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Comparison of dexamethasone intravitreal implant with intravitreal anti-VEGF injections for the treatment of macular edema secondary to branch retinal vein occlusion

A meta-analysis

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Abstract

Background: This meta-analysis compared the efficacy and safety of dexamethasone intravitreal implant (DEX) and anti-vascular endothelial growth factor (anti-VEGF) in the treatment of macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

Methods: The PubMed, Embase, Cochrane Library, and Web of Science databases were comprehensively searched for published studies comparing DEX with anti-VEGF for the treatment of ME caused by BRVO. Outcomes of the selected studies included best-corrected visual acuity (BCVA), central macular thickness (CMT), and adverse events. Review Manager (RevMan) 5.3 was used to analyze the data.

Results: Six trials comparing the efficacy and safety of DEX with anti-VEGF were included in this meta-analysis. At 1 month, DEX achieved a mean BCVA superior to that achieved by anti-VEGF (MD = −0.11, $P < .0001$), in addition to a superior mean BCVA change (MD = −0.35, $P < .00001$). At 3 months, the mean BCVA showed a significant difference (MD = −0.06, $P = .03$) between DEX and anti-VEGF treatment, while the mean BCVA change was similar to that with anti-VEGF treatment (MD = −0.06, $P = .11$). However, neither mean BCVA nor mean BCVA change showed a significant difference between DEX and anti-VEGF treatment at 6 months (MD = 0.08, $P = .06$; MD = 0.06, $P = .43$, respectively). Mean CMT and mean CMT change were significantly lower in the DEX group than in the anti-VEGF group at 1 month (MD = −53.63 μm, $P < .00001$; MD = −60.1 μm, $P = .005$, respectively). However, at 3 months, mean CMT and mean CMT change were similar between DEX and anti-VEGF treatment (MD = 17.4 μ, $P = .74$; MD = 18.01 μm, $P = .72$, respectively). Although mean CMT in the anti-VEGF group was not significantly lower than that in the DEX group at 6 months (MD = 55.53, $P = .07$), the mean CMT change from baseline achieved by the anti-VEGF treatment was significantly superior to that obtained with DEX (MD = 75.53, $P = .0002$). Concerning adverse events, no statistically significant differences were observed in the incidence of cataract (OR = 4.25, $P = .07$), but the use of DEX led to a higher risk of intraocular pressure elevation compared with anti-VEGF treatment (OR = 12.04, $P = .006$).

Conclusions: Our results show that visual acuity recovery and CMT were better in the DEX group than in the anti-VEGF group after 1 and 3 months, although the difference in CMT at 3 months was not significant. However, there were no significant differences in terms of visual acuity and CMT between the two groups after 6 months of follow-up. Therefore, DEX may be recommended as the first treatment option in ME associated with BRVO.

Abbreviations: 95% CI = 95% confidence interval, Anti-VEGF = anti-vascular endothelial growth factor, BCVA = best-corrected visual acuity, BRVO = branch retinal vein occlusion, BRVO-ME = macular edema secondary to branch retinal vein occlusion, CMT = central macular thickness, DEX = dexamethasone intravitreal implant, I^2 = inconsistency index, IOP = intraocular pressure, IVB = intravitreal bevacizumab, IVR = intravitreal ranibizumab, logMAR = logarithm of the minimum angle of resolution, MCP = monocyte chemotactic protein, MD = mean difference, ME = macular edema, OR = odds ratio, PDGF = platelet-derived growth factor, PRISMA

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1. Introduction

Branch retinal vein occlusion (BRVO), which accounts for nearly 80% of retinal vein occlusions (RVOs), is the second most common retinal vascular disorder, after diabetic retinopathy,[1,2] and macular edema (ME) secondary to BRVO is the most frequent cause of visual impairment.[3] Numerous risk factors account for this disease, including hypertension, hypercholesterolemia, diabetes mellitus, smoking, increased body mass index, hypermetropia, glaucoma, and orbital diseases.[4] The pathogenesis of ME is mainly associated with increased vascular permeability and levels of cytokines, such as VEGF, interleukins 6 and 8, monocyte chemotactic protein-1, and platelet-derived growth factor-AA.[5,6]

Currently, the most common therapeutic strategies for BRVO include injections of anti-VEGF agents and corticosteroids, such as triamcinolone acetonide. A variety of anti-VEGF agents, such as ranibizumab, bevacizumab, and aflibercept have been proven effective in the therapy of ME secondary to BRVO and with fewer side effects.[7–9] Intravitreal triamcinolone injection was found effective in treating visual impairment associated with ME secondary to BRVO, and especially beneficial for refractory edema.[10] Recently, the FDA approved a sustained release, biodegradable dexamethasone implant (Ozurdex; Allergan) as a therapy for ME,[11] and the GENEVA study revealed that the efficacy and safety of the DEX intravitreal implant was better than observation in the therapy of ME associated with BRVO.[12]

To the best of our knowledge, there has been no meta-analysis evaluating the relative efficacy and safety of intravitreal anti-VEGF treatment and DEX in the treatment of ME secondary to BRVO. We thus undertook such a meta-analysis, specifically to evaluate the effect of these treatments on best-corrected visual acuity (BCVA) and central macular thickness (CMT) in ME secondary to BRVO, and the incidence of adverse events, thus providing robust clinical evidence for ophthalmologists.

2. Methods

2.1. Search strategy

We performed a meta-analysis according to previously published studies, thus the ethical approval was not required. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[13] Two investigators (Kaibao Ji and Qinglin Zhang) performed the literature search via PubMed (http://www.ncbi.nlm.nih.gov/PubMed/), Embase (http://www.embase.com), The Cochrane Library (http://www.thecochranelibrary.com/), and the Web of Science (http://webofknowledge.com/WOS), searching for papers published until September 2018. The search terms used were "branch retinal vein occlusion," "macular edema," "macular oedema," "cystoid macular edema," "anti-VEGF," "bevacizumab," "Avastin," "ranibizumab," "Lucentis," "aflibercept," "Anti-vascular Endothelial Growth Factor," "Ozurdex," "intravitreal dexamethasone implant," "intravitreal dexamethasone," and "dexamethasone implant," so as to

maximize the number of studies considered. Studies written in English were considered eligible. A final decision about the inclusion of each study was made after the two investigators reached a consensus. A flow diagram of the search strategy process is shown in Fig. 1.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were considered eligible:

1. the study population included patients with ME secondary to branch retinal vein occlusion (BRVO-ME);
2. interventional therapies for BRVO-ME consisted of DEX implant (Ozurdex) and anti-VEGF treatment;
3. the following primary outcomes were available, allowing the calculation of odds ratios (OR) or mean differences (MD) with their 95% confidence interval (95% CI): mean BCVA expressed as logMAR (time points: baseline, 1 month, 3 months, and 6 months); mean CMT (at the same time points); total number of serious adverse events (SAEs), such as endophthalmitis, retinal detachment, or retinal breaks at the end of each study; elevation of intraocular pressure (IOP > 21 mm Hg, use of glaucoma agents for IOP control);
4. the mean number of intravitreal injections was reported.

We did not set limitations on the doses used in the studies. Patients taking bevacizumab, ranibizumab, Avastin, Lucentis, and aflibercept were placed in the anti-VEGF group. Studies were excluded if they were written in a language other than English, or in case of insufficient data. Case reports, abstracts from conferences, and review articles were also excluded.

2.3. Data extraction and quality assessment

Kaibao Ji and Qinglin Zhang independently collected the relevant data from all the studies included, and specifically

1. mean and standard deviation (SD) of the BCVA and of its change from baseline, expressed in logMAR;
2. mean and SD of the CMT and of its change from baseline, expressed in um;
3. incidence of adverse events.

The results were compared, and disagreements were resolved through discussions until consensus was achieved. The following data about the studies, their population, and their design were also extracted: first author, year of publication, country of origin, study design, interventions, sample size, mean age, gender ratio, follow-up time frames. We used the Jadad scale to assess randomized controlled trials (RCT)[14] and the Newcastle-Ottawa Scale for nonrandomized controlled studies.[15]

2.4. Statistical analysis

Review Manager (RevMan, version 5.3, Cochrane Collaboration, Oxford, UK) was used to analyze the collected data. Pooled OR and its 95% CI were used to assess dichotomous variables, and MD with its 95% CI for continuous variables. Mean changes
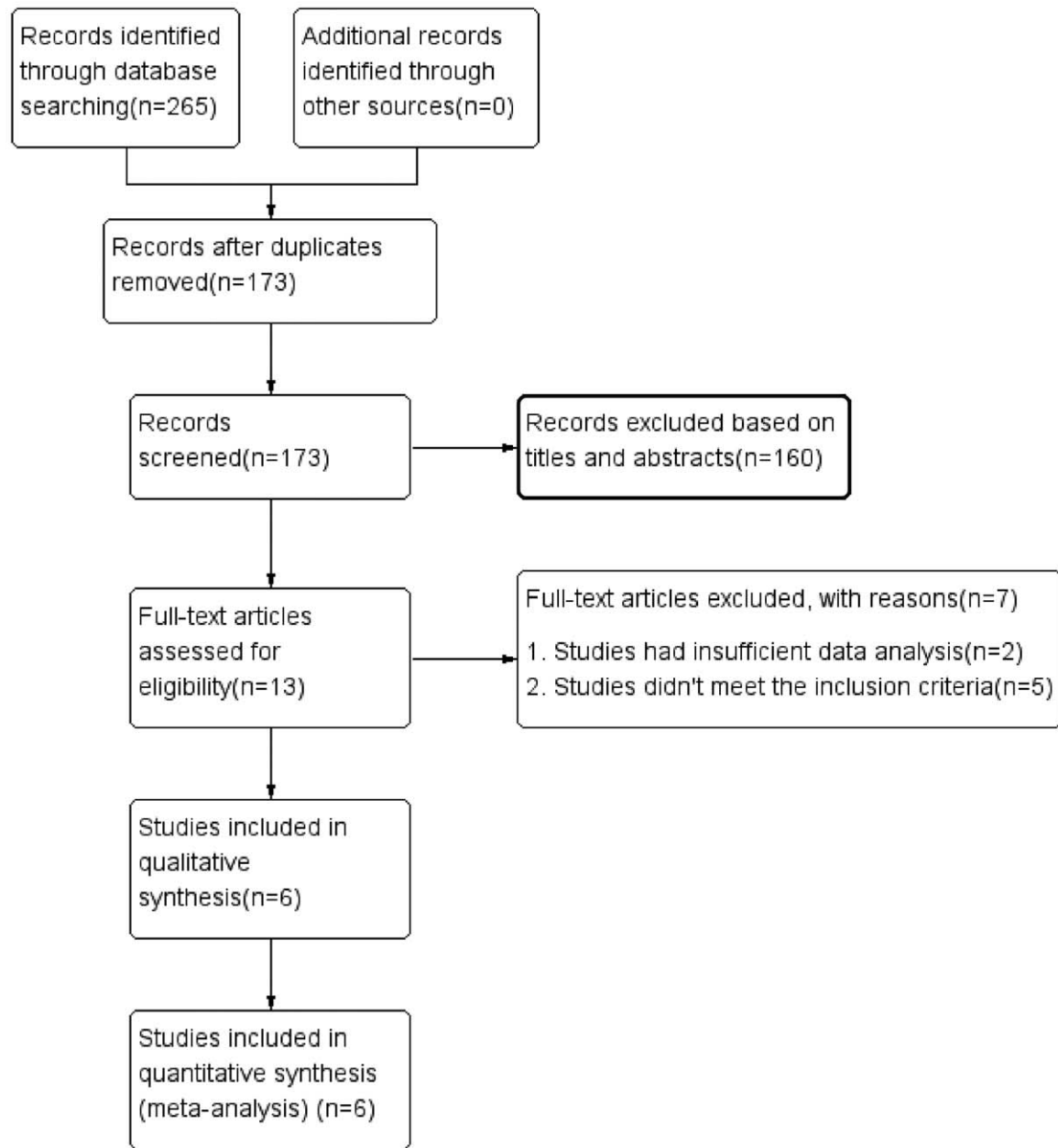
Figure 1. Flow chart of the search strategy and literature selection.

in BCVA and CMT were calculated according to the Cochrane Handbook.[16] Heterogeneity between the studies was evaluated using the chi squared test based on the values of P and (inconsistency index) I^2. I^2 statistic ranging from 50% to 100% was considered to represent substantial heterogeneity. A random-effect model was used for the meta-analysis, and P-values $< .05$ were considered statistically significant.

3. Results

3.1. Search results

A total of 265 potentially relevant records published until September 2018 were identified by our literature search (PubMed: 57; Embase: 90; Cochrane Library: 21; Web of Science: 97), of which 92 were duplicates that were excluded.

After reading the titles and abstracts, 160 more records were excluded. After reading the full text of the remaining 13 studies, 2 were excluded due to insufficient data and 5 because they did not meet the inclusion criteria. Thus, 6 studies[17–22] were eventually included in our meta-analysis (Fig. 1).

The six studies included one RCT, four retrospective studies, and one prospective pilot study; the detailed characteristics and quality assessment of the studies are described in Table 1. A total of 452 BRVO-ME eyes (212 patients in the DEX group and 240 in the anti-VEGF group) were considered in this meta-analysis. The DEX dose was the same in all the trials. The studies by Hattenbach et al,[22] Yuksel et al,[20] and Kaldırım et al[17] performed intravitreal ranibizumab (IVR) injections, while Kim et al,[19] Guignier et al,[21] and Moon et al[18] used intravitreal bevacizumab (IVB) injections.

Table 1

The characteristics and quality assessments of the included studies.

Study	Place	Study design	Type of RVO	Numbers of Participants	Interventions details	Mean age (years)	Follow-up (months)	Quality score
Kaldırım HE 2018[17]	Turkey	Retrospective case-control study	BRVO	DEX: 20 IVR: 22	DEX: 0.7 mg given at initial visit IVR:0.5 mg IVR given at initial visit, month 1and month 2	70.6±3.9 70.32±4.3	6	********
Moon SY 2018[18]	Korea	Retrospective case-control study	BRVO	DEX: 20 IVB: 26	DEX: 0.7 mg given at initial+ PRN IVB: 1.25 mg IVB monthly+ PRN	60.8±10.1 60.7±8.1	6	********
Kim M 2015[19]	Korea	Retrospective case-control study	BRVO	DEX: 28 IVB: 44	DEX: 0.7 mg at baseline and month 6 IVB: 1.25 mg IVB at initial + PRN	64.07±6.88 61.79±9.17	12	*******
Yuksel B 2018[20]	Turkey	Retrospective case-control study	BRVO	DEX: 15 IVR: 14	DEX: 0.7 mg given at initial+ PRN IVR: 0.5 mg IVR given at initial + PRN	63.5±5.6 61.7±12.7	6	******
Guignier B 2018[21]	France	Prospective case-control study	BRVO	DEX: 11 IVB: 8	DEX: 0.7 mg given at initial visit IVB: 1.25 mg IVB given at initial visit, month 1 and month 2	67.0±7.0 61.0±12.0	6	******
Hattenbach LO 2018[22]	Germany	Randomized controlled trial	BRVO	DEX: 118 IVR: 126	DEX: 0.7 mg given at initial visit IVR:0.5 mg IVR given at initial visit, month 1and month 2	65.6±10.0 65.7±10.9	6	5 points

BRVO = branch retinal vein occlusion, DEX = dexamethasone intravitreal implant, IVB = intravitreal bevacizumab, IVR = intravitreal ranibizumab.

4. Meta-analysis results

4.1. Mean BCVA at 1, 3, and 6 months

Two studies including 88 eyes (40 eyes with DEX treatment and 48 with anti-VEGF treatment) reported the BCVA at 1 month. The difference between the two treatments was significant. The MD in visual acuity of the two trials was −0.11 (95% CI: −0.16 to −0.06, $P < .0001$, Fig. 2), indicating the superiority of DEX treatment. No statistical heterogeneity was found (chi^2 = 0.84, P = .36, I^2 = 0%). At 3 months, two studies including 71 eyes (35 eyes with DEX treatment and 36 with anti-VEGF treatment) reported that the difference between the two treatments was significant. The MD in visual acuity of the two trials was −0.06 (95% CI: −0.11 to −0.00, $P = .03$, Fig. 2), and there was no

statistical heterogeneity (chi^2 = 0.02, $P = .89$, I^2 = 0%). However, we found no significant difference in BCVA between the two groups at 6 months: The MD in visual acuity of the two trials was 0.08 (95% CI: −0.00 to 0.17, $P = .06$, Fig. 2), and again there was no statistical heterogeneity (chi^2 = 0.72, $P = .40$, I^2 = 0%).

4.2. Mean BCVA change at 1, 3, and 6 months

Two studies assessing a total of 87 eyes reported an improvement in BCVA from baseline at 1 month. A statistically significant difference was found between the two groups in the mean BCVA change (MD = −0.35, 95% CI: −0.49 to −0.20, $P < .00001$, Fig. 3), indicating superior effectiveness of the DEX treatment, but there was substantial heterogeneity (chi^2 = 2.48, $P = .12$, I^2 = 60%). However, no
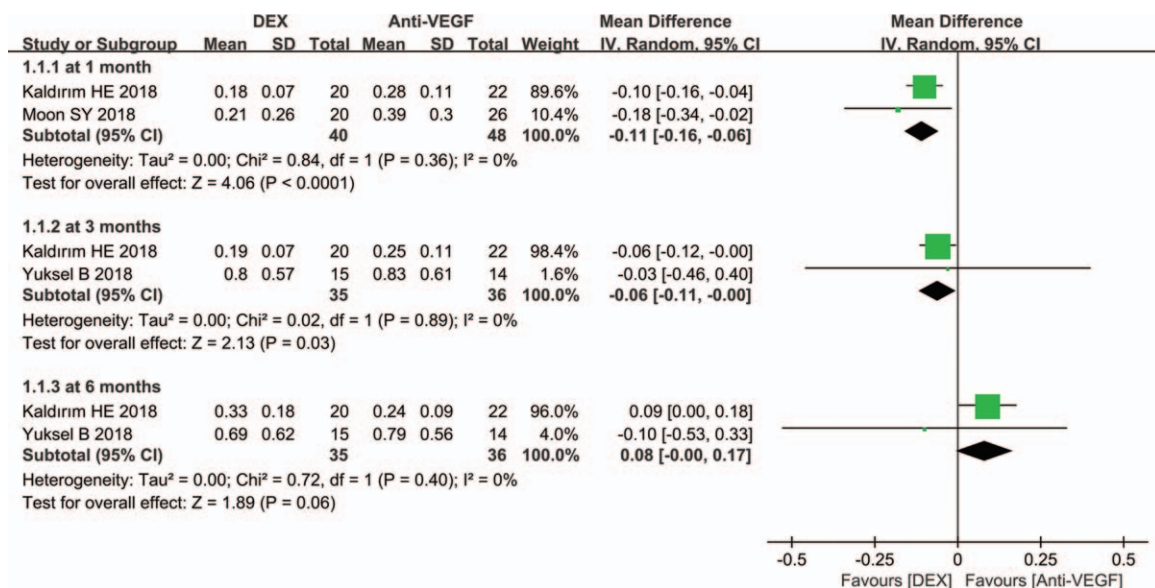
Figure 2. Forest plot for the mean BCVA (logMAR) at 1, 3, and 6 months between DEX and Anti-VEGF. Anti-VEGF = anti-vascular endothelial growth factor, BCVA = best-corrected visual acuity, DEX = dexamethasone intravitreal implant, LogMAR = logarithm of the minimum angle of resolution.
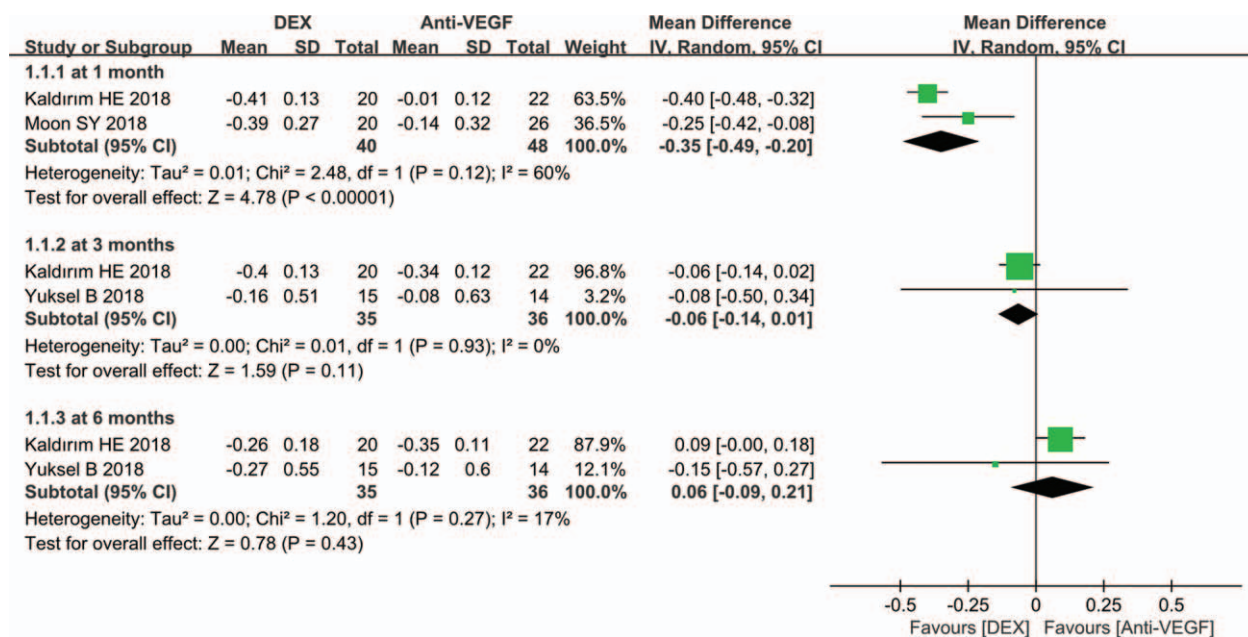
Figure 3. Forest plot for the mean change in BCVA (logMAR) at 1, 3, and 6 months between DEX and anti-VEGF. BCVA = best-corrected visual acuity; LogMAR = logarithm of the minimum angle of resolution.

significant differences were found between the two groups in the mean BCVA change at 3 and 6 months (MD = −0.06, 95% CI: −0.14 to 0.01, P = .11; MD = 0.06, 95% CI: −0.09 to 0.21, P = .43, respectively, Fig. 3), and no heterogeneity was detected (chi^2 = 0.01, P = .93, I^2 = 0%; chi^2 = 1.20, P = .27, I^2 = 17%, respectively).

4.3. Mean CMT at 1, 3, and 6 months

Three studies, including 107 eyes in total (51 eyes with DEX treatment and 56 with anti-VEGF treatment), reported CMT at 1 month after the initial treatment. Meta-analysis revealed that the difference between the two groups was remarkable: The MD of the mean CMT between the two treatments was significant (MD = −53.63, 95% CI: −71.77 to −35.50, P < .00001, Fig. 4), with the DEX treatment being superior to the anti-VEGF treatment, and with no heterogeneity (chi^2 = 1.83, P = .40, I^2 = 0%). Our meta-analysis demonstrated a lower CMT value at 3 months with DEX treatment, with the exception of the study by Yuksel et al[20] (MD = 17.40, 95% CI: −83.35 to 118.14, P = .74), with high heterogeneity (chi^2 = 13.53, P = .001, I^2 = 85%, Fig. 4). At 6 months, two of the three studies reported higher CMT values in the DEX group, the exception being the work by Guignier et al[21] (MD = 55.53, 95% CI: −5.11 to 116.17, P = .07), but also showed high heterogeneity (chi^2 = 19.06, P = .0003, I^2 = 84%, Fig. 4).

4.4. Mean CMT change at 1, 3, and 6 months

Three studies, assessing a total of 107 eyes, showed that the mean CMT reduction from baseline to 1 month in was larger in the DEX group (MD = −60.10, 95% CI: −101.72 to −18.48, P = .005, Fig. 5), and showed no heterogeneity (chi^2 = 2.00, P = .37, I^2 = 0%). At 3 months, all studies except the one by Yuksel et al[20] showed a reduction in CMT from baseline to 3 months in the DEX group (MD = 18.01, 95% CI: −81.23 to 117.25, P = .72), with high heterogeneity (chi^2 = 6.23, P = .04,

I^2 = 68%, Fig. 5). At 6 months, five studies including 406 eyes illustrated higher reduction in the DEX group in terms of mean change in CMT (MD = 75.53, 95% CI: 35.39 to 115.67, P = .0002), and showed moderate heterogeneity (chi^2 = 8.04, P = .09, I^2 = 50%, Fig. 5).

4.5. Adverse events

In our meta-analysis, no studies reported any serious adverse events during the follow-up period. Three studies involving 90 eyes revealed increased IOP after injection of DEX or anti-VEGF, with significantly higher incidence in the DEX group (OR = 12.04, 95% CI: 2.03–71.28, P = .006), and no heterogeneity (chi^2 = 1.38, P = .50, I^2 = 0%, Fig. 6). Three studies involving 358 eyes reported occurrences of cataract during the follow-up period, with larger incidence in the DEX group than in the anti-VEGF group, although the difference was not significant (OR = 4.25, 95% CI: 0.87–20.85, P = .07), and no heterogeneity was detected (chi^2 = 0.02, P = .99, I^2 = 0%, Fig. 7).

4.6. Number of intravitreal injections

In the studies by Guignier et al[21] and Hattenbach et al,[22] three injections were required in the anti-VEGF treatment, and only one in the DEX treatment. Also in the study by Kaldırım et al[17] the DEX group received one injection, while more injections (3.64 ± 0.49) were needed in the anti-VEGF group. Similarly, fewer treatments were required for the DEX treatment in comparison with the anti-VEGF treatment in other three studies.[18–20]

5. Discussion

We analyzed six studies on the efficacy of DEX and anti-VEGF in the treatment of ME secondary to BRVO. Our meta-analysis revealed that the DEX treatment could reduce CMT at 1 month
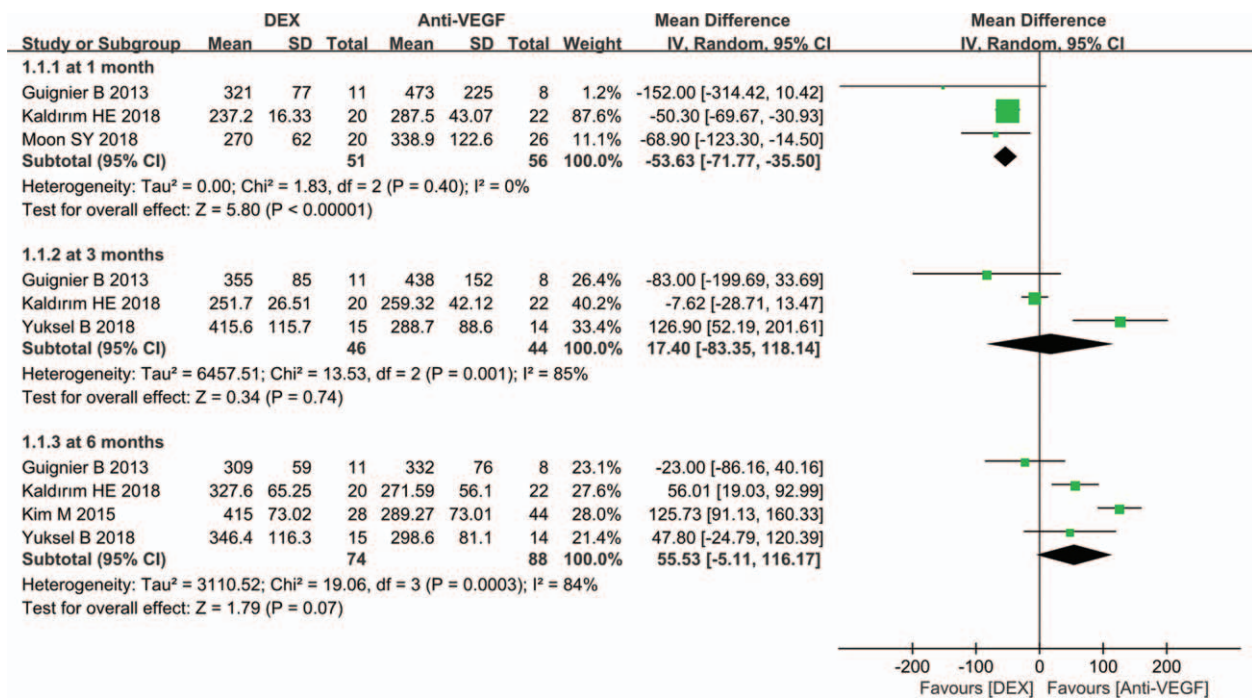
Figure 4. Forest plot for the mean CMT (μm) at 1, 3, and 6 months between DEX and anti-VEGF. Anti-VEGF=anti-vascular endothelial growth factor, CMT=central macular thickness, DEX=dexamethasone intravitreal implant.
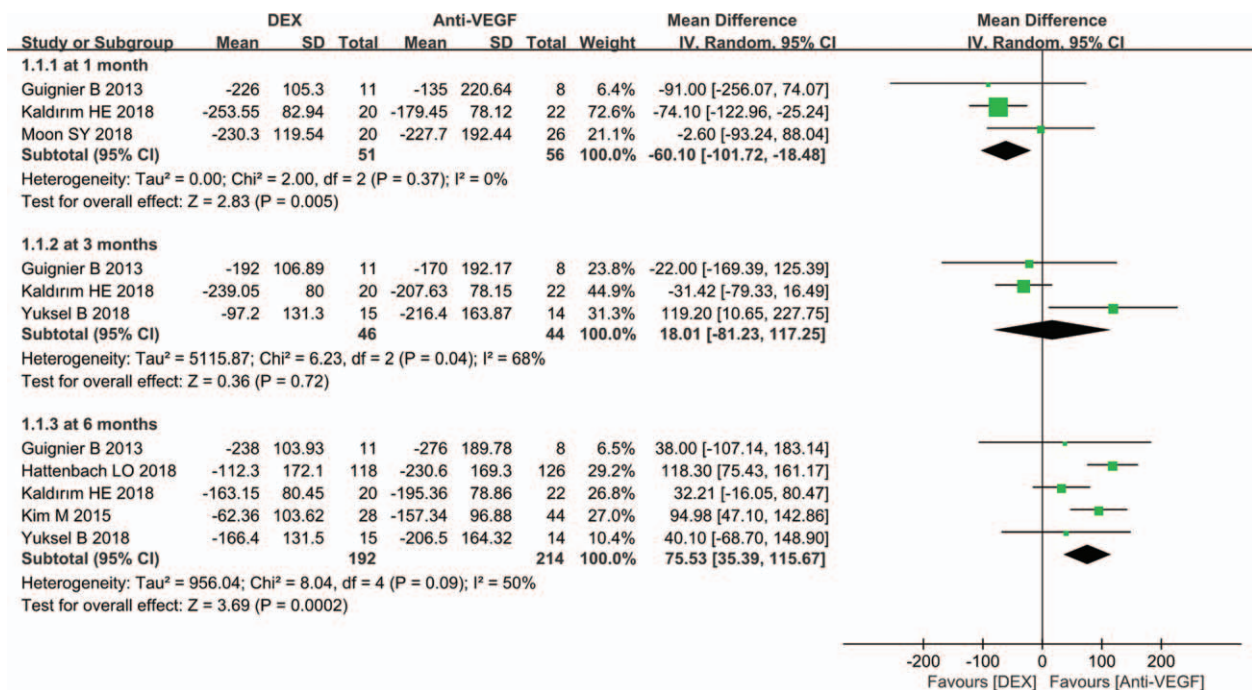
Figure 5. Forest plot for the mean change in CMT (μm) at 1, 3, and 6 months between DEX and anti-VEGF. Anti-VEGF=anti-vascular endothelial growth factor, CMT=central macular thickness, DEX=dexamethasone intravitreal implant.

significantly more than anti-VEGF treatment, but such efficacy, unfortunately, did not last until 6 months. This phenomenon can be explained by the characteristics of DEX implants, which show two main phases, with higher concentration in the early phase and lower concentration in the late phase.[23] We speculate that,

at 3 months, the heterogeneity shown by the mean CMT and the mean CMT change mainly originates from the small sample of the study by Yuksel et al.[20] Moreover, other potentially confounding factors such as age, race, and baseline state are unavoidable. The mean CMT, at 6 months, also demonstrated
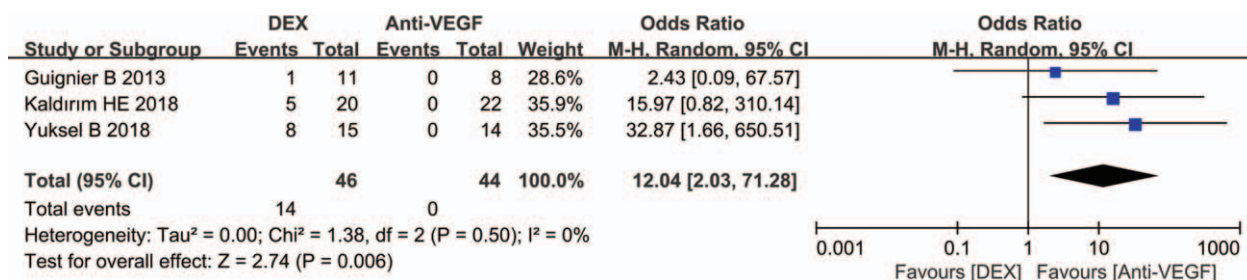
Figure 6. Forest plot showing the elevation of IOP. IOP = intraocular pressure.
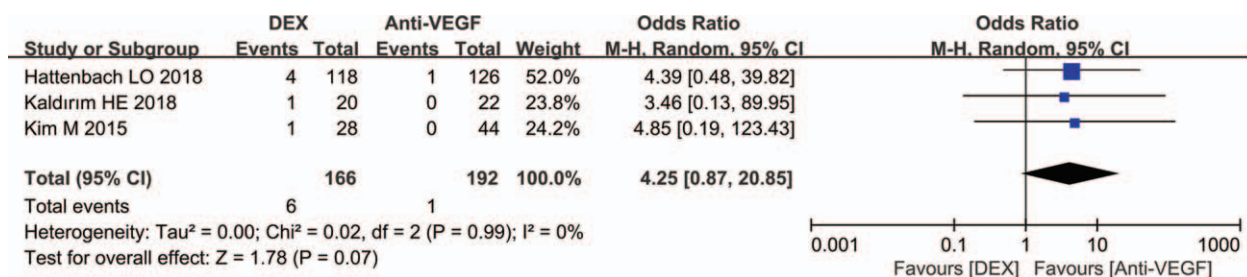

Figure 7. Forest plot showing the adverse events: cataract.

heterogeneity, mainly resulting from the pharmacokinetics and pharmacodynamics of DEX implants. Consistent with our results, a Chinese RVO study using Ozurdex to evaluate DEX treatment revealed that the mean change in CMT was significantly better with DEX treatment than in the sham group at 1 month but not at 6 months.[24]

As expected, the improvement in macular thickness in our meta-analysis translated into enhanced visual acuity outcomes at early time points. Similar to our results, the Haller study[25] showed significant improvements in BCVA, averaging 15 letters from baseline, as early as 1 month after DEX treatment, which continued until 3 months; however, the BCVA improvement was not significantly greater at 6 months. The limited improvement in visual acuity at 6 months is attributable to the pharmacokinetics and pharmacodynamics of DEX implants, and the duration of the ME may have contributed to this phenomenon.[26]

In addition to the efficacy in the treatment of BRVO-ME, the incidence of adverse events was analyzed in the two treatment groups. No serious systemic adverse events were observed in either group. Among ocular adverse events, elevated IOP and cataract are commonly observed. Our meta-analysis revealed a significantly higher risk of elevated IOP in the DEX group; the DEX group also showed higher risk of cataract, although the difference was not significant. The safety of DEX in the treatment of BRVO-ME as assessed by our meta-analysis was consistent with the results of a previous study.[27] Therefore ophthalmologists should be prudent when using DEX in patients with high IOP or in patients with clear lens.

Although anti-VEGF treatment is still the first-line treatment for BRVO-ME, the frequent injections may impose a significant cost burden and increase the risk of adverse events. Recent studies have reported an average interval between DEX injections of < 6 months for RVO.[28,29] The reduction in the cost of treatment

associated with the number of intravitreal injections is a clear advantage of the DEX treatment for BRVO-ME.[24]

For the current meta-analysis, both DEX and anti-VEGF therapies have a positive effect on the treatment of BRVO-ME. However, these two drugs have divergent pharmacological characteristics and adverse effects. DEX is considered the preferred treatment for patients who are anti-VEGF-resistant or those with refractory ME secondary to BRVO. We suggest that DEX should be proposed as the first treatment in the following cases:

1. patients without a high IOP risk at baseline;
2. patients with pseudophakic eyes;
3. patients who cannot afford the expenses associated with frequent intravitreal injections;
4. patients who have refractory ME secondary to BRVO.

The average time to DEX re-treatment in clinical practice is approximately 5 months.[30]

Our meta-analysis had some limitations. First, the sample size of our study is relatively small, and the quality of the included trials was relatively low, as only one RCT was included. Second, the follow-up time of the studies was quite short. Third, heterogeneity was inevitable, given the different anti-VEGF therapies used in the studies. A fourth potential limitation is that BRVO can be classified into two subtypes, ischemic and non-ischemic, and this distinction was not considered. To verify the validity of our meta-analysis, randomized clinical trials comparing different anti-VEGF drugs with DEX treatment, with longer follow-up times, should be carried in the near future.

6. Conclusions

This meta-analysis demonstrated that, despite some ocular adverse events, DEX appears to be relatively more effective than anti-VEGF therapy in the treatment of ME secondary to

BRVO, when considering early follow-up times. However, no significant differences in terms of visual acuity between the two treatments could be observed after 6 months of follow-up. We thus suggest that DEX should be recommended as the first-line treatment option in ME associated with BRVO, and that randomized clinical trials comparing anti-VEGF drugs with DEX in terms of both efficacy and safety, with long-term follow-up, should be carried out in the near future.

Acknowledgments

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