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Comparison of intravitreal dexamethasone implant and anti-VEGF drugs in the treatment of retinal vein occlusion-induced oedema: a meta-analysis and systematic review

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ABSTRACT

Objective To compare the efficacy and safety of intravitreal dexamethasone (DEX) implant and anti-vascularendothelial growth factor (anti-VEGF) agents in the treatment of macular oedema secondary to retinal vein occlusion (RVO).

Design Systematic review and meta-analysis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Data sources PubMed, Cochrane Library and *ClinicalTrials.gov* registry were searched from inception to 10 December 2019, without language restrictions.

Eligibility criteria Randomised controlled trials (RCTs) and real-world observation studies comparing the efficacy of DEX implant and anti-VEGF agents for the treatment of patients with RVO, naïve or almost naïve to both arms, were included.

Data extraction and synthesis Two reviewers independently extracted data for mean changes in best-corrected visual acuity (BCVA), central subfield thickness (CST) and product safety. Review Manager V.5.3 and GRADE were used to synthesise the data and validate the evidence, respectively.

Results Four RCTs and 12 real-world studies were included. An average lower letter gain in BCVA was determined for the DEX implant (mean difference (MD) = −6.59; 95% CI −8.87 to −4.22 letters) administered at a retreatment interval of 5–6 months. Results were similar ($MD_{6 months}$=−12.68; 95% CI −21.98 to −3.37 letters; $MD_{12 months}$=−9.69; 95% CI −12.01 to −7.37 letters) at 6 and 12 months. The DEX implant resulted in comparable or marginally less CST reduction at months 6 and 12 but introduced relatively higher risks of elevated intraocular pressure (RR=3.89; 95% CI 2.16 to 7.03) and cataract induction (RR=5.22; 95% CI 1.67 to 16.29). Most real-life studies reported an insignificant numerical gain in letters for anti-VEGF drugs relative to that for DEX implant. However, the latter achieved comparable efficacy with a 4-month dosage interval.

Conclusion Compared with anti-VEGF agents, DEX implant required fewer injections but had inferior functional efficacy and safety. Real-life trials supplemented the efficacy data for DEX implant.

Strengths and limitations of this study

► All the included studies were designed to compare the arms comprising the application of first-line treatments to naïve or almost naïve retinal vein occlusion (RVO)-induced macular oedema patients.
► Real-life trials were reviewed according to their RVO types to add evidence for the results of the meta-analysis of randomised controlled trials (RCTs).
► The data were quantitatively analysed according to short-term and long-term time points and follow-up intervals.
► Only a limited number of RCTs were included.
► Certain results were clearly explained but were heterogeneous.

INTRODUCTION

Macular oedema (MO), the abnormal thickening of the macula, is associated with fluid accumulation in the outer layers of the central retina and is often caused by pathological hyperpermeability of the retinal blood vessels.[1] It is a leading cause of central vision impairment in diabetes, retinal vein occlusion (RVO) and posterior segment inflammation.[2–4] Increases in the levels of inflammatory mediators and upregulation of vascular endothelial growth factor (VEGF) contribute to vascular leakage, breakdown of blood–retinal barrier[5–7] and MO. Anti-inflammatory and anti-angiogenic pharmacotherapies have been developed for MO. However, intraocular drug concentrations cannot be sustained for extended periods after a single administration, necessitating multiple intraocular injections in severe cases. This increases the risk of numerous injection-associated side effects.[8 9]

The dexamethasone intravitreal implant (DEX implant; Ozurdex) is a recently introduced biodegradable device for the sustained

release of DEX in the vitreous humour. It inhibits the expression of inflammatory cytokines and strengthens the blood–retinal barrier.[10] In June 2009, based on the results of a global clinical study, GENEVA, the US Food and Drug Administration (FDA) approved the DEX implant for the treatment of MO secondary to RVO. It was also approved by the European Union (EU) in 2010 and by the CFDA of China in October 2017.[11] Based on a 3-year MEAD study,[12] the DEX implant was approved for administration to diabetic MO patients in the USA. In the EU, the DEX implant was approved for administration to poorly responding diabetic MO patients and for those who are pseudophakic or ineligible for other therapies.

VEGF inhibitors, such as ranibizumab (RNB) and bevacizumab (Bev), are commonly used as anti-angiogenic agents for the treatment of ME. The BRAVO[13] and its extension study[14] demonstrated the short-term and long-term efficacy of RNB in the treatment of branch retinal vein occlusion (BRVO). Ranibizumab was also reported to be effective in the treatment of MO secondary to central retinal vein occlusion (CRVO).[15 16] Ranibizumab was approved by the US FDA in June 2010 and by the EU in June 2011 for the treatment of MO secondary to BRVO. Bevacizumab could improve vision in BRVO eyes, as effectively as RNB,[17] and was not inferior to aflibercept (Afl) with respect to visual acuity after 6 months of treatment of eyes with CRVO.[18] Bevacizumab has not yet been approved by the FDA for ocular indications but is widely used as an off-label treatment for MO associated with RVOs owing to its cost-effectiveness.

Both the DEX implant and the anti-VEGF agents are effective in the treatment of MO secondary to RVO. They improve vision and decrease central retinal thickness (CRT). However, few systematic reviews or meta-analyses have been performed to compare their clinical effects and safety. Here, we performed a meta-analysis of randomised controlled trials (RCTs) and a systematic review of real-world evidence to compare these two treatments.

METHODS
Search strategy
A literature search was performed using the Medline and the Cochrane Library electronic databases from inception to 10 December 2019, with no language restrictions. The search items are listed in the online supplementary tables S1,S2. The keywords 'retinal vein occlusion' and relevant outcomes were not restricted to include more studies. Other searches were conducted using the *ClinicalTrials.gov* registry. The original studies and review articles identified in the electronic search were manually examined to identify other potentially eligible papers.

Inclusion and exclusion criteria
Eligible studies had to meet the following criteria: (1) the study population had MO secondary to RVO; (2) the treatment arms were DEX implant and anti-VEGF drug monotherapies; (3) the main outcomes were visual acuity and/or central macular thickness; (4) treatment duration was ≥6 months; (5) studies gathered from *ClinicalTrials.gov* had a 'completed' status and their results were posted; (6) 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 several drugs; (2) treatments were switched in the trial during follow-up.

Outcome measurement
The efficacy outcomes included mean average change in best-corrected visual acuity (BCVA) and mean change in CRT at months 6 and 12. The mean average change in BCVA over time (from the baseline until the end of the first month) reflected the area under the curve and was also recorded, if applicable. Visual acuity was measured using a letter or a logMAR chart, according to the Early Treatment Diabetic Retinopathy Study (ETDRS). The CRT indicators included subfield, foveal thickness and central macular thickness, and were evaluated by optical coherence tomography. The safety outcomes were (1) the total number of serious adverse events (SAEs) and other adverse events (AEs) during the RCTs, (2) an elevation of the intraocular pressure (IOP), (3) cataract progression and (4) the other top five AEs.

Data extraction
Two investigators (SM and KX) 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 and consensus. A standard form was used to compile baseline characteristics, numbers of patients, drug doses, key outcome indicators 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. The formula SD=SE × sqrt (n) was used to calculate the SD when only the SE was reported. GetData software was used to estimate the means and SDs when only charts and graphs (figures) were presented in the paper. To ensure the accuracy and completeness of the collected data, the extracted results were posted to the *ClinicalTrial.gov* registry as supplements to the published data.

Assessment of study evidence and risk of bias
The RoB V.2.0 tool in the Cochrane Collaboration[19] was implemented to assess the risk of bias for the RCTs. The domains 'randomization process', 'deviations from intended interventions', 'missing outcome data', 'measurement of the outcome' and 'selection of the reported result' were rated as 'low risk', 'some concerns' or 'high risk'. Assessment of the risk of bias for real-life studies was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.[20] Four of the main domains were assessed and graded as 0 (inadequate), 1 (unclear) or 2 (adequate). The global ideal score was eight points.
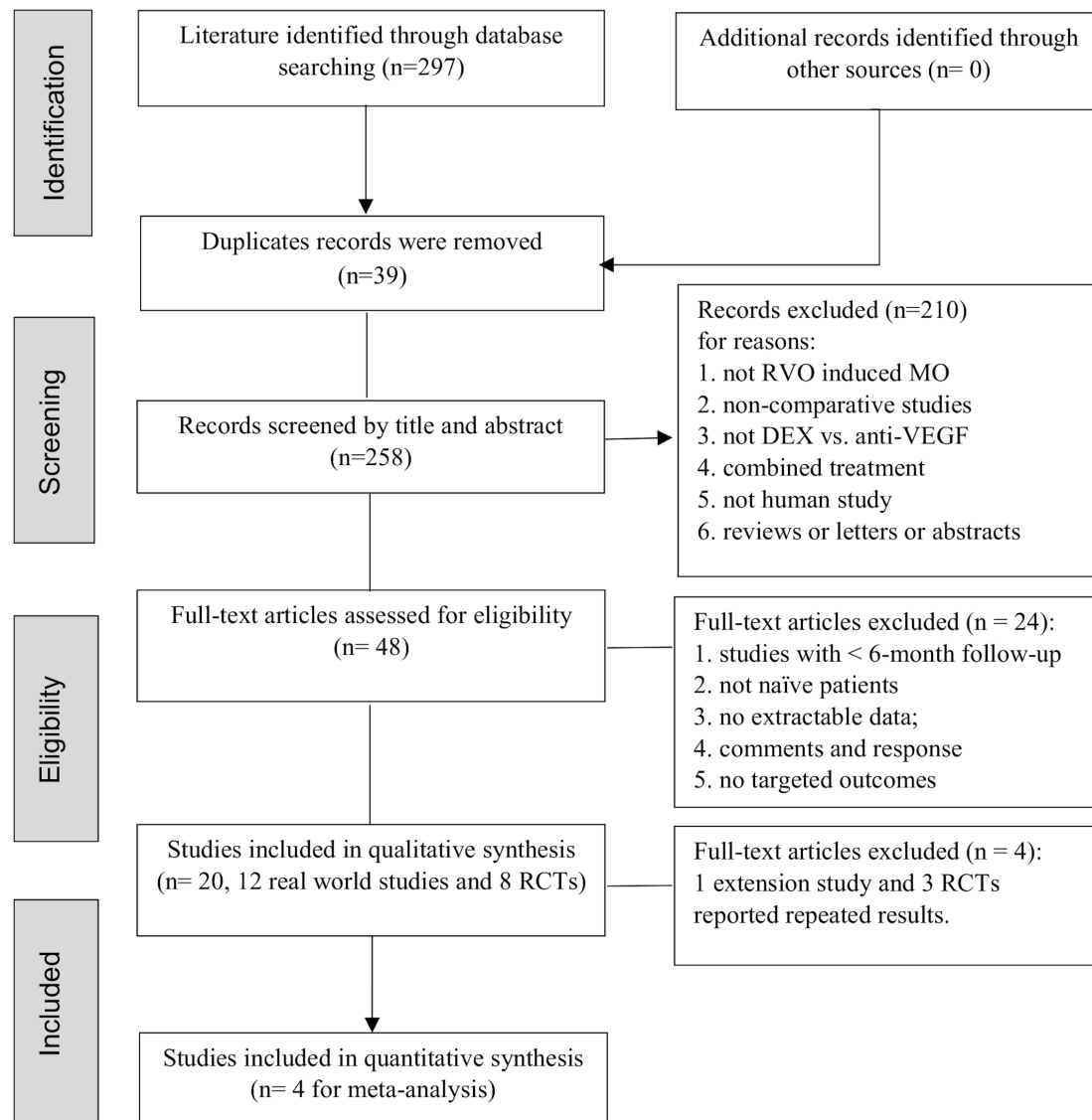
Figure 1 Flowchart of literature search and study selection. DEX, dexamethasone; MO, macular oedema; RCTs, randomised controlled trials; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

The strength of the RCT evidence was assessed with the GRADEpro V.3.6 tool according to the quality levels 'high', 'moderate', 'low' and 'very low'.

Patient and public involvement

The relevant literature was analysed and the data therein were compiled. No patients were directly involved in the present study.

Statistical analysis

Relative therapeutic efficacy was evaluated by identifying differences in the outcomes between the DEX implant and anti-VEGF agent arms. The mean differences (MDs) were calculated by pooling the study-specific estimates in RevMan V.5.2. The interstudy heterogeneity was assessed by estimating the I^2 statistic that quantifies the percentage variation across all studies. $I^2 > 50\%$ and/or $p < 0.05$ were considered to indicate statistical heterogeneity. Subgroup analyses were performed to localise heterogeneity only when more than 10 of the included RCTs were available. An a priori

random-effects model (DerSimonian-Laird method) was applied even in the absence of statistically significant interstudy heterogeneity because it yielded highly conservative estimates in the presence of residual heterogeneity. This study adheres to PRISMA's evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (online supplementary table S3).

RESULTS

Study identification

Figure 1 shows the process employed for the selection of studies. The search strategy returned 244 possibly relevant records (PubMed: 190; Cochrane Library: 95; *ClinicalTrials.gov*: 22). Thirty-nine duplicate records were eliminated and 258 potentially eligible studies were identified by reading their titles and abstracts. There were 210 exclusions and 24 other studies were ruled out according to the exclusion criteria after evaluating the full-text articles. Of the 12 real-world studies and 8 RCTs included in

the qualitative assessment, 3 clinical trials identified from *ClinicalTrials.gov* were excluded. One clinical trial (No. NCT01580020) was an extension study[21] of two previously published RCTs; we referred to the information presented in this study in our meta-analysis but did not add it to the list of RCTs. Thus, 16 studies were systematically reviewed and data from four RCTs were used for the meta-analysis.

Characteristics of the included studies

Table 1 lists the characteristics of the four selected RCTs.[22–25] The sample sizes ranged from 20 to 307 eyes. The mean ages and proportions of the sexes were statistically similar for all trials. The anti-VEGF agents were injected monthly for the first 3–5 months and *pro re nata* (PRN) thereafter. The frequency of DEX implant injection varied from 3 to 6 months. The BCVA and CRT baselines were comparable for both arms. Ranibizumab was administered in three studies[22–24] and Bev was used in another study.[25] The assessment of risk of bias is shown in figure 2. According to the Cochrane criteria, the 'measurement of outcome' and 'randomization process' domains were low risk. Studies with open label[22] and high rates of lost to follow-up[24] could increase the risk of bias with respect to 'missing outcome data' and 'deviations from intended interventions'. The overall assessment (online supplementary table S4) revealed concerns about the potential risk of bias.

Table 2 summarises the characteristics of 12 real-world retrospective studies[26–36] included in the systematic review. All these studies included naïve or almost naïve participants. Two studies had a three-arm design.[27 30] Ranibizumab was used in the anti-VEGF arm in most of the studies, except in two studies in which Afl was used,[27 30] and one study in which Bev was used[34]; an unspecified anti-VEGF therapy was performed in one study.[35] The baseline BCVA and CRT were comparable in both arms except in one study[26] wherein the recruited patients presented with relatively severe BCVA and CRT. After one baseline injection, DEX was administered as PRN every 4[27 32 35] or 6 months,[31 34] or at an unreported interval. A PRN protocol was applied monthly in the anti-VEGF arms. Four studies[27 29 34 35] had a low risk of bias. None of the real-world trials reported adequate control measures for confounding variables. Flawed outcome reporting tended to lower the scores.

Results of the meta-analysis
Average change in BCVA
At month 6, two studies[23 24] reported improvements in BCVA in 487 eyes, measured based on letters according to ETDRS. At month 12, three studies[22–24] involving 478 eyes reported BCVA data. Data extracted from an extensive study[21] (No. NCT01580020) were added to the two aforementioned studies.[23 24] The meta-analysis indicated an average reduction in letter gain for BCVA in the DEX implant arm during each study period (MD=−6.59; 95% CI −8.87 to −4.22 letters) when the drug was administrated at a retreatment interval of 5–6 months. A single DEX implant injection was less effective in improving

BCVA than the anti-VEGF injection administered at the standard frequency ($MD_{month\ 6}$=−12.68, 95% CI −21.98 to −3.37 letters) at month 6. With a retreatment interval of 5–6 months, where required, the DEX implant could still achieve a comparatively lower letter gain at month 12 ($MD_{month\ 12}$=−9.69; 95% CI −12.01 to −7.37 letters; figure 3).

Average change in CRT
Gado *et al*[25] did not report details of the data for CRT improvement at month 6. However, we estimated these values on the basis of the information reported in a letter[37] written by the authors in response to queries posed by a peer reviewer of their study. Thus, three studies[23–25] with 547 eyes and three studies[22–24] with 457 eyes were analysed at months 6 and 12, respectively. A meta-analysis of reduction in CST at month 6 numerically favoured the anti-VEGF therapy. There was no significant difference between the two arms ($MD_{month\ 6}$=100.01 µm, 95% CI −25.53 to 225.56 µm); however, there was heterogeneity (p<0.001; I^2=95%). At month 12, the combined MD in CST slightly favoured the anti-VEGF group ($MD_{month\ 12}$=41.72 µm, 95% CI 5.03 to 78.40 µm; figure 3). No heterogeneity was found in the pooled results at month 12 (p=0.59, I^2=0%).

Safety
Three RCTs[22–24] reported detailed safety information for each arm during follow-up. Meta-analysis showed that incidences of total SAEs, eye pain, vitreous floaters and conjunctival haemorrhage occurred at similar risk levels in both arms (p>0.05). The DEX arm was much more likely to present with the other AEs (but not SAEs; RR=1.27, 95% CI 1.16 to 1.39), elevated IOP (RR=3.89, 95% CI 2.16 to 7.03), ocular hypertension (RR=11.03, 95% CI 2.61 to 46.66), and cataract (RR=5.22, 95% CI 1.67 to 16.92; figure 4).

Review of the real-world studies
BRVO-induced me
Nine real-world studies[26 28–30 32–34 36 38] reported the efficacy of anti-VEGF and DEX implant in the treatment of BRVO-induced MO. All the nine studies showed significant reduction in CRT after anti-VEGF and DEX treatments. BCVA tended to be associated with a gain in letters and improvement in logMAR following the administration of anti-VEGF and DEX. Two studies revealed no statistically significant change in the DEX arm[26] or the worsening of logMAR[34 38] with respect to the improvement of BCVA (table 3).

Three studies favoured anti-VEGF therapy because of its relatively superior efficacy in improving BCVA.[26 30 34] Kaldirim *et al*[30] used only one DEX implant with a 6-month follow-up, and reported that anti-VEGF therapy was comparatively more efficient in maintaining an increase in visual acuity and in reducing CRT. When the DEX implant was administered PRN at 6-month intervals, the DEX arm presented with 0.19 logMAR visual loss (0.21

Table 1 Characteristics of the randomised controlled trials included in the review

Study	Study period (months)	Treatment arms	Age (years)	Sex (M/F)	MO duration (months)	Drug regimen	Aetiology	Mean dose frequency (months)	No. of injections/ implants	Eyes (n)	Baseline BCVA (letters)	Baseline CRT (µm)
COMO[22]	12	DEX implant 0.7 mg	68.4 (10.6)	92/62	NA	1 implant at months 0, 5; 1 optional implant at month 10 or 11	BRVO	4.8	2.5	154	56.6 (10.9)	547 (163)
		Ranibizumab 0.5 mg	65.5 (12.0)	87/66	NA	5× monthly doses, then PRN	BRVO	1.5	8	153	59.2 (10.9)	544 (168)
COMRADE-B[23]	6*	DEX implant 0.7 mg	65.6 (10.0)	61/57	≤6	1 implant at month 0	BRVO	6.0	1.0	118	57.2 (11.9)	NA
		Ranibizumab 0.5 mg	65.7 (10.9)	50/76	≤6	3× monthly doses, then PRN	BRVO	1.2	4.9	126	58.1 (12.0)	NA
COMRADE-C[24]	6*	DEX implant 0.7 mg	66.9 (12.4)	73/46	1.17 (1.87)	1 implant at month 0	CRVO	6.0	1.0	119	51.5 (15.6)	705.2 (231.1)
		Ranibizumab 0.5 mg	65.3 (11.4)	72/52	1.27 (1.20)	3× monthly doses, then PRN	CRVO	1.3	4.5	124	51.7 (16.5)	723.8 (245.9)
Gado et al[25]	6	DEX implant 0.7 mg	68.4 (11.48)	20/10	NA	2× per 3 months	CRVO	3.0	2.0	30	0.6 logMAR	548.5 (68.7)
	6	Bevacizumab 1.25 mg	69.1 (8.56)	20/10	NA	3× monthly doses, then PRN	CRVO	1.4	4.3	30	0.6 logMAR	544.1 (48.7)

*Extension study with follow-up time prolonged by another 6 months (not shown in the table).

BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; DR, diabetic retinopathy; F, female; M, male; MO, macular oedema; NA, not available; PRN, pro re nata.
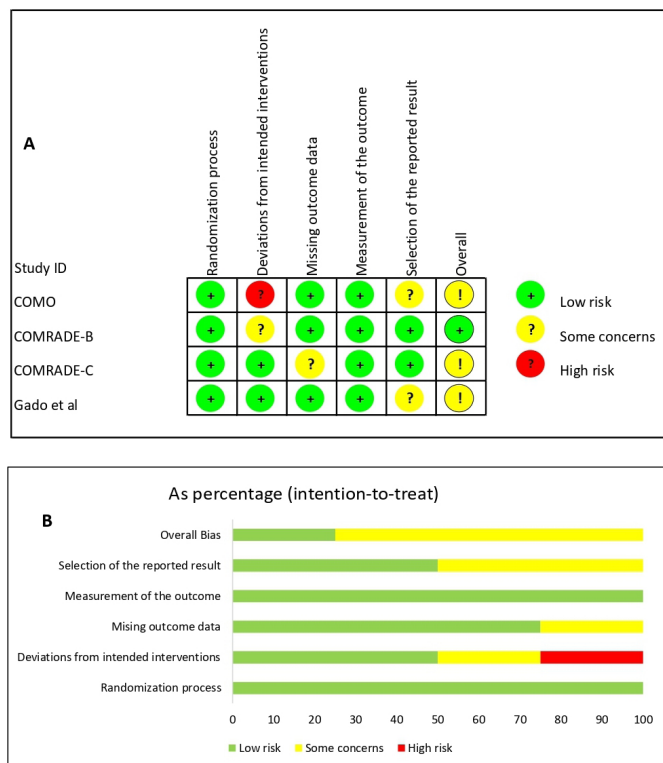
Figure 2 Assessment of the risk of bias in included studies. (A) Risk of bias summary: review authors' judgements regarding each risk of bias item for each included randomised control trial (RCT) study. (B) Risk of bias graph: review authors' judgements of each risk of bias item presented as percentages across all included RCT studies.

logMAR gain in bevacizumab; p=0.053) and relatively less CRT reduction (48.98 µm vs 157.15 µm; p<0.05) at 6 months.[34] After another injection at 6 months, the DEX implant attained comparable efficacy in terms of the improvement of BCVA (0.19 logMAR vs 0.23 logMAR) and reduction of CRT (−140.7 µm vs −160.1 µm) by the end of the study.[34] Ozkaya et al[26] validated the therapeutic advantage of anti-VEGF therapy in a follow-up study for a longer duration (24 months). When an average of 2.7, rather than 5.6, injections were administered, the DEX implant did not significantly improve BCVA (0.06 logMAR gain) by the end of month 24. When 5.6 injections were administered, RNB was effective in terms of visual (0.15 logMAR gain) and anatomical (CRT: 193 µm reduction) outcomes (table 3).

Gu et al[32] designed another DEX implant that can be installed after 4 months, if required. After 1.2 DEX and 3.5 RNB injections, DEX attained equal efficacy in terms of functional (5.8 letters vs 6.3 letters BCVA gain) and anatomical (139.8 µm vs 84.6 µm CRT reduction) outcomes by month 6. The results of three other studies[28 33 36] favoured both the drugs because they achieved comparable gain in BCVA and reduction in CRT. However, the intervals at which the DEX implant was administered were not reported (table 3). Yuksel et al[29] reported a contrasting low-frequency administration of RNB (2.4±1.4) and DEX (1.9±0.7) for the treatment of

BRVO. Low-frequency RNB injection limited the potential visual gain that could be realised with the RNB therapy (0.11 logMAR gain vs 0.2 logMAR gain in the DEX arm) but nonetheless achieved numerically a greater reduction of CRT (241.3 µm vs 146.6 µm; not statistically validated) (table 3).

CRVO-induced MO
In six studies,[27 28 31–33 36] patients with CRVO-induced MO were recruited. Most of the patients demonstrated substantial CRT reduction and visual gain after the anti-VEGF and DEX treatments. Yucel et al[27] performed a Bonferroni correction (p=0.016) but failed to establish that RNB, Afl and DEX were associated with different visual acuities. Winterhalter et al[28] reported that the RNB group presented with only slight visual gain (0.10 logMAR gain, p=0.071) by month 6. There was a slight visual deterioration (0.08 logMAR loss, p=0.305) when only one implant was administered in the DEX arm.

The administration of DEX implant at a 6-month PRN interval did not reduce CRT (−228.0 vs −303.3, p=0.003) by month 6, as recurrence of MO was observed in the DEX group. However, RNB and DEX were significantly comparable at increasing VA (8.4 letters vs 6.9 letters) and reducing CRT (−260 µm vs −197 µm)[31] by month 12. In three other studies, it was confirmed that anti-VEGF and DEX therapy were equally effective in treating MO secondary to CRVO[32 33 36] (table 3).

RVO-induced MO
The DEX implant increased BCVA from the baseline by month 6 (0.3 logMAR gain, p=0.001) and month 12 (0.3 logMAR gain, p=0.005). In contrast, the anti-VEGF drugs were only effective at month 6 (0.1 logMAR gain, p=0.02). There were no significant differences in the augmentation of VA or in the reduction of CRT at 6-month and 12-month visits.[35] The long-term (12 month) anatomical and visual outcomes were similar for both the DEX and anti-VEGF groups.

Safety
No SE data were reported in the real-world studies. We, therefore, only reviewed the progression of cataract and increase in IOP. Only small increases in IOP and low cataract progression rates were observed in the anti-VEGF arm. In contrast, patients receiving the DEX implant were relatively more susceptible to increases in IOP and cataract opacity (table 3).

DISCUSSION
The anti-VEGF and DEX therapies for RVO showed similar effectiveness. Because only a few RCTs were included, the results suggested that one DEX injection every 6 months was comparatively less effective in improving the visual acuity. Even when DEX injections at month 5 or PRN at 5–6 month intervals were added, the anti-VEGF drugs resulted in greater letter gains by month 12. The

Table 2 Characteristics of the real-world studies included in the review

Study (year, country)	Study design	n (eyes)	Pretreatment	MO aetiology	Duration of follow-up (months)	Duration of MO (months)	Drug regimen	No. of injections	BCVA baseline (logMAR or letter)	CRT (µm) baseline	Risk of bias
Kumar et al (2019, India)[38]	Prospective, open-label study	RNB: 15	Naïve	BRVO	6	3.71±1.72	3× monthly doses	3	0.68±0.13	487.5±105.9	6
	–	DEX: 15	Naïve	–	–	3.33±1.26	0.7 mg, 1 implant	1	0.64±0.15	493.7±100.8	–
Ozkaya et al (2018, Turkey)[26]	Retrospective study	RNB: 46	Naïve	BRVO	24	<3	3× monthly doses, repeated PRN	5.6±1.8	0.64±0.48*	530±150*	6
		DEX: 41	Naïve	–	–	–	1 implant, repeated PRN	2.7±1.1	0.98±0.56	591±113	–
Yucel et al (2018, Turkey)[27]	Retrospective single-centre study	RNB: 18	Naïve	CRVO	≥6	3.38±2.8	0.5 mg, PRN	2.56±1.0	0.91±0.44	587.8±140.9	7
		Afl: 16	Naïve	–	–	5.31±5.1	2 mg, PRN	2.68±0.9	1.14±0.50	782.8±248.8	–
		DEX: 24	Naïve	–	–	5.04±4.3	0.7 mg, PRN every 4 months	1.62±0.5	1.11±0.46	668.7±193.5	–
Winterhalter et al (2018, Germany)[28]	Retrospective observational study	RNB: 59	Naïve	BRVO or CRVO	6	BRVO: 2 (1–5) CRVO: 2 (1–3)	0.5 mg, PRN	BRVO:3.59±1.12 CRVO:3.63±0.98	BRVO: 0.51±0.26 CRVO: 0.69±0.26	BRVO: 481 (395–561) CRVO: 529 (358–747)	6
		DEX: 48	93.75% naïve		–	BRVO: 3 (1–5) CRVO: 3 (2–7)	0.7 mg at baseline, then PRN	BRVO: 1.13±0.34 CRVO: 1	BRVO: 0.61±0.22 CRVO: 0.65±0.24	BRVO: 458 (384–578) CRVO: 617 (451–790)	–
Yuksel et al (2018, Turkey)[29]	Retrospective study	RNB: 14	Naïve	BRVO	≥6	4.1	0.5 mg, PRN	1.9	0.91±0.64	505.1±189.1	7
		DEX: 15	Naïve	–	–	2.6	0.7 mg, PRN	1.3	0.96±0.41	512.8±142.7	–
Kaldirim et al (2017, Turkey)[30]	Retrospective comparative study	RNB: 22	Naïve	BRVO	6	3.41±0.5	3× monthly doses of 0.5 mg, then PRN monthly	3.64±0.49	0.59±0.12	466.95±90.17	5
		Afl: 20	Naïve	–		3.35±0.5	3× monthly doses of 2 mg, then PRN monthly	3.35±0.49	0.57±0.15	483.65±61.18	–
		DEX: 20	Naïve	–		3.5±0.51	1 DEX 0.7 mg	1	0.59±0.15	490.75±89.89	–
Chatziralli et al (2017, Greece)[31]	Retrospective observational study	RNB: 25	Naïve	CRVO	≥12	68%<3	3× monthly doses of 0.5 mg, then PRN monthly	5.1±1.1	54.8±7.1	586.9±141.3	6
		DEX: 17	Naïve	–	–	32%<3	0.7 mg at baseline, then PRN every 6 months	2.1±0.6	53.7±11.1	597.3±148.8	–

Continued

Table 2 Continued

Study (year, country)	Study design	n (eyes)	Pretreatment	MO aetiology	Duration of follow-up (months)	Duration of MO (months)	Drug regimen	No. of injections	BCVA baseline (logMAR or letter)	CRT (µm) baseline	Risk of bias
Gu et al (2017, China)[32]	Retrospective study	RNB: 32	Naïve	CRVO: 26 BRVO: 6	6	NA	One at baseline, repeat once recurrence of MO after 1 months	CRVO: 3.4±1.4 BRVO: 3.5±0.8	CRVO: 19.5±18.9 BRVO: 26.8±15.7	CRVO: 767.5±121.6 BRVO: 582.8±63.6	5
		DEX: 32	Naïve	CRVO: 26 BRVO: 6	–	NA	One at baseline, repeat once recurrence of MO after 4 months	CRVO: 1.7±0.7 BRVO: 1.2±0.4	CRVO: 11.8±16.2 BRVO: 28.8±17.9	CRVO: 910.6±346.4 BRVO: 463.0±134.0	–
Mayer et al (2015, German)[33]	Retrospective case series	RNB: 52	Naïve	CRVO: 27 BRVO: 25	12	<3	3× monthly doses of 0.5mg, then PRN monthly	CRVO: 5.4 BRVO: 3.9	CRVO: 18.6±11.2 BRVO: 25.6±9.9	CRVO: 589.3±199.1 BRVO: 484.2±181.7	5
		DEX: 60	Naïve	CRVO: 31 BRVO: 29	–	<3	NR	CRVO: 2.3 BRVO: 1.5	CRVO:20.8±10.3 BRVO: 24.5±12.0	CRVO: 612.4±205.5 BRVO: 515.4±198.2	–
Kim et al (2015, Korea)[34]	Retrospective, interventional case series	Bev: 44	Naïve	BRVO	12	5.10±6.78	1.25mg, PRN	2.92±1.38	0.55±0.45	446.61±109.91	7
		DEX: 28	Naïve	–	–	7.23±5.99	0.7 mg at baseline then, PRN every 6 months	1.71±0.47*	0.49±0.40	477.36±118.59	–
Chiquet et al (2015, France)[35]	Retrospective multicentre study	anti-VEGF: 44	Naïve	RVO	12	6.1±8	3× monthly doses	6±1.5	0.7±0.5	558±176	7
		DEX: 33	Naïve	–	–	5.9±10	PRN every 4 months	1.6±0.6	0.9±0.5	527±199	–
Nghiem-Buffet et al (2014, France)[36]	Retrospective study	RNB: 24	Naïve	CRVO: 7 BRVO: 17	BRVO: 15.8 CRVO: 18.4	BRVO: 5.2±4 CRVO: 3.8±4.3	3× monthly doses then, PRN	BRVO: 5.8±2.9 CRVO: 7.7±5.6	NR	NR	5
–	–	DEX: 19	Naïve	CRVO: 7 BRVO: 12	12.5	–	PRN	BRVO: 1.75±0.8 CRVO: 1.9±1.0	NR	NR	–

*Statistical difference between anti-VEGF and DEX.
Afl, aflibercept; Bev, bevacizumab; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DEX, dexamethasone implant; NR, not reported; RNB, ranibizumab; VEGF, vascular endothelial growth factor.
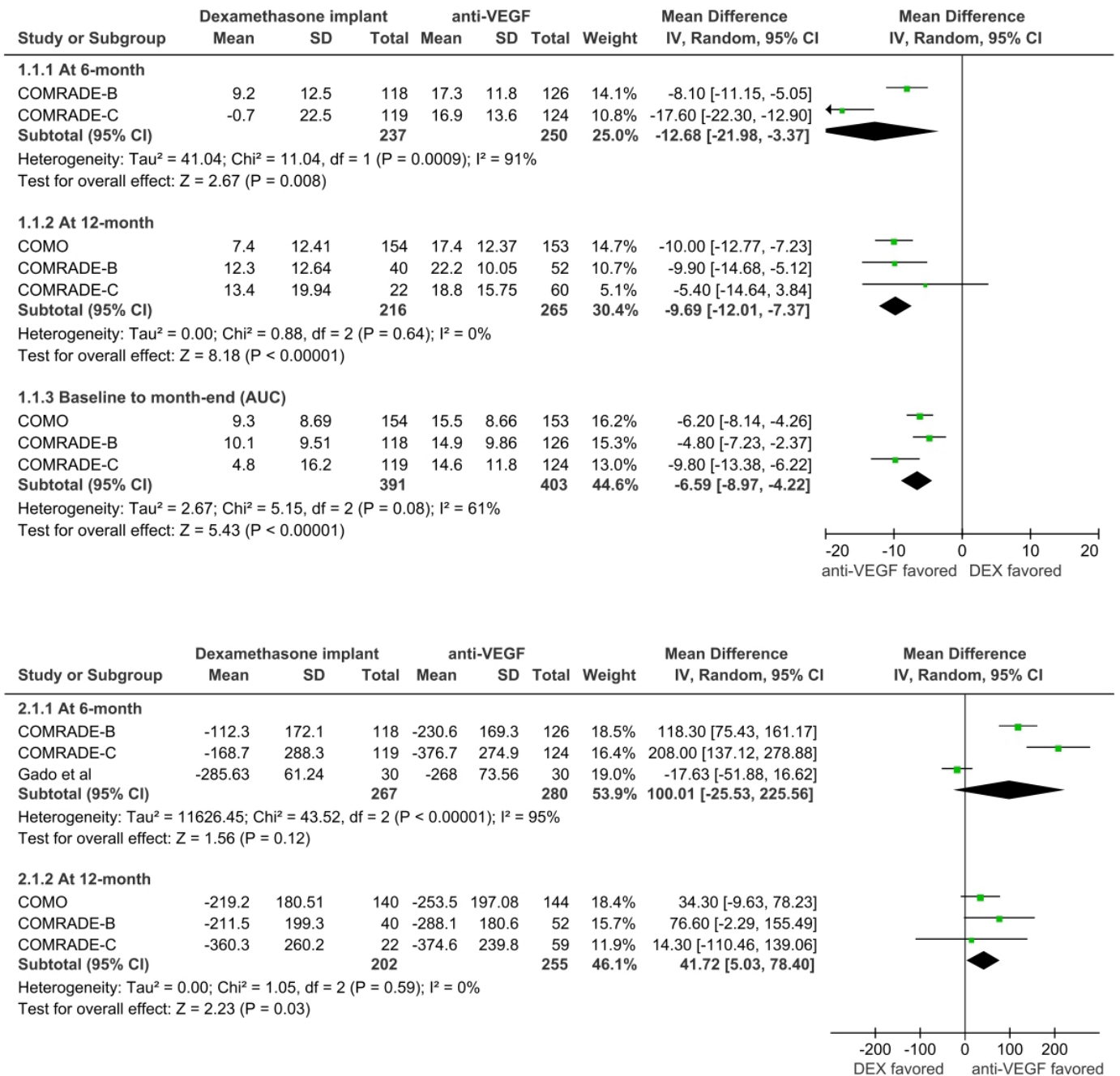
Figure 3 A forest plot diagram showing the mean change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT), comparing dexamethasone (DEX) with anti-vascular endothelial growth factor (anti-VEGF) treatment at different times.

GRADE assessment indicated that the overall strength was moderate (online supplementary table S5). The reductions in CRT at month 6 were slightly lower for the DEX group than for the others. A network meta-analysis of comparative efficacy[39] revealed that anti-VEGF monotherapy had 84% probability of being the most effective treatment for BRVO-induced MO, whereas the DEX implant had a 0% chance for the same. The combined CRVO and BRVO cases in the present review corroborate this conclusion.

An earlier review evaluated real-world studies on the safety and efficacy profiles of the DEX implant for diabetic MO.[40] Here, we assessed the same profiles in

RVO-induced MO. Pielen et al[41] reviewed the general intravitreal therapy for RVO-induced MO. However, the relative efficacies of the DEX implant and anti-VEGF therapies have seldom, if ever, been investigated. One strength of the current study is that in all the trials included, these profiles in both the arms were directly compared. A previous study[42] showed that patients unresponsive to anti-VEGF therapy responded well to the DEX implant. In the long term after the diagnosis of MO, patients might switch from an anti-VEGF to a DEX regimen. By selecting naïve or almost naïve RVO patients, recently diagnosed with MO (eg, within 3 months), we lowered the risk of bias and provided evidence for first-line RVO treatment.
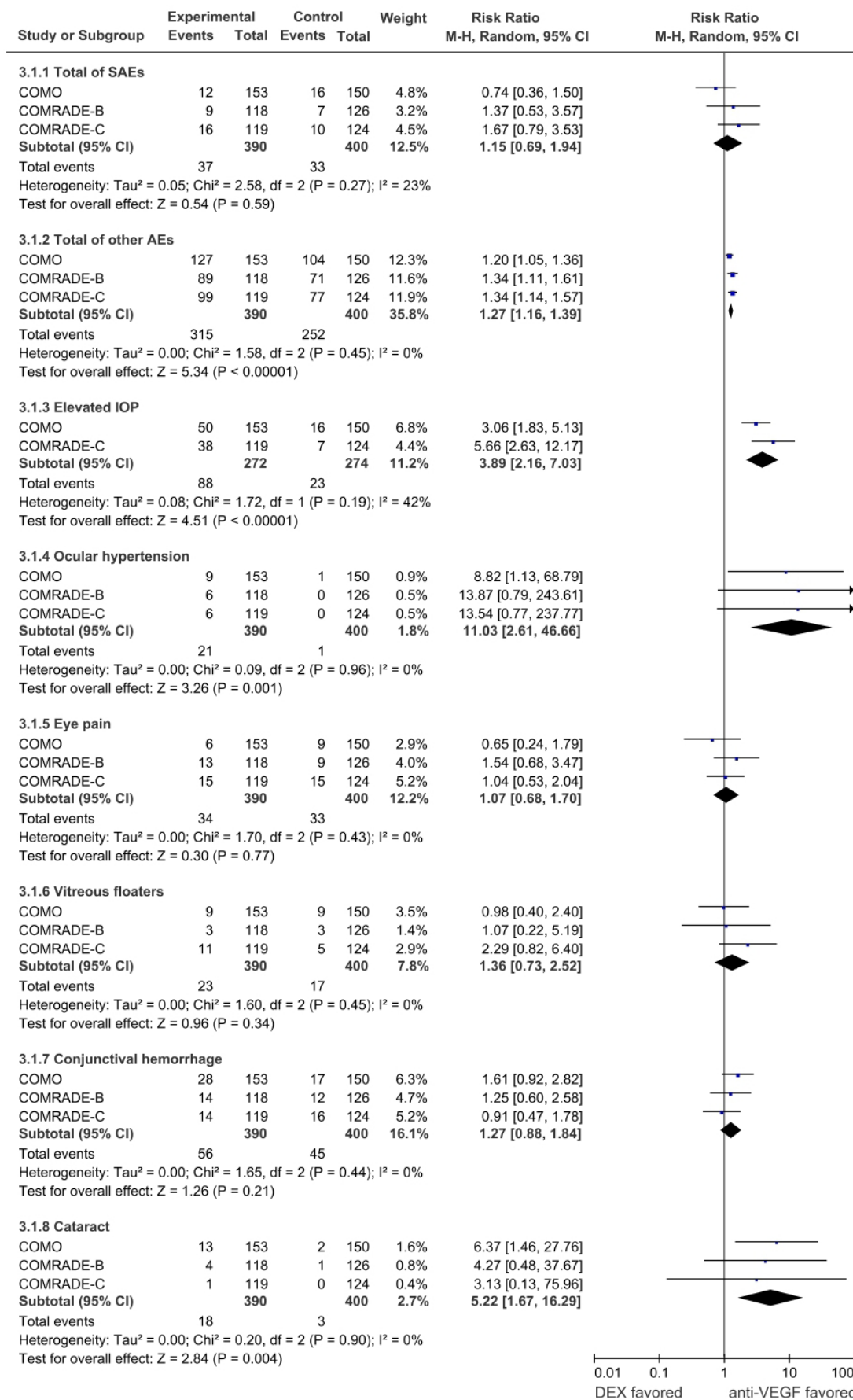
Figure 4 A forest plot diagram showing the safety data, including serious adverse events (SAEs), other adverse events (AEs), and the other top five AEs in dexamethasone (DEX) and anti-vascularendothelial growth factor (anti-VEGF) arms.

Table 3 Summary of the efficacy and safety in real-world studies

Study (year, country)	Endpoint time (months)	Arms	Change in mean BCVA at month 6	Change in CRT (µm) at month 6	Comparison of the changes in BCVA and CRT	Change in BCVA at month 12 or at the end of follow-up	Change in CRT (µm) at month 12	Comparison of the changes in BCVA and CRT	Safety
Kumar et al (2019, India)[38]	6	RNB	+18 letters†	−213.81†	More gain, equal reduction	NR	NR	NR	IOP increase
	6	DEX	+9.5 letters†	−207.27†	Less gain, equal reduction	NR	NR	NR	More IOP increase
Ozkaya et al (2018)[26]	6, 12, 24	RNB	−0.11 logMAR†	−133†	Gain, reduction	−0.15 logMAR†# (month 24)	−193† (month 24)	Gain, reduction	Cataract progression: 5.7%*, no IOP increase >10mmHg
	6, 12, 24	DEX	−0.08 logMAR	−171†	No change, reduction	−0.06 logMAR (month 24)	−256† (month 24)	No change, reduction	Cataract progression: 46.1%, IOP increase >10mmHg: 22%
Yucel et al (2018, Turkey)[27]	6	RNB	−0.20 logMAR†	−162.7†	Numerical gain, equal reduction	NR	NR	NR, NR	Cataract (%): 1 (5.6%), IOP increase >25mmHg: 2 (11.1%)
	6	Afl	−0.27 logMAR†	−310.1†	Numerical gain, equal reduction	NR	NR	NR, NR	Cataract (%): 1 (6.3%), IOP increase >25mmHg: 1 (6.3%)
	6	DEX	−0.11 logMAR	−193.8†	Numerical gain, equal reduction	NR	NR	NR, NR	Cataract (%): 7 (29.2%), IOP increase >25mmHg: 5 (20.8%)
Winterhalter et al (2018, Germany)[28]	6	RNB	BRVO: +8 letters, −0.16 logMAR† CRVO: +5 letters, −0.10 logMAR	BRVO: −194† CRVO: −204†	BRVO: equal gain, equal reduction CRVO: no change	Comparable BCVA gains and CRT reduction in BRVO	NR	NR, NR	No systemic AE
	6	DEX	BRVO: +10 letters, −0.19 logMAR† CRVO: −4 letters, 0.08 logMAR	BRVO: −149† CRVO: −208†	BRVO: equal gain, equal reduction CRVO: slight loss, equal reduction	Undertreatment in CRVO	NR	NR, NR	IOP increase >3mmHg: 6/15 (53.3%)
Yuksel et al (2018, Turkey)[29]	6–11.9	RNB	+7.1 letters, −0.12 logMAR	−206.5 (40.9%)	Less gain, more reduction (numerically)	−0.11 logMAR†	−241.3 (47.8%)	Less gain, more reduction (numerically)	IOP mean increase: −0.6mmHg
	6–13.9	DEX	+13.5 letters, −0.27 logMAR	−166.4 (32.5%)	More gain, less reduction (numerically)	+13.5 letters, −0.27 logMAR†	−146.5 (28.6%)	More gain, less reduction (numerically)	IOP mean increase: 3mmHg*
Kaldirim et al (2017, Turkey)[30]	6	RNB	−0.35 logMAR†	−195.36†	More gain, more reduction	NR	NR	NR	IOP mean decrease: 0.31 mmHg
	6	Afl	−0.38 logMAR†	−241.06†	More gain, more reduction	NR	NR	NR	IOP mean decrease: 0.15mmHg
	6	DEX	−0.26 logMAR†	−163.15†	Less gain*, less reduction* (ANOVA test)	NR	NR	NR	IOP mean increase: 1.8mmHg*

Continued

Table 3 Continued

Study (year, country)	Endpoint time (months)	Arms	Change in mean BCVA at month 6	Change in CRT (μm) at month 6	Comparison of the changes in BCVA and CRT	Change in BCVA at month 12 or at the end of follow-up	Change in CRT (μm) at month 12	Comparison of the changes in BCVA and CRT	Safety
Chatziralli et al (2017, Greece)[31]	6–12	RNB	+8.9 letters	−303.3	More gain, more reduction (numerically)	+8.4 letters†	−260 μm†	Equal gain, equal reduction	Cataract: 1/25 (4%), IOP increase: none
	6–12	DEX	+4.1 letters	−228.0	Less gain, less reduction (numerically)	+6.9 letters†	−197 μm†	Equal gain, equal reduction	Cataract: 3/17 (17.6%), IOP increase: 2/17 (11.8%)
Gu et al (2017, China)[32]	6	RNB	CRVO: +10.5 letters† BRVO: +6.3 letters†	CRVO:−283.2† BRVO: −84.6†	Equal gain and reduction; Equal gain and reduction	NR	NR	NR	Stable lens opacities and IOP
	6	DEX	CRVO: +6.9 letters† BRVO: +5.8 letters†	CRVO:−444.6† BRVO:−139.8†	Equal gain and reduction; Equal gain and reduction	NR	NR	NR	Stable lens opacities, IOP elevation but quite stable
Mayer et al (2015, German)[33]	6, 12	RNB	CRVO: +8.9 letters, −0.2 logMAR; BRVO: +8.6 letters, −0.2 logMAR	CRVO: −90.3† BRVO: −82.9†	NR, NR	CRVO: +6.9 letters BRVO: +12.5 letters	CRVO: −200.1† BRVO: −215.8†	CRVO: equal gain, NR; BRVO: equal gain, NR	No systemic AE
	6, 12	DEX	CRVO: +7.6 letters, −0.15 logMAR; BRVO: +17.9 letters, −0.35 logMAR	CRVO:−181.9† BRVO:−191.4†	NR, NR	CRVO: +8.4 letters BRVO: +10.7 letters	CRVO: −303.9† BRVO: −194.1†	CRVO: equal gain, NR; BRVO: equal gain, NR	Cataract progression: 50%, IOP increase >5mmHg: 50%
Kim et al (2015, Korea)[34]	6–12	Bev	−0.21 logMAR*	−157.15*	Gain, more reduction	−0.23 logMAR	Bev: −160.09	Equal gain and reduction	No lens opacity increase ≥2 grades, no IOP increase
	6–12	DEX	+0.19 logMAR	−48.98	Loss, less reduction	−0.19 logMAR	DEX: −140.70	Equal gain and reduction	one eye lens opacity increase ≥2 grades, no IOP increase
Chiquet et al (2015, France)[35]	6–12	anti-VEGF	−0.1 logMAR†	−138 (−20%)†	Equal gain, equal reduction	−0.1 logMAR	−210 (−32%)†	Equal gain and reduction	Cataract surgery: 10.9%, IOP>21 mmHg: 3.1%*
	6–12	DEX	−0.3 logMAR†	−153 (−17%)†	Equal gain, equal reduction	−0.3 logMAR†	−137 (−20%)†	Equal gain and reduction	Cataract surgery: 7.9%, IOP>21 mmHg: 21%
Nghiem-Buffet et al (2014, France)[36]	BRVO: 15.8 CRVO: 18.4	RNB	NR	NR	—	BRVO: +9.2 letters† CRVO: +18.2 letters†	—	NR, NR	No cataract progression, no IOP rise >10mmHg
	BRVO: 13.2 CRVO: 11.4	DEX	NR	NR	—	BRVO: +5.8 letters† CRVO: +16.8 letters†	—	NR, NR	Cataract progression: 1 (2.4%), IOP rise >10mmHg: 7 (17%)

*Statistically significant difference between anti-VEGF and DEX.
†Statistically significant difference from baseline.
Afl, aflibercept; ANOVA, analysis of variance; BCVA, best-corrected visual acuity; Bev, bevacizumab; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; DEX, dexamethasone implant; IOP, intraocular pressure; NR, not reported; RNB, ranibizumab; VEGF, vascular endothelial growth factor .

Heterogeneity and bias

The advantage of the DEX implant is that it releases dexamethasone slowly for ≤6 months.[10 12] However, it is maximally effective only at ~2 months after administration. Thereafter, its effectiveness declines steadily to a level that is not significantly better than that of a sham treatment.[11 43] Gado et al[25] added a second DEX implant after the third month. In COMRADE C and COMRADE B,[23 24] a single implant was used for the comparison of reduction in CRT during 6 months of follow-up. This heterogeneity could undermine the conclusion of our meta-analysis regarding anatomical outcomes. Further, BRVO and CRVO are different disease entities. Eyes with CRVO did not respond as well to anti-VEGF as those with BRVO.[14 43] Unlike the COMRADE B study (BRVO), the COMRADE C study (CRVO) reported consistent letter gains (16.9 letters vs 17.3 letters) in the anti-VEGF arm but markedly decreased letter gains (−0.7 letters vs 9.2 letters) in the DEX arm. A similar scenario was observed for the anatomical outcomes. These results partially accounted for the substantial heterogeneity that arose when the functional and anatomical outcomes were combined for month 6.

In the COMO study,[22] BRVO patients were administered DEX therapy on day 1, month 5, and month 10 or 11 (optional). In this randomised head-to-head trial, the efficacy of the DEX implant was not non-inferior to that of eight RNB injections at month 12. In an extension[21] of the COMRADE B and COMRADE C studies, German patients who were followed for another 6 months after adding an optional DEX implant under a European label (retreatment interval ≥6 months) were selected. The meta-analysis demonstrated significant functional and slightly better anatomical improvements without heterogeneity in the anti-VEGF group. Nevertheless, caution must be exercised when interpreting the results. The aforementioned study[21] was open-label and phase IV and its core only included certain parts of the population. Selection bias might have also attenuated the evidence and mitigated the reliability of our conclusion. Fortunately, all the patients included in the extension follow-up had comparable baseline characteristics because the core study was effectively controlled. RCTs with multiple DEX injections administered at intervals of <6 months are nonetheless required to draw a robust conclusion.

Safety concerns

Based on the RCTs, no new safety issues were identified for the anti-VEGF or DEX implant treatments. The anti-VEGF treatment proved to be safer than the DEX treatment for ocular AEs, including elevated IOP, ocular hypertension and predictable cataract progression. These differences in safety risks were verified in our review of the real-world studies. RVO patients with relatively higher baseline IOPs or histories of ocular hypertension and/or glaucoma might benefit from the anti-VEGF treatment performed in accordance with the guidelines. Frequent monitoring of IOP and cataract progression can enable DEX to be effective and safe for patients who are reluctant to receive frequent injections. The study showed that visit burdens did not markedly differ between RVO patients receiving ranibizumab injections and those being administered DEX; the mean numbers of ophthalmology visits were 7.2 vs 6.2 for CRVO and 7.1 vs 6.3 for BRVO, respectively.[44] Physicians must still focus on the clinical benefits of the drugs when they evaluate treatment options for RVO.

Real-world evidence

As there were only a few head-to-head RCTs, real-world comparisons of the DEX implant and anti-VEGF treatments furnish guidance for drug administration. Our systematic review showed that real-world studies reported first-line DEX use and anti-VEGF therapy in naïve patients. The studies reflected the efficacy of medication under practical conditions in the short (6 months) and intermediate (12 months) terms. Similarly, most studies demonstrated the relative superiority of anti-VEGF drugs in terms of letter gains in visual acuity for BRVO and CRVO patients. However, the differences were not usually statistically significant. There are several possible explanations for the discrepancy between the outcomes of the RCTs and real-life studies. First, compared with that in real-world scenarios, the dosages of anti-VEGF agents were effectively controlled in the RCTs. The typical protocol included three to six consecutive monthly injections followed by PRN. In real-world situations, it is difficult to maintain high injection frequencies, and undertreatment has been reported to occur often during a long-term therapy.[26 29] Second, unlike in the random allocation design of the RCTs, the choice of therapy depended mainly on the ophthalmological and systemic history of the patients in the real-world studies. Third, patients were selected for the clinical trials according to strict and specific criteria, whereas the patients in daily practice did not meet these restrictions.

Retreatment interval

The injection frequency influenced the treatment efficacy in both the groups. Poorer visual outcomes were observed for undertreated patients in the anti-VEGF group.[29] Under the approved dose regimen, protocols administering DEX according to an as-needed retreatment protocol at 6-month intervals showed significantly[34] or numerically lower[30 31] efficacy than those administering anti-VEGF drugs. The recurrence of MO was also observed by month 5 in the DEX group.[31] In contrast, when DEX was readministered at 4-month intervals, it resulted in comparable[23] or superior visual letter gains[30] and reduction in CRT.[27] However, the differences were not statistically significant. As shorter dosage intervals were suspected to increase the number of complications,[45] the DEX implant must be readministered at ~4–5 month intervals to maintain an efficacy comparable with that of the anti-VEGF drugs. Hence, greater emphasis and attention should be directed toward real-life trials as their treatment intervals generally approach 4 months.

Limitations

All studies included in the present review were head-to-head RCTs or real-world studies directly comparing the administration of anti-VEGF and DEX for the management of RVO. A major limitation was that only four studies were included in this meta-analysis. Thus, we could not analyse the outcomes for the various types of aetiologies (CRVO/BRVO) or for different anti-VEGF agents (RNB or Bev). Therefore, potential heterogeneities associated with these deficiencies were not resolved based on the short-term data. Second, certain studies in which the DEX implant was administered under the European label might have reported underestimates. Third, our review was based on a 6-month or 12-month treatment duration and included no long-term (>2 years) efficacy trials. Real-world reports help to elucidate outcomes but more RCTs are required to validate our meta-analysis.

CONCLUSIONS

The DEX implant demonstrated inferior functional efficacy than the anti-VEGF agents and was not better in terms of short-term and intermediate-term anatomical outcomes. The short-term data might suggest that patients administered a single DEX implant were undertreated. Although it entails relatively fewer injections, the DEX implant must be dialectically administered for the treatment of MO secondary to RVO because it can result in comparatively higher incidences of AEs, such as elevated IOP and cataract in a first-line treatment scenario. The overall advantages of anti-VEGF drugs were verified in the real-world studies and it was confirmed that the DEX implant could achieve efficacy comparable with that of anti-VEGF therapy when it is administered according to the appropriate treatment protocol. Further RCTs are nonetheless required to reinforce our current analysis.

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