 15.4	683.2 \pm 234.5 638.7 \pm 224.7	6, 12
Ding, 2011 ³⁴	China	IVB: 16 IVTA: 16 IVB: 30	1.25 mg at baseline and then PRN 4 mg at baseline and then PRN 1.25 mg every 6 weeks for 12 months	53.6 \pm 16.8 55.5 \pm 11.9 70.6 \pm 12.6	9 (56.3) 9 (56.3) 19 (63.3)	26.2 \pm 30.35 27.4 \pm 26.65 44.4 \pm 15.3	783.82 \pm 412.61 734.94 \pm 288.72 712 \pm 330	6 6, 12
Epstein <i>et al</i> , 2012 ^{32, 33}	Sweden	Sham: 30	sham injection every 6 weeks for 6 months, then 1.25 mg IVB every 6 weeks for 6 months	70.4 \pm 10.4	17 (56.7)	43.9 \pm 16.0	729 \pm 195	6, 12
ROCC, 2010 ³⁰	4 sites in Norway	IVR: 16 Sham: 16	0.5 mg for 3 consecutive monthly then PRN Sham injection for 3 consecutive monthly	- -	- -	45 \pm 23 41 \pm 22	661 \pm 161 587 \pm 154	6
Ramezani <i>et al</i> , 2014 ³¹	Iran	IVB: 43 IVTA: 43	1.25 mg for 3 consecutive monthly 2 mg, 2 times, 2 months apart	60 \pm 8 59 \pm 9	24 (56) 23 (54)	41.5 \pm 24.5 44.5 \pm 22.5	473 \pm 223 438 \pm 202	6
BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DEX, dexamethasone; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVTA, intravitreal triamcinolone acetonide; PRN, pro re nata; RCT, randomised controlled trial.								

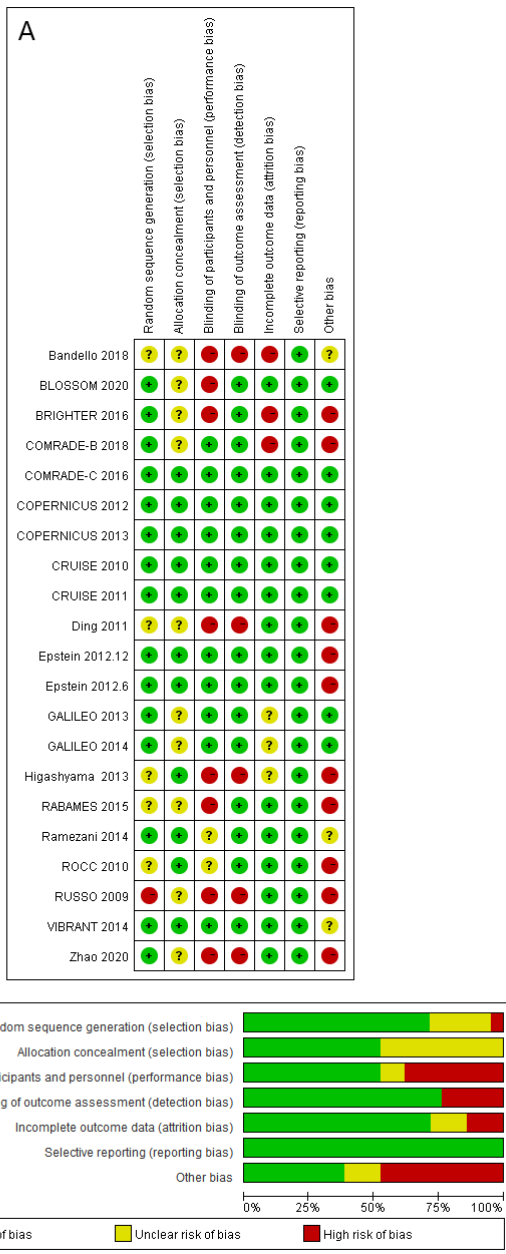


Figure 2 Assessment of the risk of bias in the included studies. (A) Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Bias risk was classified as low (+), unclear (?) or high (-). (B) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Meta-analysis results

Mean change in BCVA

The anti-VEGF group had a significantly greater improvement in BCVA compared with the sham group at both 6 (MD 14.01 letters, 95% CI 9.10 to 18.92, $p < 0.00001$) and 12 months (MD 7.36 letters, 95% CI 5.64 to 9.09, $p < 0.00001$). High heterogeneity was found at 6 months ($\chi^2 = 32.02$, $p < 0.00001$, $I^2 = 84\%$). Compared with laser, the anti-VEGF group had a

significantly greater improvement in BCVA at both 6 (MD 8.74 letters, 95% CI 6.57 to 10.91, $p < 0.00001$) and 12 months (MD 5.50 letters, 95% CI 0.28 to 10.72, $p = 0.04$). Unfortunately, the outcome of 12 months was limited to only one trial for only 15 participants in each group (Russo *et al*³⁵). The anti-VEGF group had a significantly greater improvement in BCVA compared with the steroid group at both 6 (MD 11.28 letters, 95% CI 4.40 to 18.16, $p = 0.001$) and 12 months (MD 9.67 letters, 95% CI 7.02 to 12.31, $p < 0.00001$). High heterogeneity was found at 6 months ($\chi^2 = 13.41$, $p = 0.004$, $I^2 = 78\%$) (figure 3).

Improvement of 15 or more ETDRS letters

The anti-VEGF group showed better outcome in the number of patients who gained VA ≥ 15 ETDRS letters than the sham group at both 6 (RR 2.69, 95% CI 1.94 to 3.73, $p < 0.00001$) and 12 months (RR 1.6, 95% CI 1.37 to 1.87, $p < 0.00001$). Compared with laser, the anti-VEGF group showed better outcome in the number of patients who gained VA ≥ 15 ETDRS letters than the laser group at 6 months (RR 1.82, 95% CI 1.42 to 2.33, $p < 0.00001$). The result of 12 months showed no significant difference, but also only one trial of Russo³⁵. The anti-VEGF group showed better outcome in the number of patients who gained VA ≥ 15 ETDRS letters than the steroid group at both 6 (RR 2.25, 95% CI 1.16 to 4.36, $p = 0.02$) and 12 months (RR 1.76, 95% CI 1.36 to 2.28, $p < 0.0001$). High heterogeneity was found at 6 months ($\chi^2 = 7.43$, $p = 0.006$, $I^2 = 87\%$). Unfortunately, the outcome of 12 months was limited to only one trial (Bandello *et al*²¹) (figure 4).

²¹online supplemental figure S1

Central retinal thickness

The results showed a significantly greater reduction in the anti-VEGF group compared with the sham group both at 6 (MD -230.48 μm , 95% CI -334.45 to -126.51, $p < 0.0001$) and 12 months (MD -204.20 μm , 95% CI -302.76 to -105.64, $p < 0.0001$). High heterogeneity was found at 6 months ($\chi^2 = 50.50$, $p < 0.00001$, $I^2 = 90\%$) and the result of 12 months was from only one trial (GALILEO²⁴). Compared with laser, the results showed a significantly greater reduction in the anti-VEGF group both at 6 (MD -135.71 μm , 95% CI -165.43 to -105.98, $p < 0.00001$) and 12 months (MD -143 μm , 95% CI -228.28 to -57.72, $p = 0.001$). But the result of 12 months was also from only one trial (Russo *et al*³⁵). The results also showed a significantly greater reduction in the anti-VEGF group compared with the steroid group both at 6 (MD -124.34 μm , 95% CI -184.18 to -64.51, $p < 0.0001$) and 12 months (MD -39.25 μm , 95% CI -74.14 to -4.36, $p = 0.03$). Moderate heterogeneity was found at 6 months ($\chi^2 = 9.74$, $p = 0.02$, $I^2 = 69\%$) (online supplemental figure S1).

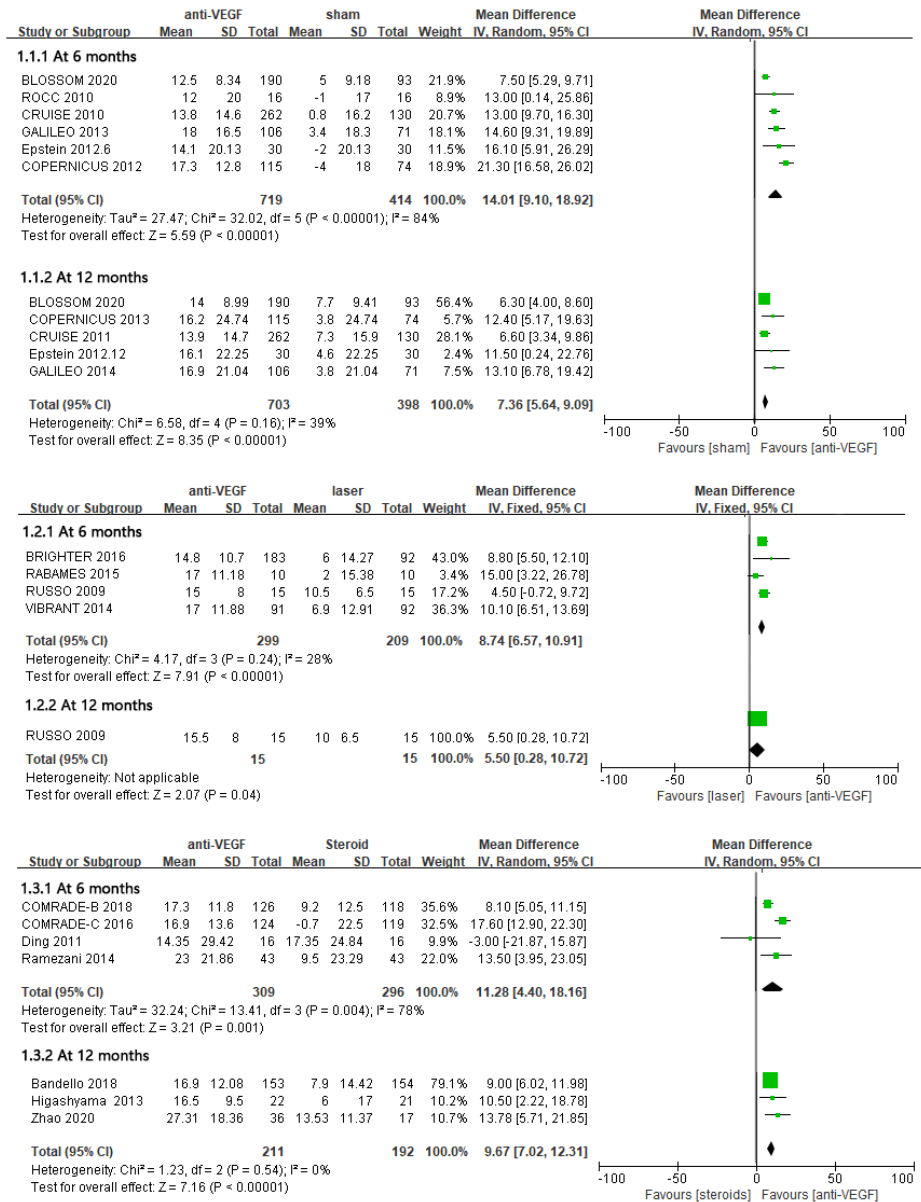


Figure 3 A forest plot diagram comparing the mean change in BCVA of anti-VEGF with sham, laser and steroids at 6 and 12 months. BCVA, best-corrected visual acuity; VEGF, vascular endothelial growth factor.

Loss of 15 or more ETDRS letters

The anti-VEGF group showed better outcome in the number of patients who lost VA ≥ 15 ETDRS letters than the sham group at both 6 (RR 0.15, 95% CI 0.08 to 0.27, $p < 0.00001$) and 12 months (RR 0.31, 95% CI 0.18 to 0.53, $p < 0.0001$). There was no available data for the laser group. Compared with steroid, the anti-VEGF group showed better outcome in the number of patients who lost VA ≥ 15 ETDRS letters at both 6 (RR 0.04, 95% CI 0.01 to 0.19, $p < 0.0001$) and 12 months (RR 0.07, 95% CI 0.01 to 0.51, $p = 0.009$). Also, the outcome of 12 months was limited to only one trial (Bandello *et al*²¹) (online supplemental figure S2).

Quality of life

The mean improvement in quality of life (QoL) on the National Eye Institute Visual Functioning Questionnaire-25

(NEI-VFQ 25) was significantly higher in the anti-VEGF group compared with the sham group both at 6 (MD 5.33, 95% CI 3.79 to 6.86, $p < 0.00001$) and 12 months (MD 4.53, 95% CI 1.64 to 7.42, $p = 0.002$). Moderate heterogeneity was found at 12 months ($\chi^2 = 2.14$, $p = 0.14$, $I^2 = 53\%$). Compared with laser, the mean improvement in QoL on the NEI-VFQ 25 was no significant difference in the anti-VEGF group at 6 months (MD 1.69, 95% CI -0.48 to 3.87, $p = 0.13$). There were no results available for 12 months. The mean improvement in QoL on the NEI-VFQ 25 was significantly higher in the anti-VEGF group compared with the steroid group at both 6 (MD 4.2, 95% CI 2.16 to 6.24, $p < 0.0001$) and 12 months (MD 3.1, 95% CI 0.23 to 5.97, $p = 0.03$). The outcome of 12 months was also limited to only one trial (Bandello *et al*²¹) (online supplemental figure S3).

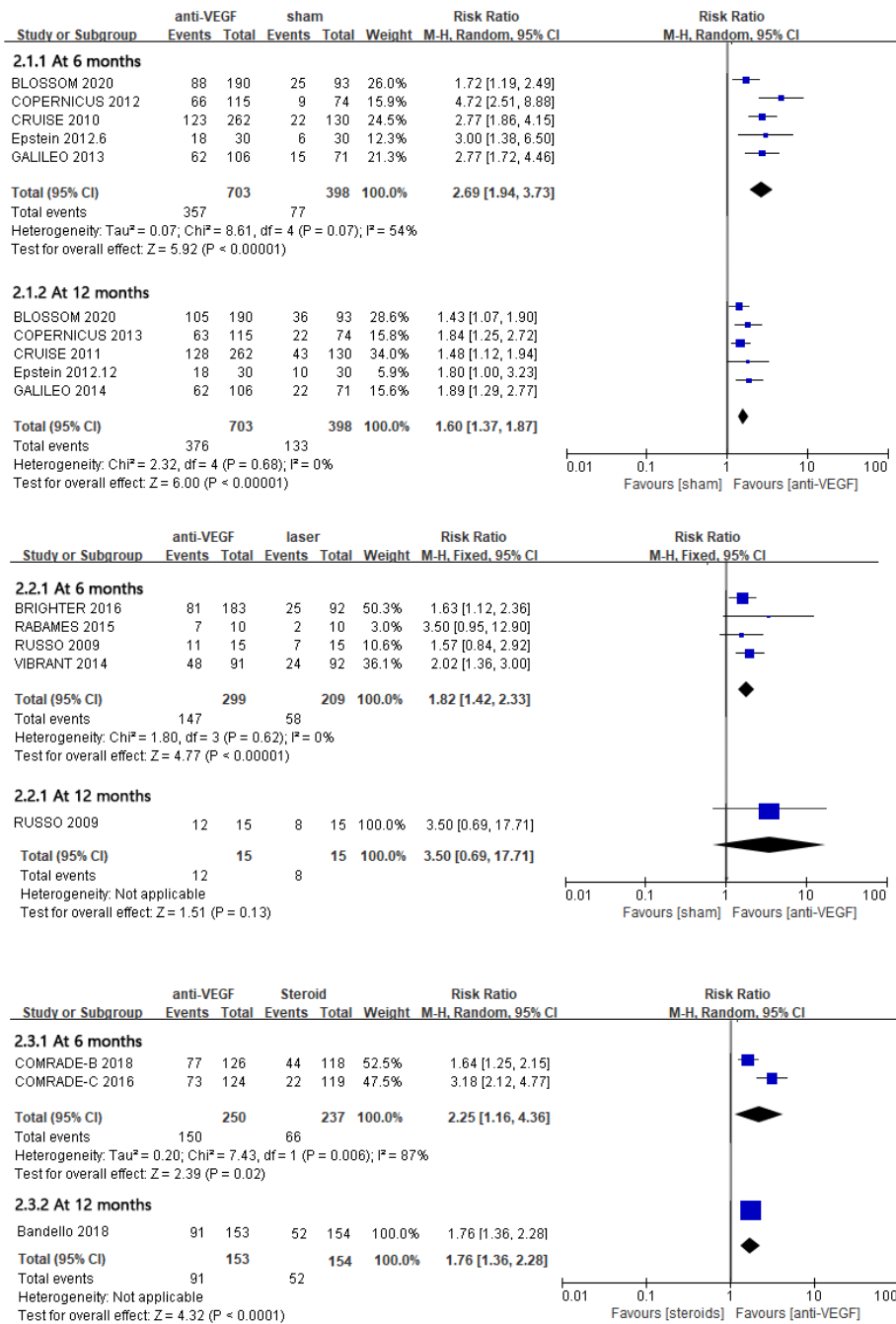


Figure 4 A forest plot diagram comparing the proportion of eyes gaining of 15 ETDRS letters or more of anti-VEGF with sham, laser and steroids at 6 and 12 months. ETDRS, Early Treatment in Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

Adverse events

The anti-VEGF and sham groups reported similar incidence of non-ocular SAEs, elevated intraocular pressure (IOP), cataract and conjunctival haemorrhage, but the incidence of eye pain was significantly higher in the anti-VEGF group (RR 2.20, 95% CI 1.15 to 4.21, p=0.02, online supplemental figure S4). Compared with laser, the anti-VEGF group reported similar incidence of non-ocular SAEs and eye pain, but there was a significant increase in the incidence of ocular AEs and conjunctival

haemorrhage in the anti-VEGF group (RR 1.67, 95% CI 1.18 to 2.37, p=0.004 and RR 5.56, 95% CI 2.05 to 15.08, p=0.0007, respectively, online supplemental figure S5). The anti-VEGF and steroid groups reported similar incidence of non-ocular SAEs, eye pain and conjunctival haemorrhage, but there was a significantly increase in the incidence of ocular AEs, elevated IOP, and cataract in the steroid group (RR 0.7, 95% CI 0.61 to 0.80, p<0.00001; RR 0.22, 95% CI 0.15 to 0.32, p<0.00001 and RR 0.17,

95% CI 0.09 to 0.31, $p < 0.00001$, respectively, online supplemental figure S6).

Subgroup analysis results

Subgroup analysis was executed based on the type of RVO (BRVO and CRVO). Compared with sham and steroids, anti-VEGF agents showed better efficacy both in BRVO and CRVO subgroups except for the outcome of the number of patients who lost VA ≥ 15 ETDRS letters (online supplemental table S1). For this outcome, there was no statistical difference in BRVO subgroup but with a significant difference in CRVO subgroup (online supplemental figure S7). The efficacy and safety of anti-VEGF agents in BRVO and CRVO groups were comparable.

Sensitivity analysis

To assess the reliability of the results, we performed a sensitivity analysis by sequentially excluding individual studies. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of the meta-analysis.

DISCUSSION

The rationale for anti-VEGF therapy of ME following RVO is based on the observation that intraretinal VEGF mRNA transcription and intraocular VEGF levels were increased in patients with RVO compared with a control group.^{19 38–41} VEGF increases vessel permeability by increasing the phosphorylation of tight junction proteins and is thus an important mediator of the blood-retinal barrier breakdown leading to vascular leakage and ME.⁴⁰ Therefore, therapy that inhibits VEGF is an effective therapeutic modality targeting the underlying pathogenesis of ME in RVO.^{39 42} Anti-VEGF agents have been recommended as the standard treatment for ME secondary to RVO in many guidelines. But several anti-VEGF agents were still used as the off-label medications in many countries. All anti-VEGF agents had been proved with greater visual improvements in both multiple prospective clinical studies and retrospective observational studies. Therefore, we need stronger evidence to verify that anti-VEGF agents do have better efficacies than non-anti-VEGF treatment in patients with ME secondary to RVO.

Multiple meta-analyses have demonstrated the superior efficacy and safety of anti-VEGF agents compared with other interventions including intravitreal steroids, laser therapy and sham injection on ME both secondary to BRVO or CRVO. Our results support the previous findings of better mean change of BCVA, more patients with ≥ 15 ETDRS letters gained and fewer patients with ≥ 15 ETDRS letters lost, and more effective at reducing CRT and improving the quality of life with anti-VEGF agents. We also found that the incidence of non-ocular SAEs or ocular AEs over the study period was similar between anti-VEGF agents and the sham group, and the risk of ocular AEs and conjunctival haemorrhage was higher in the anti-VEGF group than in the laser group at 6 months. In

our results, intravitreal steroids presented a significantly higher risk of IOP elevation and cataract development compared with anti-VEGF agents over 12 months. Another two meta-analyses^{8 10} also found that people treated with intravitreal steroids were more likely to develop cataract or raised pressure in the eye compared with anti-VEGF treatments. In total, we did not find intravitreal anti-VEGF agents were associated with an increased risk of non-ocular SAEs. A systematic review and meta-analysis found that intravitreal anti-VEGF agents were not associated with an increased risk of major cardiovascular events or its components compared with non-anti-VEGF controls, with no influence on the type of drug, ocular disease, study quality, or duration of follow-up, but that caution might be advisable in older patients with age-related macular degeneration who may be a higher risk of haemorrhagic events when receiving ranibizumab.¹⁵

A meta-analysis⁴³ of 11 RCTs revealed that anti-VEGF agents are more effective for treating BRVO than CRVO. But in our study, BRVO and CRVO both presented similar efficacy and safety for anti-VEGF treatments. We did not make direct head-to-head comparisons of anti-VEGF agents because of limited available evidence. In some studies, both bevacizumab and aflibercept outperformed ranibizumab in both anatomical and visual outcomes.^{44–48} But a recent systematic review and network meta-analysis⁴⁹ concluded that available evidence could not identify the significant difference in BCVA improvement and central macular thickness (CMT) reduction among intravitreal triamcinolone acetonide (IVA), intravitreal bevacizumab (IVB) and intravitreal ranibizumab (IVR) at short-term treatment.

In our study, all studies comparing anti-VEGF agents and laser treatments were in BRVO cases, as laser treatment monotherapy is not indicated for the treatment of CRVO-induced ME. A systematic review⁵⁰ indicated that laser photocoagulation did not appear to be effective in improving the VA in the ischaemic type of CRVO, but in preventing complications. Therefore, laser was recommended only after iris neovascularisation was visible, requiring a weekly or biweekly follow-up of patients with extensive capillary non-perfusion.

This meta-analysis had some limitations. First, the main limitation of our study is the differences in baseline characteristics between different studies, including VA and indicators of retinal thickness, CRT, central macular thickness, and central subfield thickness. Second, there were also varying sample sizes and study designs. Thirdly, most studies had a short period of follow-up of only 6 or 12 months. Fourthly, there was no reported data on the subgroup of pseudophakic participants except in one study, who do not suffer from visual loss due to cataract progression, so we can not remove the confounding effect of steroid-induced cataract when comparing the efficacy between anti-VEGF agents and steroids. Lastly, none of the included studies differentiated between ischaemic and non-ischaemic RVO, which may have introduced a major bias.

CONCLUSION

Based on all of this evidence and the findings of the current meta-analysis, we conclude that intravitreal anti-VEGF agents are the better choice for patients with ME secondary to RVO when compared with sham, laser or intravitreal steroids. We need more direct head-to-head comparison studies and a longer study period to assess the treatment effects of anti-VEGF in the future, including the novel anti-VEGF agents.

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