Review Article

Comparison between Ozurdex and intravitreal anti-vascular endothelial growth factor treatment for retinal vein occlusion–related macular edema: A systematic review and meta-analysis of randomized controlled trials

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This systematic review aimed to evaluate the effectiveness and safety of intravitreal dexamethasone (DEX) implant and intravitreal anti-vascular endothelial growth factor (VEGF) treatments for macular edema (ME) secondary to retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), and branch retinal vein occlusion (BRVO). The electronic databases comprehensively searched for the studies that compared DEX with anti-VEGF treatments in patients suffering from RVO-related ME. The effectiveness was estimated using best-corrected visual acuity (BCVA), central retinal thickness (CRT), and intraocular pressure (IOP). All data were analyzed by Review Manager (RevMan) 5.3. According to the meta-analysis from five randomized control trials, both DEX implant and anti-VEGF agent treatments were effective, but no significant differences in BCVA and CRT were observed between these two treatments. Novartis' two studies indicated that anti-VEGF agents significantly reduced the CRT compared with DEX implant at 6 months [weighted mean difference: 158.53 μm, 95% confidence interval (CI): (71.09, 245.96), $P = 0.0004$]. Furthermore, anti-VEGF agents showed some advantages on cataract formation [risk ratio (RR): 3.43, 95% CI: (1.35, 8.71), $P = 0.009$] and other adverse events [RR: 1.19, 95% CI: (1.09, 1.31), $P = 0.0002$] without heterogeneity ($P = 0.20$, $I^2 = 35\%$). Anti-VEGF agents were also effective treatments for cataract formation or less adverse events for RVO-related ME. In contrast, DEX implant had higher risk for IOP elevation and lower cataract incidence than anti-VEGF agents. Hence, complementary and alternative treatments are expected.

Key words: Anti-VEGF, dexamethasone implant, macular edema, meta-analysis, Ozurdex, retinal vein occlusion

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The literature searches were performed with a strict strategy using the following databases: PubMed, EMBASE, Web of Science, Cochrane Library, and clinicaltrials.gov. Statistical analyses were performed using Review Manager software (version 5.3; Cochrane Collaboration, London, UK). The mean ± standard deviation (SD) and/or weighted mean difference (WMD) and risk ratio (RR) were used to assess continuous variable outcomes and dichotomous outcomes with a 95% confidence interval (CI), respectively. Chi-square tests and I^2 value were used to quantify the statistical heterogeneity between two studies. The methodological quality and a bias risk assessment were performed according to Cochrane.

Retinal vein occlusion (RVO) is the second common retinal vascular disease, secondary to diabetic retinopathy. RVO has a 1%–2% of prevalence in people more than 40 years old, and the prevalence of branch retinal vein occlusion (BRVO) is four times more than that of central retinal vein occlusion (CRVO).[1] Generally, RVO is thought to result from mechanical damage in vascular wall or a local inflammation, thereby causing thrombosis, hypercoagulation, and stasis.[2]

Many therapies have been developed to treat RVO, such as surgical intervention, laser therapy, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents, corticosteroid preparations, and other agents, in which the laser photocoagulation has been the primary treatment for RVO in the past decades.[3,4] However, two studies in 1995 indicated that there was no significant improvement in vision with laser treatment compared with control.[5,6] On the contrary, intravitreal anti-VEGF agent injection was regarded as another effective treatment for RVO[7] demonstrating that it could significantly improve visual acuity (VA) and anatomical outcomes in patients suffering from RVO and RVO-related macular edema (ME).[8,9] In addition, a BRAVO study indicated that ranibizumab (a kind of anti-VEGF agent) had a better therapeutic effect relative to laser treatment alone.[10] Meanwhile, a GENEVA study showed that another useful therapy, sustained-release dexamethasone (DEX) implant (Ozurdex®),

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also had more significant improvement than control.[11] Further studies indicated that some anti-VEGF agents had similar therapeutic mechanisms, and the meta-analyses for previous clinical trials have already analyzed the differences in the effectiveness among different anti-VEGF agents.[12,13] Therefore, the comparison between anti-VEGF agent and DEX implant treatments for RVO-related ME is more expected.

This meta-analysis combined different anti-VEGF agents (ranibizumab, bevacizumab, and aflibercept) as one therapy and did not separate CRVO and BRVO patients to expand the sample size. Our study will help ophthalmologists choose the best treatment options for patients suffering from RVO and predict the adverse events (AEs) in advance during therapeutic processes.

Methods

Search strategy

This study was conducted in accordance with Cochrane Handbook for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The literature searches were performed on the papers and trials published up to August 2018 using the following databases: PubMed, EMBASE, Web of Science, Cochrane Library, and clinicaltrials.gov. The keywords including retinal vein occlusion (retinal vein thrombosis/thromboses), macular edema, intravitreal DEX implant (Ozurdex), and anti-VEGF agents (ranibizumab/bevacizumab/aflibercept/lucentis/avastin/VEGF-trap/eylea) were used to maximize the search accuracy [Table 1]. When titles and/or abstracts fitted our search terms, abstracts were carefully reviewed to exclude irrelevant studies. Full-text reading was performed when necessary. The literature selections are shown in the PRISMA flow diagram [Fig. 1].

Inclusion and exclusion criteria

Studies were chosen for inclusion in our analyses using the following inclusion criteria: (1) randomized control trials (RCTs), (2) interventional studies that compared the treatment efficacy of anti-VEGF agents and DEX implant (Ozurdex), (3) study subjects including patients with RVO-related ME, (4) treatment outcomes including best-corrected visual acuity (BCVA), central retinal thickness (CRT), and intraocular pressure (IOP), and (5) subjects who were followed for at least 1 month after initiating treatment. Studies that met any of the following exclusion criteria were excluded from our meta-analysis: (1) review articles or case reports, (2) duplicate publication, (3) did not obtain sufficient information, and (4) subjects with RVO not receiving any treatments for ME.

Data extraction and bias assessment risk

The following information on study characteristics and clinical treatments were collected from all included studies: publication metrics (name of first author, year of publication, study location, and trial design), subject information (age, gender, length of follow-up period), treatment information (treatment method, the number of subjects in each interventional group), and treatment outcomes at a specific time [including post-therapy logarithm of the minimum angle of resolution (logMAR), decimals or Early Treatment Diabetic Retinopathy Study BCVA, CRT, and IOP].

Statistical analysis

Statistical analyses were performed using Review Manager software (version 5.3; Cochrane Collaboration). Data were presented as mean ± SD. If the data were presented as standard error (SE), a formula, SD = SE × √N, was used to calculate SD. The mean ± SD and/or WMD and RR were used to assess continuous

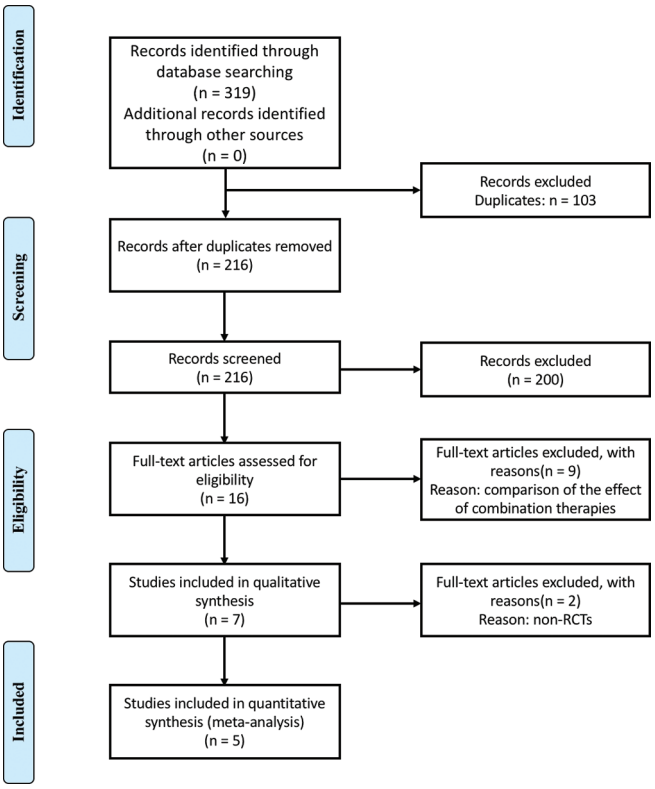

Figure 1: Flow diagram of included studies

Table 1: Search strategy in PubMed

No.	Query	Item numbers
1	Search macular edema or macular oedema	11,826
2	Search retinal vein occlusion or retinal vein thrombosis Search retinal vein thromboses or RVO or CRVO or BRVO	6163
3	Search intravitreal dexamethasone implant or dexamethasone or ozurdex	67,217
4	Search anti-vascular endothelial growth factor or anti VEGF or ranibizumab or bevacizumab or aflibercept or lucentis or avastin or VEGF-trap or eylea	33,412
5	1 and 2 and 3 and 4	119

5: Macular edema or macular oedema and retinal vein occlusion or retinal vein thrombosis or retinal vein thromboses or RVO or CRVO or BRVO and intravitreal dexamethasone implant or dexamethasone or ozurdex and anti-vascular endothelial growth factor or anti-VEGF or ranibizumab or bevacizumab or aflibercept or lucentis or avastin or VEGF-trap or eylea

variable outcomes and dichotomous outcomes with a 95% CI, respectively. $P < 0.05$ was considered as statistical significance. Chi-square tests were used to quantify statistical heterogeneity between two studies. If no heterogeneity ($P > 0.1$ or $I^2 < 50\%$) was observed, the fixed effect model was used to analyze data. If heterogeneity was observed, the random effect model was used. Forest plots were created to summarize weighted estimates.

Data extraction and quality assessment

The evidence quality of all included outcomes was evaluated, and the following information on study characteristics and clinical treatments were collected from all included studies: publication metrics (name of first author, year of publication, study location, and trial design), subject information (age, gender, length of follow-up period), treatment information (treatment method, the number of subjects in each interventional group), and treatment outcomes at a specific time (post-therapy BCVA, CRT, and IOP). Included studies were examined for biases with random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (report bias), and other factors that contribute to biases.

Results

Search results

A total of 319 potential records up to August 2018 were identified with electronic-based search (PubMed = 119, EMBASE = 86, Cochrane Library = 12, Web of Science = 69, and clinicaltrials.gov = 33). After excluding 103 duplicates, a total of 216 potentially eligible studies were retrieved. After carefully reading the title and abstract, 200 studies were excluded, and 11 studies were excluded after full-text examination. In these 11 studies, 9 studies compared the effects of combined therapy and the remaining 2 studies compared anti-VEGF agent and DEX implant therapies, but were not RCTs.[14,15] Therefore, five studies were ultimately included in this systematic review.[16-22]

Characteristics of included studies

Five studies including a total of 873 patients (ranging from 19 to 307 per study) suffering from RVO (CRVO or BRVO)-related ME were included in this meta-analysis. Basic study characteristics are summarized in Table 2. The five included studies were all RCTs, in which three studies were associated with BRVO (570 patients, 65.3%) and the remaining two studies were associated with CRVO (303 patients, 34.7%). Four studies included 316 patients with AEs, and 37 patients with serious adverse events (SAEs) were excluded from 401 patients during the process. In addition, patients receiving anti-VEGF treatment in either eye within 3 months or systemic anti-VEGF treatment within 6 months in Allergan's study were excluded; patients receiving anti-VEGF-treatment in the study or the fellow eye 3 months prior to baseline were excluded in Novartis' studies; patients treated with macular laser previously were excluded in Guignier *et al.*'s study; patients with any previous treatment were excluded in Gado and Macky's study. The baseline data of BCVA and CRT were not obtained; however, patient demographic and baseline ocular characteristics were similar between the two arms.[22]

Briefly, follow-up duration varied from 1 to 12 months, and subject age and gender distributions did not significantly vary between anti-VEGF agent and DEX treatment groups. In addition, the methodological quality and a bias risk assessment were performed [Fig. 2]. The bias assessment revealed that the selection bias was the most prevalent bias among included studies.

Meta-analysis results

Best-corrected visual acuity

BCVA is one of the most important methods to evaluate treatment efficacy by functional measurement. Patients suffering from RVO-related ME usually have significant differences in BCVA compared with baseline level at different time points [Fig. 3]. The pooled results of Novartis' studies revealed that subjects suffering from RVO who had received anti-VEGF agent treatments had a greater BCVA improvement than those subjects who had received DEX implant treatments [Figs. 4 and 5]. In

Table 2: The summary of characteristics of included clinical trials

Trials (first author, year)	Country	Type of RVO	Treatment (patients)	Age (years)	Gender (M/F)	BCVA at baseline (letters, *n*)	CRT at baseline (μm)	Follow-up (Months)
Guignier, 2013[16]	France	BRVO	IVB (*n*=8) DEX (*n*=11)	61±12 67±7	3/5 7/4	42.5±19.3 57.4±11.2	608±216 547±120	1, 3, 4, 6
Gado, 2014[17]	Egypt	CRVO	IVB (*n*=30) DEX (*n*=30)	69.13±8.56 68.41±11.48	20/10 20/10	0.6 log MAR 0.6 log MAR	544.13±48.68 548.53±68.67	1, 3, 6
Novartis, 2014[20]	Czech Republic, Germany, Hungary, Poland, United Kingdom	BRVO	IVR (*n*=126) DEX (*n*=118)	65.7±10.9 65.6±10.0	50/76 61/57	NA NA	NA NA	1-6
Novartis, 2016[18]	Germany, Hungary, Poland, United Kingdom	CRVO	IVR (*n*=124) DEX (*n*=119)	65.3±11.4 66.9±12.4	72/52 73/46	51.7±16.5 51.5±15.6	723.8±245.9 705.2±231.1	1-6
Allergan, 2016[19]	France, Germany, Israel, Italy, Spain, United Kingdom	BRVO	IVR (*n*=153) DEX (*n*=154)	65.5±12.04 68.4±10.58	87/66 92/62	59.2±10.92 56.6±10.89	561.0±188.93 553.2±170.15	1, 12

BCVA: Best-corrected visual acuity; RVO: Retinal vein occlusion; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; M: Male; F: Female; NA: Not available; DEX: Dexamethasone; IVB: Intravitreal bevacizumab; IVR: Intravitreal ranibizumab. Data are presented as mean±standard deviation where applicable

Guignier *et al*.'s study,[16] significant improvements in mean VA were observed between anti-VEGF agent and DEX treatment groups at 1, 3, 4, and 6 months, and the results showed that there were no significant differences in mean VA between these two groups at 1, 3, and 4 months. The mean VA was much higher in DEX group than that in anti-VEGF agent group at 1 month. Gado and Macky's study[17] also indicated that there was significant improvement from baseline level at 6 months, and no significant difference in BCVA was observed between these two groups. The change in BCVA over time is summarized in Table 3.

Central retinal thickness

CRT could be considered as an anatomical outcome to evaluate ME after treatment. The comparison between two Novartis' studies indicated that compared with DEX implant, anti-VEGF agents significantly reduce the CRT at 6 months [WMD: 158.53 μm, 95% CI: (71.09, 245.96), P = 0.0004] with substantial heterogeneity (P = 0.03, I^2 = 78%) [Fig. 6]. The heterogeneity existed due to the different types of RVOs involved in these two studies. The change in CRT over time is summarized in Table 4.

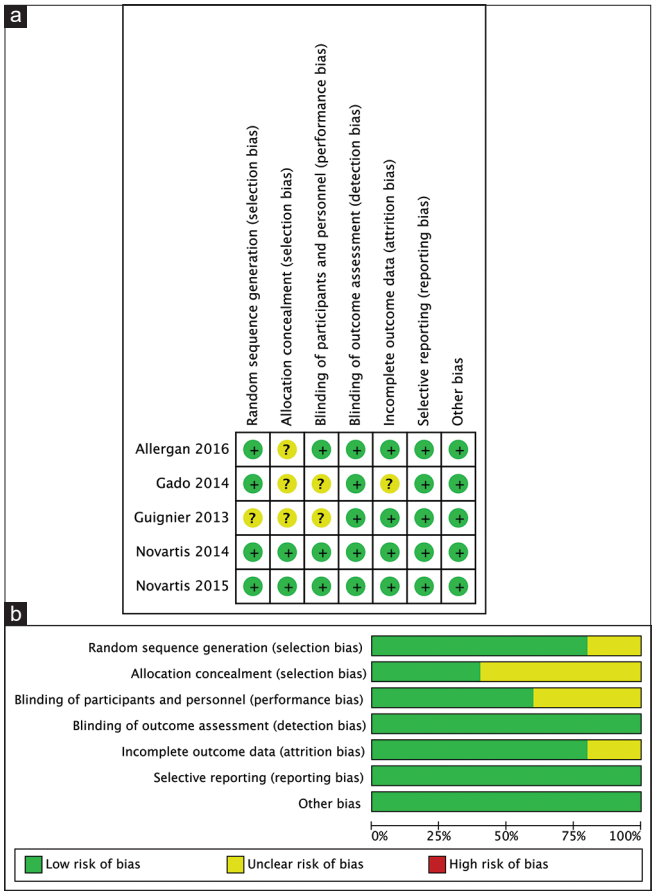

Figure 2: The assessment of bias risk of included studies. (a) Bias risk summary. Bias risk was classified as low (+), unclear (?), or high (–). (b) Bias risk graph. Reviewing authors' judgements about the bias risk of each item, and they were shown as percentages across all included studies

Adverse events

Drug delivery–related adverse effects were reported in the included studies. AEs were separated into SAEs and AE. Serious cardiac disorders, ear and labyrinth disorders, eye disorders, gastrointestinal disorders, vascular disorders, renal and urinary disorders, psychiatric disorders, and other general or organic disorders were included in SAE group. Mild eye disorders, infections and infestations, nervous system disorders, and vascular disorders were included in AE group. The comparison results between SAE and AE groups are summarized in Fig. 7. The number of participants with AE risk was much higher in DEX group than that in anti-VEGF group [RR: 1.19, 95% CI: (1.09, 1.31), P = 0.0002] without heterogeneity (P = 0.20, I^2 = 35%). However, this difference was not reported in SAE group [RR: 0.92, 95% CI: (0.55, 1.53), P = 0.75] without identified heterogeneity (P = 0.59, I^2 = 0) [Fig. 7].

Intraocular pressure

One of the most common AEs associated with intravitreal therapy for retinal diseases was elevated IOP.[23,24] Only one article included in this systematic review described IOP-related data,[17] indicating that IOP elevation was much higher in DEX group than that in anti-VEGF group from 3 to 6 months after initiating therapy. No significant differences were observed at 1 and 2 months [Fig. 8]. In addition, the only AE in Guignier *et al*.'s study was that there was an ocular hypertension case in DEX group.

Cataract

Cataract was one of most common adverse effects caused by all types of corticosteroid administrations and was more frequent in patients with long-term corticosteroids.[25] The comparison between DEX and anti-VEGF groups was performed, and the results are shown in Fig. 9 [RR: 3.43, 95% CI: (1.35, 8.71), P = 0.009] without heterogeneity (P = 0.20, I^2 = 38%). The results showed that cataract incidence was much higher in DEX group than that in anti-VEGF group.

Discussion

Previous studies indicated that eyes with different types of RVOs increased the vitreal level of VEGF,[26] and VEGF-A was proved to play an important role in the pathogenesis of ME.[27] Therefore, it is very crucial to maintain retinal perfusion for getting better visual outcomes.

Table 3: The change in best-corrected visual acuity over time

Study	Group	Baseline	1 month	2 months	3 months	4 months	5 months	6 months
Guignier	Anti-VEGF†	42.5	54.5	NA	61.2	65.3	NA	61.7
Guignier	DEX†	57.4	71.8	NA	69.2	58.3	NA	68.6
Gado	Anti-VEGF‡	0.24	0.36	0.54	0.61	0.56	0.62	0.64
Gado	DEX‡	0.21	0.38	0.48	0.57	0.51	0.59	0.65

VEGF: Vascular endothelial growth factor; DEX: Dexamethasone; BCVA: Best-corrected visual acuity. †BCVA in Early Treatment Diabetic Retinopathy Study letters. ‡BCVA in decimals

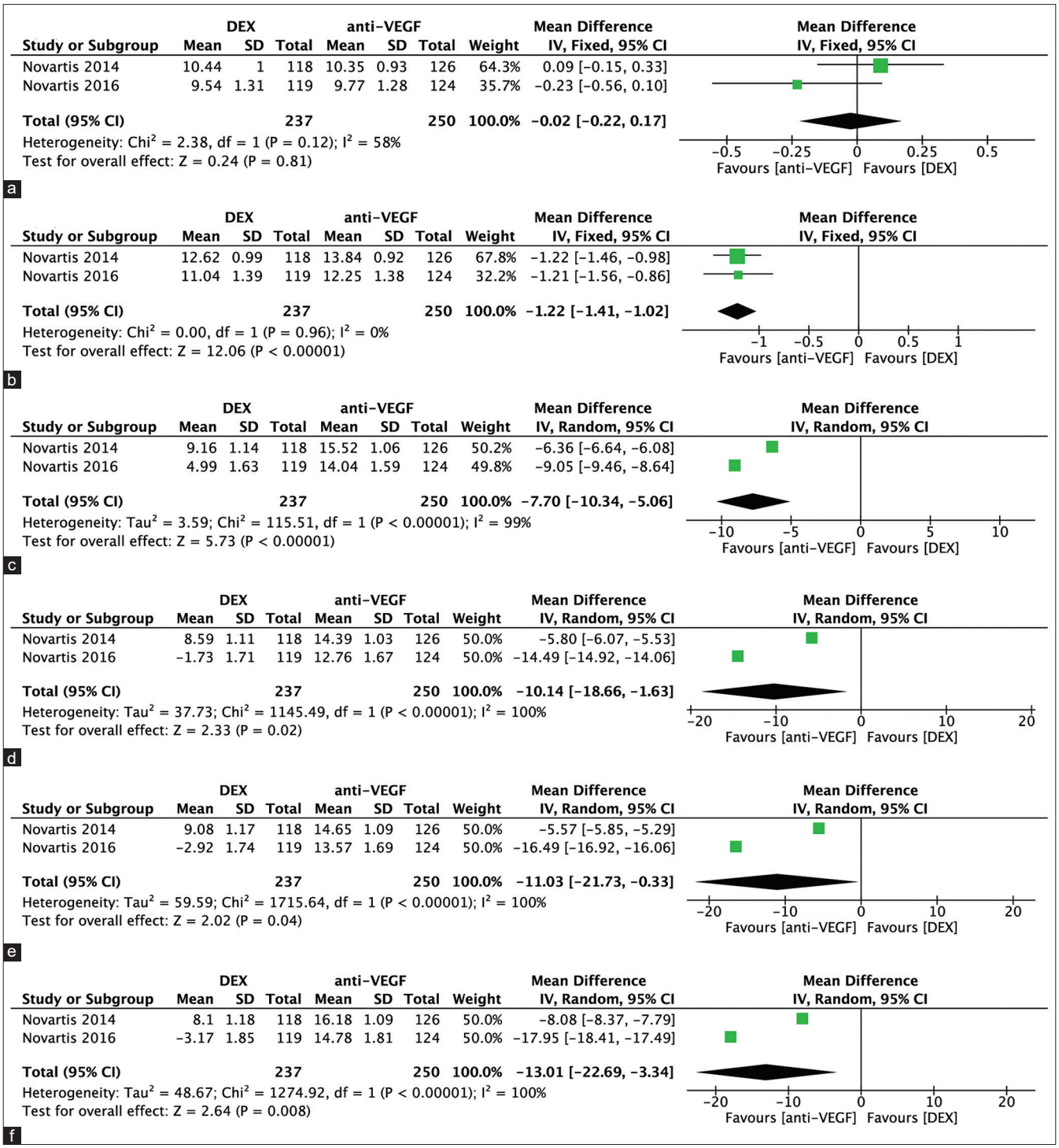

Figure 3: A forest plot diagram showing the mean change in BCVA from baseline level in the eyes suffering from RVO-related ME after treatments with anti-VEGF agents and DEX. Follow-up examinations occurred at 1 (a), 2 (b), 3 (c), 4 (d), 5 (e), and 6 months (f) after initiating therapy. Dots represent the estimated mean differences, and error bars indicate 95% CIs. Data are presented as mean [95% CI]. IV, inverse variance

Table 4: The change in central retinal thickness over time (μm)

Study	Group	Baseline	1 month	2 months	3 months	4 months	5 months	6 months
Guignier	Anti-VEGF	608	473	NA	438	422	NA	332
Guignier	DEX	547	321	NA	355	517	NA	309
Gado	Anti-VEGF	543.16	364.21	296.84	277.90	301.05	277.90	277.90
Gado	DEX	547.37	429.47	324.21	271.58	292.63	265.26	263.16

VEGF: Vascular endothelial growth factor; DEX: Dexamethasone

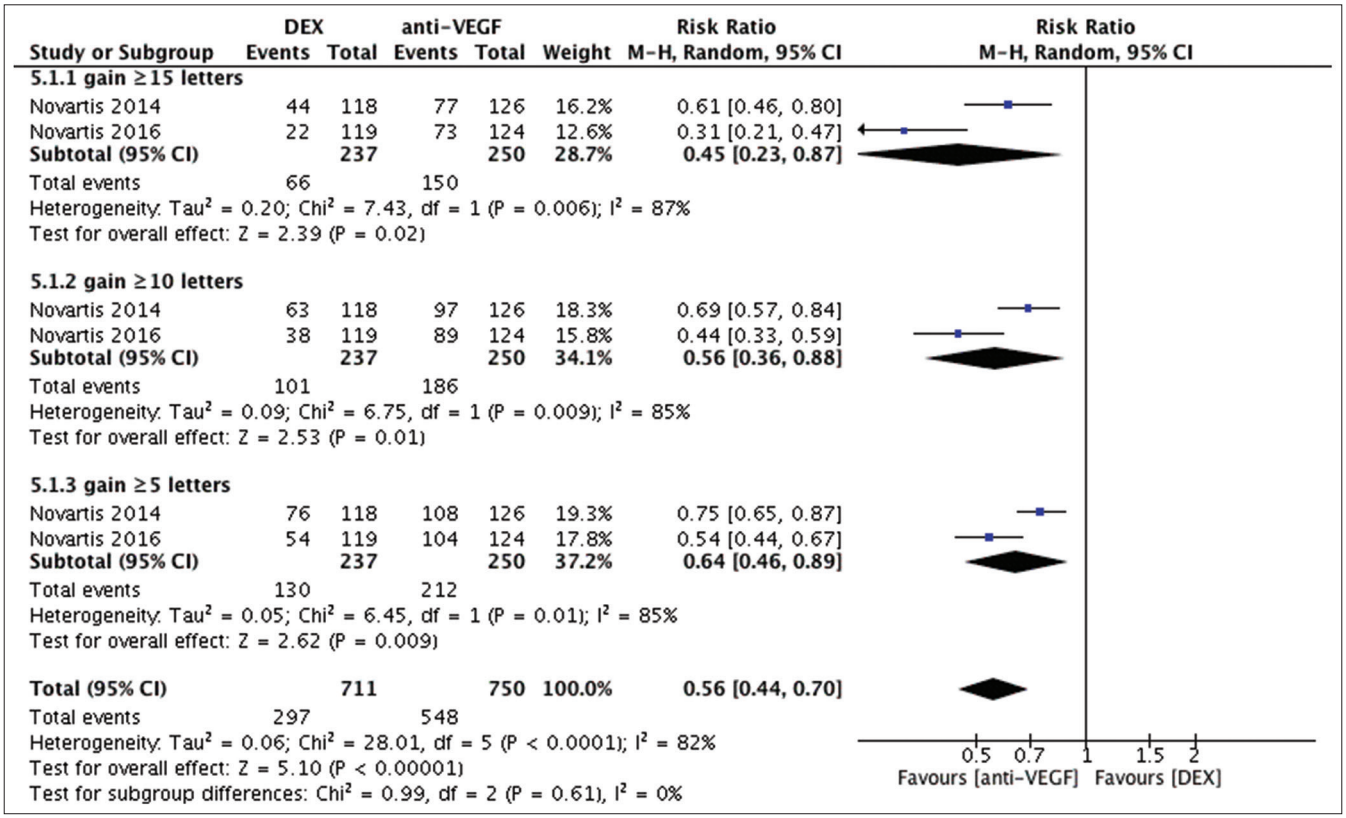

Figure 4: A forest plot diagram showing the number of patients gaining letters after 6 months of treatments. Data are presented as mean [95% CI]. IV, inverse variance

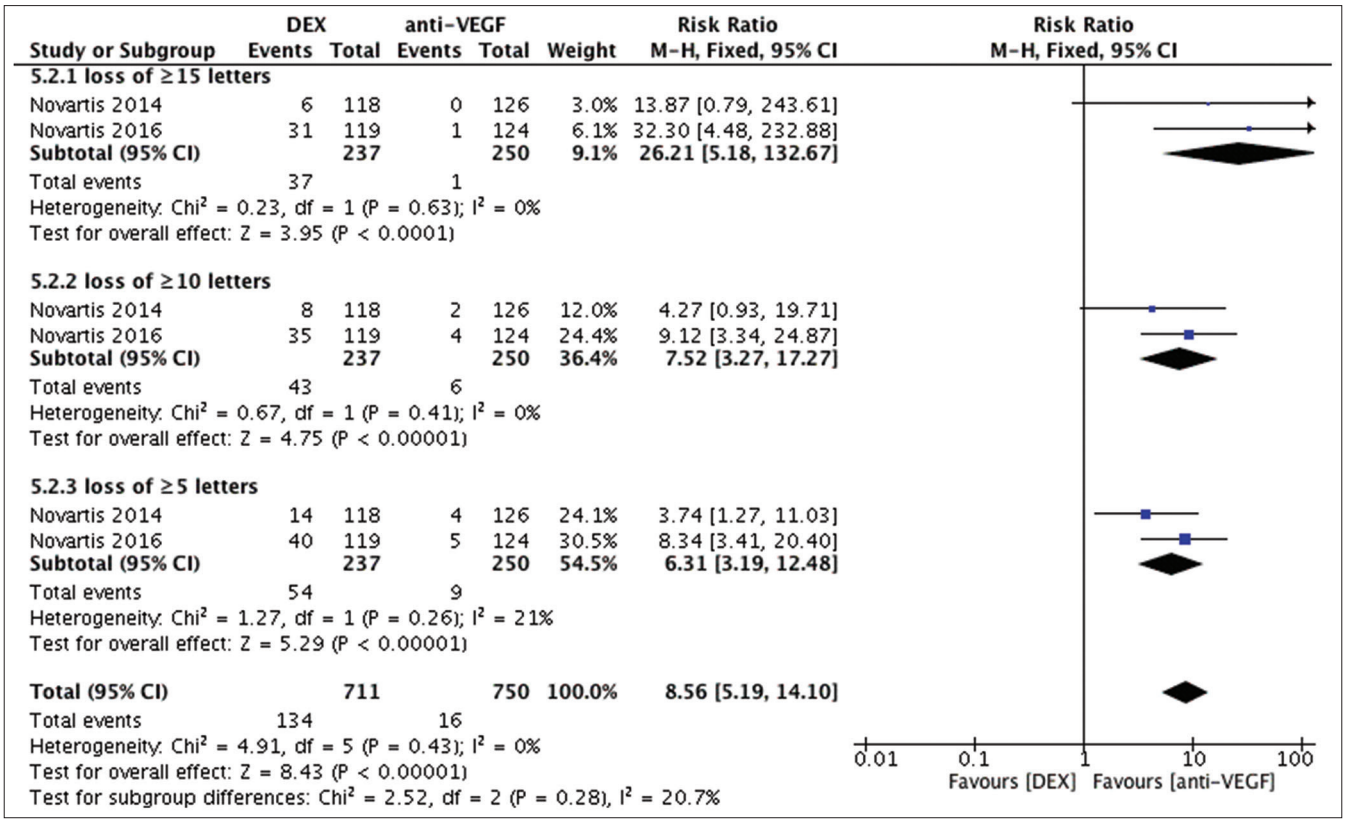

Figure 5: A forest plot diagram showing the number of patients losing letters after 6 months of treatments. Data are presented as mean [95% CI]. IV, inverse variance

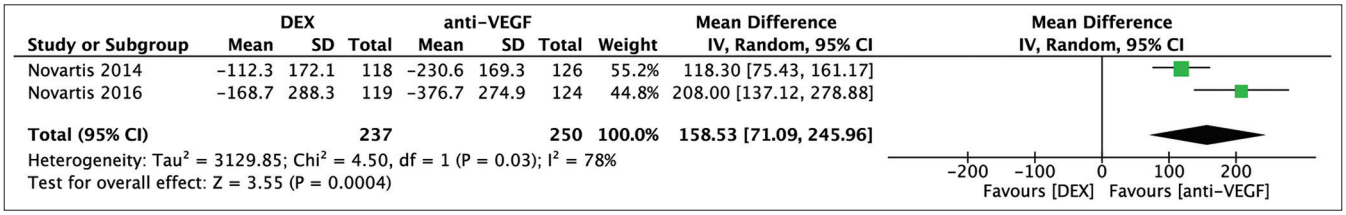

Figure 6: A forest plot diagram showing the mean change in CRT from baseline level in the eyes suffering from RVO-related ME after treatments with anti-VEGF agents and DEX. The follow-up examinations occurred at 6 months, the endpoint of clinical trial. Data are presented as mean [95% CI]. IV, inverse variance

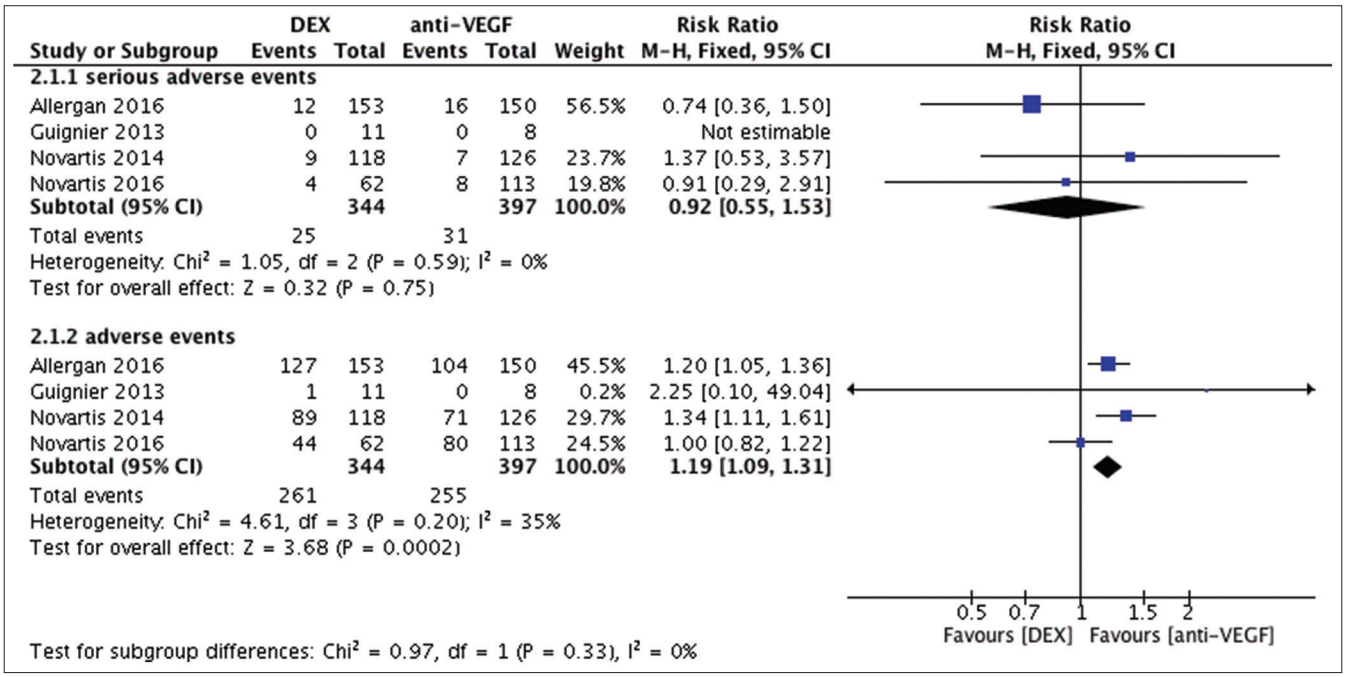

Figure 7: A forest plot diagram showed the serious adverse events and adverse events

A previous study showed that anti-VEGF agents could maintain retinal perfusion in most patients suffering from RVO.[28] The treatment with anti-VEGF agents for patients suffering from RVO-related ME improved BCVA, but reduced CRT and VEGF levels.[29] In addition, intravitreal DEX was another option for treating RVO, and it has been proved to be an effective therapy for RVO-related ME with a favorable long-term safety profile.[30] As a biodegradable, sustained-release drug delivery system, the intravitreal DEX implant could secrete low doses of DEXs into the vitreous cavity over a period of 6 months.[29] Therefore, comparison of safety and effectiveness between anti-VEGF agent and DEX implant groups is needed in patients suffering from RVO-related ME.

In this systematic review, five RCTs were included to evaluate the safety and effectiveness of DEX implant and anti-VEGF agents for treatments of RVO-related ME. However, optimization of study design is necessary. Ischemic and non-ischemic RVO showed differences, and they should be separated into different groups. The results showed that both these therapies could achieve significant functional and anatomical improvements during the therapeutic processes, and no significant differences were observed between these two groups. However, the Novartis' study reported in 2016 did not support our results demonstrating that a reduction in BCVA was observed during late treatment (≥4 months). It may be due to cataract formation resulting from DEX implant. Moreover, Gado and Macky's study indicated that IOP elevation was much higher in DEX group than that in anti-VEGF group during late treatment (≥3 months), which was also not consistent with our results. In Guignier *et al*.'s study, DEX implant more rapidly played a role than bevacizumab (a kind of anti-VEGF agent), but a rebound effect was observed after 4 months in DEX group.

Among the three anti-VEGF agents, although bevacizumab was a cheaper alternative agent used off-label, ranibizumab and aflibercept have been licensed for treating various retinal diseases with tremendous costs. The effectiveness and safety of these anti-VEGF therapies have been confirmed by previous RCTs.[31-33] A previous systematic review also reported that there were no significant differences in BCVA improvement and CRT reduction among intravitreal ranibizumab, aflibercept, and bevacizumab during short-term treatments for RVO-related ME.[34] However, the benefits from anti-VEGF agents for patients suffering from RVO-related ME were always companied with more frequent injections.

Recently, the DEX intravitreal implant (Ozurdex) became popular and was increasingly used to treat RVO-related ME,

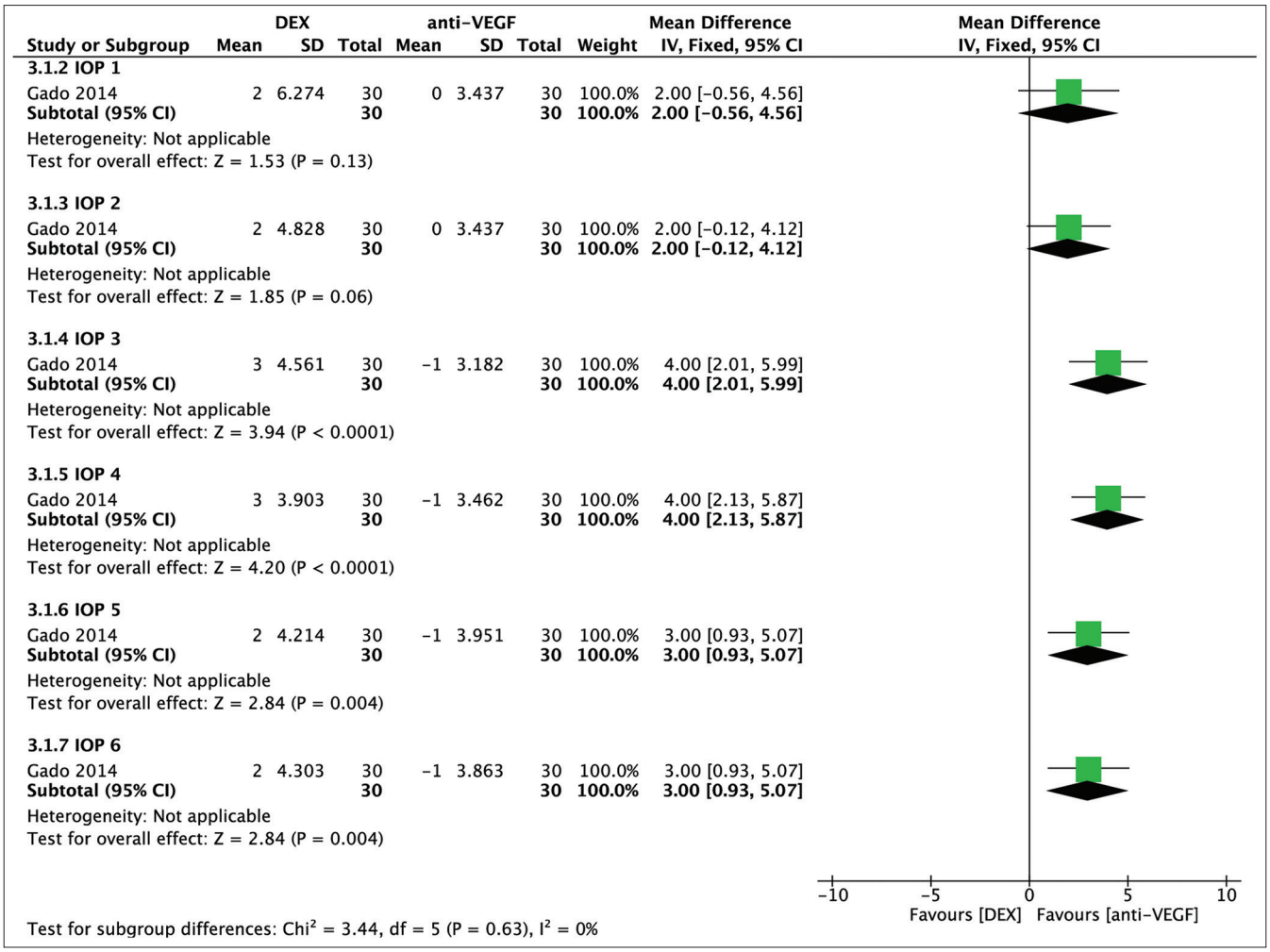

Figure 8: A forest plot diagram showed the mean change of IOP over time in eyes suffered with RVO-related ME after treatments with anti-VEGF agents and DEX. Follow-up examinations occurred at 1 (a), 2 (b), 3 (c), 4 (d), 5 (e) and 6 months (f) after initiating therapy. Data were presented as mean [95% CI]. IV, inverse variance

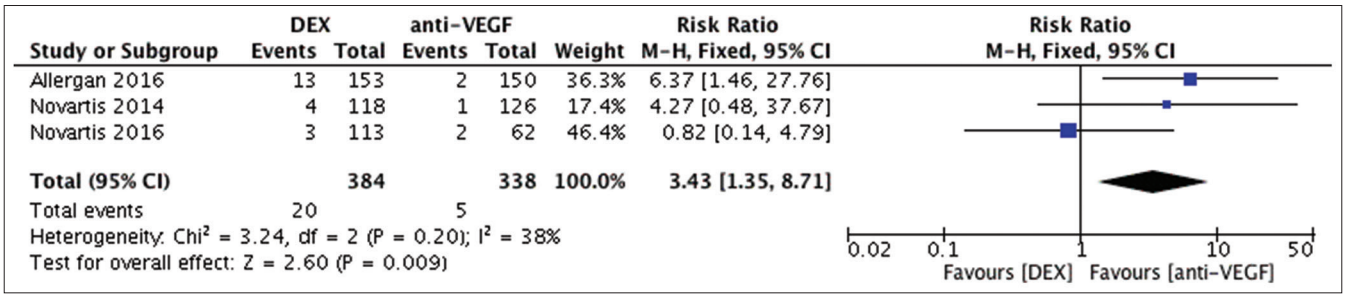

Figure 9: A forest plot diagram showed one of the adverse events, cataract, in the eyes suffered with RVO-related ME after treatments with anti-VEGF agents and DEX. The follow-up examinations occurred at 6 months, the endpoint of clinical trial. Data were presented as mean [95% CI]. IV, inverse variance

which is the only indication for DEX in China. However, some adverse effects, such as cataract, ocular hypertension, and other side effects, caused by DEX seemed to be unavoidable.[35] Our results also demonstrated that after DEX treatment, BCVA initially improved during the first 2 months but began to decrease at the third month. In general, DEX was a better choice for pseudophakic eyes and anti-VEGF-resistant eyes, and IOP level and cataract incidence should be monitored when patients were treated with DEX, particularly patients suffering from RVO.

Thus, a combined or alternative therapy may be another therapeutic option for RVO-related ME to reduce injection frequency of anti-VEGF agents and the risk of cataract or ocular hypertension caused by DEX. In addition, more short- or long-term RCTs including anti-VEGF agents and DEX implant are also expected to explore the difference between these two

therapies, thereby helping ophthalmologists to choose the best treatment strategy for ME secondary to RVO.

Limitations

This meta-analysis had several limitations. At first, only five RCTs were included in this study. Second, follow-up data collection was sporadic and inconsistent. Third, we did not differentiate between ischemic and non-ischemic or central and branch RVOs to extend the sample size, which might bring biases for meta-analysis. Finally, more long-term RCTs with comprehensive outcomes are needed to evaluate the safety and effectiveness for the treatment of RVO-related ME.

Conclusion

In conclusion, our meta-analysis from five RCTs indicated that anti-VEGF agents and DEX implant had similar therapeutic effects for treating RVO-related ME. In addition, anti-VEGF treatment showed an advantage that caused less AEs during therapeutic process. Therefore, through comprehensively considering the cost, anti-VEGF agents may be the first-line treatment for RVO-related ME and DEX implant can be another choice in some special cases, such as pseudophakic eyes, anti-VEGF-resistant eyes, and other conditions. Moreover, development of complementary and alternative therapies is expected to enhance the therapeutic effectiveness and to reduce adverse effects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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