• Meta-Analysis •

Clinical efficacy of intravitreal corticoid as an adjunctive therapy to anti-VEGF treatment of neovascular age-related macular degeneration: a Meta-analysis

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Abstract

● **AIM:** To evaluate the efficacy and safety of intravitreal corticoid as an adjunctive therapy to anti-vascular endothelial growth factor (VEGF) treatment of neovascular age-related macular degeneration (nvAMD).

● **METHODS:** Four databases including PubMed, Embase, Cochrane Library, and the clinicaltrials.gov were comprehensively searched for studies comparing intravitreal corticoid plus anti-VEGF (IVC/IVA) *vs* anti-VEGF monotherapy (IVA) in patients with nvAMD. GRADE profiler was used to assess the quality of outcomes. Best-corrected visual acuity (BCVA), central macular thickness (CMT) and adverse events including the occurrence of severe elevation of intraocular pressure (IOP) and the progress of cataract were extracted from the eligible studies. Review Manager (RevMan) 5.3 was used to analyze the data.

● **RESULTS:** There was no statistic difference of mean change in BCVA at 6 and 12mo between IVC/IVA and IVA group [95% confidence interval (CI): -2.28 to 4.24, *P*=0.55; 95%CI: -3.01 to 8.70, *P*=0.34]. No statistic difference was found in the change of CMT between two groups at 6mo time point (95%CI: -17.98 to 16.42, *P*=0.93) while the CMT reduction in IVC/IVA group was significantly more obvious than IVA group at 12mo time point [mean difference (MD)=-44.08, 95%CI: -80.52 to -7.63, *P*=0.02]. The risk of occurrence of severe elevation of IOP in the IVC/IVA group was higher than that in the IVA group (95%CI: 1.92 to 9.48; *P*=0.0004). Cataract progression risk was calculated no statistic difference between two groups (95%CI: 0.74 to 4.66; *P*=0.18).

● **CONCLUSION:** No visual or anatomical benefits are observed in IVC/IVA group at 6mo. At 12mo, the CMT of the IVC/IVA group is significantly lower than that of the IVA group. Risk of severe elevation of IOP is significantly higher when treated by IVC/IVA.

● **KEYWORDS:** age-related macular degeneration; dexamethasone; triamcinolone; anti-vascular endothelial growth factor; Meta-analysis

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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of severe and irreversible vision loss worldwide, especially in developed countries[1-2]. In recent years, intravitreal injection of anti-vascular endothelial growth factor (VEGF) has become the first-line treatment of neovascular AMD (nvAMD). However, there are still a large number of patients with poor efficacy or resistance and reduced efficacy during anti-VEGF monotherapy, and corticosteroids has been recommended desensitize tachykinin[3-5]. Meanwhile, continuous retreatment adds a heavy financial burden to patients[6]. Studies have also shown that the progression of retinal pigment epithelium and choroidal atrophy is related to the total number of anti-VEGF injections[7]. Therefore, it is particularly important to find an alternative treatment plan.

In animal models, intravitreal injection of corticosteroids can simultaneously reduce VEGF production and choroidal neovascularization, inhibit inflammation, and reduce photoreceptor cell apoptosis which provide a theoretical basis for the synergy with anti-VEGF treatment[8-11]. On the other hand, intravitreal injections of triamcinolone acetonide (TA)

and dexamethasone (DEX) combined with photodynamic therapy in the treatment of nvAMD have been proven to be safe and effective previously[12-13]. Hence, additional corticosteroids seem to have the ability to target chronic inflammation when combined with anti-VEGF with safety. Although DEX implant and direct intraocular corticosteroid injection have similar side effects—increasing risk of glaucoma and cataract progression, *etc.*, these can be effectively controlled by anti-glaucoma drugs or surgery[14-15].

Up to now, there are studies (including series of single-arm researches) showing that the addition of glucocorticoids on the basis of anti-VEGF can promote disease remission, however, the issue still remains under debate. This Meta-analysis aimed to evaluate the efficacy and safety of the intraocular corticoid as adjunctive therapy to anti-VEGF in nvAMD comprehensively.

MATERIALS AND METHODS

Literature Search A comprehensive literature search was conducted using 4 databases: including PubMed, Embase, Cochrane Library, and the clinicaltrials.gov, up to August 2020. The following MeSH terms were used: 1) "Macular Degeneration", 2) "Bevacizumab" or "Ranibizumab"or "Aflibercept" or "Conbercept", 3) "Triamcinolone" or DEX. There were no language or publication date restrictions and the reference list of retrieved articles was checked to identify potentially relevant studies. The flow diagram is shown in Figure 1. This systematic review and Meta-analysis was designed, performed, and reported based on the quality standards of the reported Meta-analysis. The study was conducted in accordance with the Cochrane Handbook for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16].

Selection Criteria The study was considered qualified if met the following criteria: 1) The study population includes nvAMD patients; 2) The intervention group includes intraocular corticoid treatment (DEX implant or injection of TA or DEX) combined with anti-VEGF treatment; 3) There is a comparison between the combined treatment group with anti-VEGF monotherapy group; 4) The research design should be a randomized controlled trial (RCT).

Through the preview of the study, we determined two main outcomes: 1) The improvement of best-corrected visual acuity (BCVA) from baseline (time point: 6 and 12mo). 2) The average change of the central macular thickness (CMT) on the optical coherence tomography (OCT) from the baseline (time point: 6 and 12mo) and two additional outcomes: 1) Severe increase in intraocular pressure (IOP) that need to be controlled by anti-glaucoma drugs; 2) Cataract progression related events.

Quality Assessment Based on the GRADE system, the evidence quality of all included studies was evaluated by two independent researchers (Yang H and Cui BH)[17]. Factors

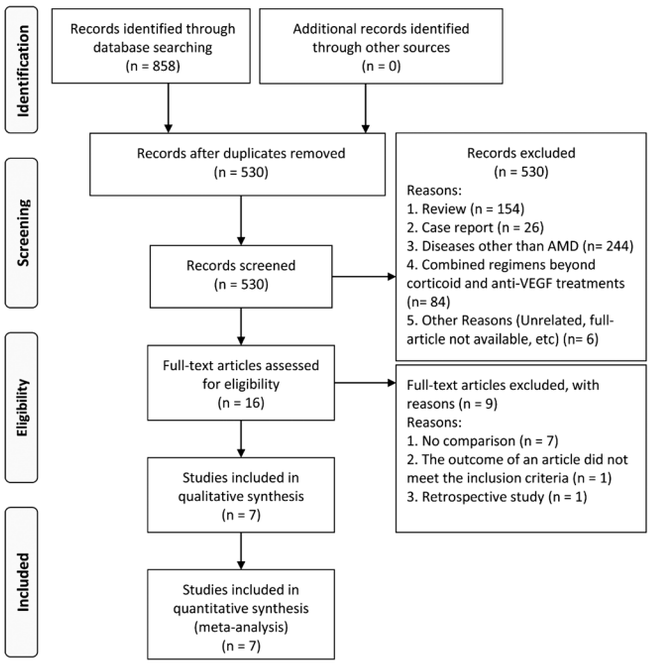

Figure 1 Flow chart of the literature search.

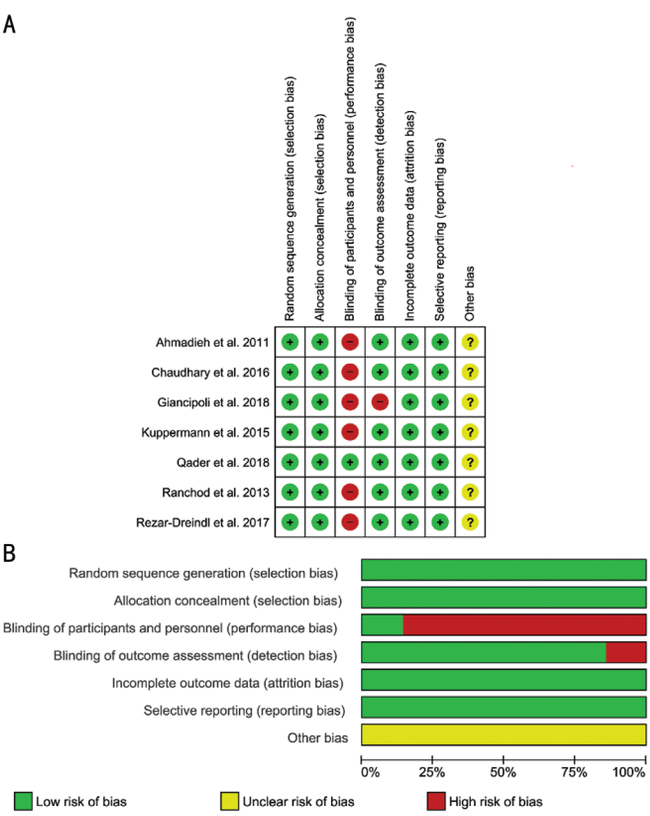

Figure 2 Evaluation of the risk of bias in included studies A: Risk of bias summary; B: Risk of bias graph.

resulting in rating down the quality of evidence such as risk of bias, incomplete results were fully estimated. Four grades (high, moderate, low and very low-quality evidence) were finally used to classify these studies (Figure 2).

Data Extraction Data were extracted independently by two reviewers (Dong YL and Wang WW) using a standard data extraction form, including: first author's surname, year of

publication, study design, country of study, sample size, the average age of patients, sex ratio, follow-up time, geographical location of the research and outcome. The data conflicts were resolved by discussing the process of data extraction. Get Data software was used to estimate the mean and the standard deviation (SD) from the reported graphs.

Statistical Methods RevMan 5.3 software was used to statistically analyze the effects of the included outcomes. If there is no statistical heterogeneity among the studies (P>0.1, I^2≤50%), the fixed effects model is used for the combined analysis, otherwise, the random effects model is used for the combined analysis. Mean difference (MD) was used to express the outcome index for continuous variables and odds ratio (OR) for categorical variables. P values <0.05 were considered statistically significant.

RESULTS

Search Results Totally 858 potentially relevant studies have been found up to August 2020 (PubMed=525, Embase=166, Cochrane Library=69, and the clinicaltrials.gov=98). After removing duplicate researches (n=328) and articles that do not meet the requirements (n=514), 16 studies remained. Finally, all the RCTs (n=7) that meet the inclusion criteria were included in the Meta-analysis[18-24]. The characteristics of these studies are summarized in Table 1.

Mean Change in BCVA at 6 and 12mo Six studies evaluated the BCVA changes in 559 eyes at 6mo from baseline, and low heterogeneity were found among the studies (P=0.14, I^2=39%). Both groups demonstrated improvement on BCVA, however, there was no statistic difference between the two groups [MD=0.98, 95% confidence interval (CI): -2.28 to 4.24, P=0.55]. At 12mo from baseline, 3 studies including 213 eyes were used for combined analysis and high heterogeneity were found (P=0.07, I^2=63%). The BCVA changes in IVC/IVA group still showed no difference when compared to IVA group (MD=2.85, 95%CI: -3.01 to 8.70, P=0.34; Figure 3).

Mean Change of Central Macular Thickness at 6 and 12mo A total of 434 eyes in 5 studies were assessed CMT at 6mo after the initial treatment and low heterogeneity were found among the studies (P=0.29, I^2=20%). Similar to BCVA results in 6 months, no statistically significant difference were found in CMT at this time point (MD=-0.78, 95%CI: -17.98 to 16.42, P=0.93). At 12mo from baseline, 2 studies, including 173 eyes were used for combined analysis and no heterogeneity were found (P=0.84, I^2=0). Statistically significant differences were discovered between the IVC/IVA and IVA treatment groups, in favor of the IVC/IVA group (MD=-44.08, 95%CI: -80.52 to -7.63, P=0.02; Figure 4).

Occurrence of Severe Elevation of Intraocular Pressure Except for the lack of data at the 6-month time point in the study by Ranchod *et al*[19], a Meta-analysis of the other 6

Table1 Summary of the characteristics of the included studies

Study	Place	Conditions	Participant number	Interventions details	Age	Patients in each group	BCVA at baseline	CMT at baseline (μm)
Ahmadieh *et al* 2011[18]	Iran	nvAMD	115	IVC+IVA: 3 injections of 1.25 mg bevacizumab every 6wk +2 mg/0.05 mL of TA added in the first injection. IVA: 3 injections of 1.25 mg bevacizumab every 6wk.	IVC+IVA: 71.2±7.5 IVA: 71.4±7.6	IVC+IVA: 55 IVA: 60	IVC+IVA: 33±18 IVA: 37±21	IVC+IVA: 351.5±151.4 IVA: 341.9±140.8
Ranchod *et al* 2013[19]	USA	nvAMD	37	IVC+IVA: 0.5 mg DEX/0.05 mL+ranibizumab 0.5 mg/0.05 mL monthly in the first 4mo followed by injection as needed. IVA: ranibizumab 0.5 mg/0.05 mL monthly in the first 4mo followed by injection as needed.	IVC+IVA: 79.5 IVA: 82.7	IVC+IVA: 17 IVA: 20	IVC+IVA: 61.9±11.3 IVA: 55.6±11.3	IVC+IVA: 342.2±108.8 IVA: 291.9±108.8
Kuppermann *et al* 2015[20]	USA	nvAMD	243	IVC+IVA: DEX implant+0.5 mg ranibizumab within 1wk from baseline, up to 5 additional ranibizumab were administered as needed at weeks 5, 9, 13, 17, and 21. IVA: sham procedure+0.5 mg ranibizumab within 1wk from baseline, up to 5 additional ranibizumab were administered as needed at weeks 5, 9, 13, 17, and 21.	IVC+IVA: 76±8.8 IVA: 76.2±8.5	IVC+IVA: 123 IVA: 120	IVC+IVA: 55.5±15.3 IVA: 58.1±12.6	IVC+IVA: 218±77.2 IVA: 224±77.3
Chaudhary *et al* 2016[21]	Canada	nvAMD	10	IVC+IVA: 3-month loading period followed by DEX+0.5 mg/0.05 mL ranibizumab for 6mo *pro re nata*. IVA: after 3-month loading period 0.5 mg/0.05 mL ranibizumab for 6mo *pro re nata*.	IVC+IVA: 86.2±7.1 IVA: 75.6±6.1	IVC+IVA: 5 IVA: 5	IVC+IVA: 48±7.3 IVA: 47.8±5.7	IVC+IVA: 269.4±85.7 IVA: 348.4±89.4
Rezar-Dreindl *et al* 2017[22]	Austria	nvAMD	40	IVC+IVA: DEX implant+0.5 mg/0.05 mL ranibizumab injection as needed. IVA: 0.5 mg/0.05 mL ranibizumab injection as needed.	IVC+IVA: 75±7.5 IVA: 77±7.1	IVC+IVA: 20 IVA: 20	IVC+IVA: 68±12 IVA: 62±15	NA
Giancipoli *et al* 2018[23]	Italy	nvAMD	16	IVC+IVA: DEX implant +ranibizumab 0.5 mg or aflibercept 2 mg as needed. IVA: ranibizumab 0.5 mg or aflibercept 2 mg as needed.	IVC+IVA: 73.2±8.7 IVA: 79.2±8.4	IVC+IVA: 11 IVA: 5	IVC+IVA: 44±48.9 IVA: 65±14.1	IVC+IVA: 387.6±138.7 IVA: 488.2±161.9
Motarjemizadeh *et al* 2018[24]	Iran	nvAMD	142	IVC+IVA: 1.25 mg/0.05 mL bevacizumab administered as needed+4 mg/0.05 mL of TA added in the first injection. IVA: 1.25 mg/0.05 mL bevacizumab administered as needed.	IVC+IVA: 69.8±9.0 IVA: 72.2±9.1	IVC+IVA:71 IVA:71	IVC+IVA: 34.2±14.2 IVA: 35.1±13.1	IVC+IVA: 351.5±151.4 IVA: 341.9±140.8

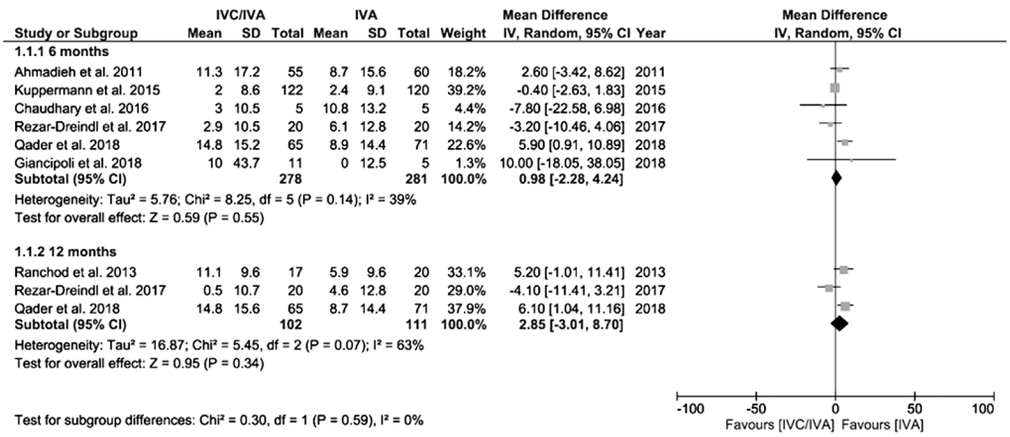

Figure 3 A forest plot diagram showing the mean BCVA and the associated 95%CI, comparing IVC/IVA with IVA treatment at 6 and 12mo.

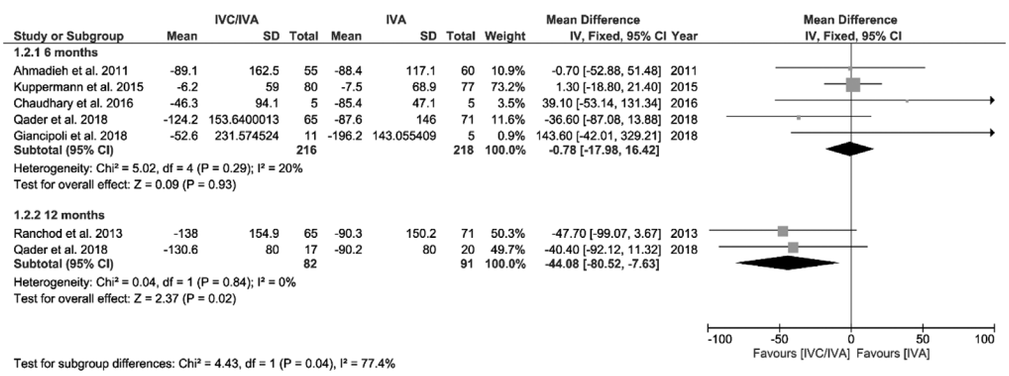

Figure 4 A forest plot diagram showing the mean change in CMT and the associated 95%CI, comparing IVC/IVA with IVA treatment at 6 and 12mo.

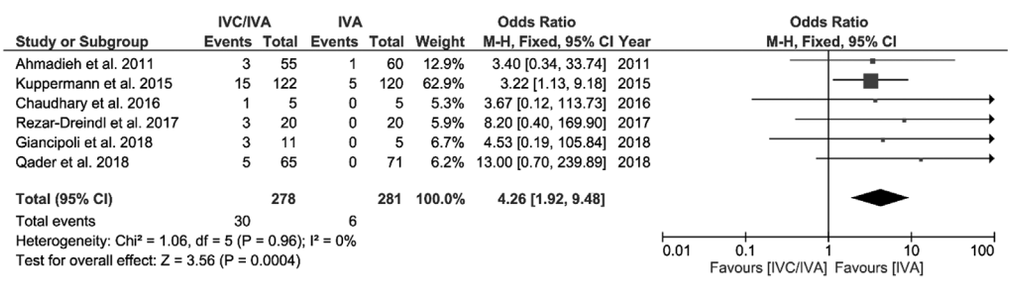

Figure 5 A forest plot diagram showing the severe elevation of IOP.

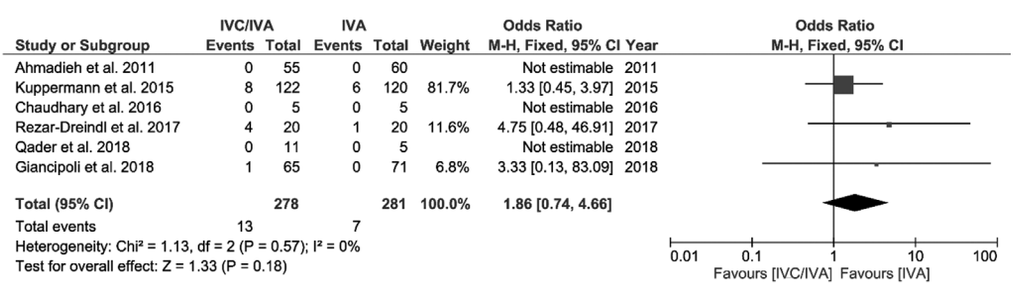

Figure 6 A forest plot diagram showing the progression of cataract.

studies including 559 eyes showed that the risk of pathological increase of IOP in the IVC/IVA group was significantly higher than that in the IVA group (OR=4.26; 95%CI: 1.92 to 9.48; *P*=0.0004; Figure 5). No heterogeneity was found among the studies (*P*=0.96, I^2=0).

Cataract Progression Events Totally 6 studies including 559 eyes assessed the risk of cataract progression within 6mo between IVC/IVA and IVA group and no heterogeneity were found among the studies (*P*=0.57, I^2=0). After combination, the risk of cataract progression was calculated and no statistic difference was found (OR =1.86; 95%CI: 0.74 to 4.66; *P*=0.18; Figure 6).

DISCUSSION

The expectation on combined therapy is mainly based on the anti-inflammation effect of the corticoid, and can suppress pathways participating in AMD other than VEGF. Some researches have shown that corticosteroids combined with anti-VEGF can effectively treat macular edema (ME) caused by retinal vein occlusion by increasing visual acuity and prolonging the time between injections and reduce retinal thickness of diabetic ME[25-26]. However, there is still much controversy about the effect of this combination therapy compared with anti-VEGF monotherapy in nvAMD. Accumulating evidence indicates that the overactivation of immune processes is important in AMD pathogenesis, among which the complement pathway is the most well-established and accepted as contributing to AMD[27]. Other dysregulated immune mechnisms including inflammasome activation and the recruitment immune cell were also observed in the pathogenesis of AMD. Thus, corticosteroids seem to be a promising alternative for nvAMD based on the assumption that the anti-inflammation function may have beneficial effects in the disease[28].

In this study, we evaluated 7 RCTs to evaluate the efficacies of IVC/IVA and IVA therapy in the treatment of nvAMD. The BCVA and CMT changes at 6 and 12mo and the occurrence of cataract and severe elevation of IOP were assessed. This Meta-analysis shows that compared with anti-VEGF monotherapy, the addition of cortcoids has little significance in improving BCVA. On the other hand, although the IVC/IVA group and IVA group show no statistical difference in the change of CMT thickness within 6mo from baseline, the IVC/IVA therapy can reduce CMT more significantly at 12mo. The average numbers of anti-VEGF injections were not combined for analysis due to the lack of standardized data in included studies, however, the similar results of reduction in the central retinal thickness and the decreasing number of the average anti-VEGF injection in patients were observed in many studies[18,20-21,24]. Since the anatomical changes on the OCT are often essential evidence for ophthalmologists to determine whether to continue the anti-VEGF therapy, these results are consistent with our findings related to central foveal thickness changes demonstrated above. Our systematic review suggests that the improvement of anatomical outcomes did not convert to the restorement on visual acuity and this situation is also common in glucocorticoid or anti-VEGF therapy for other fundus diseases[29-31]. Similarly, a Meta-analysis published by He *et al*[29] found DEX implant improved anatomical outcomes significantly but not translate to improved visual acuity in the diabetic ME compared with anti-VEGF. The modest effect of additive anti-inflammatory therapy found in this study was possibly due to the progression of cataract or the lack of understanding of the complex cell type-, pathological context-, temporal- and pathway-specific aspects of immune mechanisms in nvAMD progress.

Although the IVC/IVA therapy seems to show very limited benefits to nvAMD and bring about increase the IOP, its benefits in reducing the CMT and number of the average anti-VEGF injection should not be neglected as well. With the progress in administration mode of corticoid, the invention of DEX implant solved the problem of maintaining significant drug levels into the vitreous cavity to some extent. Moreover, DEX implant performed better in the safety and less frequent injections compared to TA. DEX released from the implant is less lipophilic and does not accumulate to the same extent in the trabecular meshwork, with a lower risk of IOP increase and the IOP increase after DEX implant is typically noticed within the first 2wk, peaks at day 60 and starts decreasing gradually baseline values within 180d[32-33]. Thus, DEX implant is a valuable device to reduce required anti-VEGF retreatments considering its long-lasting effect and relatively few adverse events.

It is true that the anti-VEGF as the first-line therapy to nvAMD has good treatment effects and fewer adverse effects compared to intraocular corticosteroid, however, repeated injections still carry increased risk of intraocular inflammation, and even stroke or myocardial infarction[34]. Therefore, the IVC/IVA therapy still has its value for patients without a high IOP risk at baseline or patients reluctant to receive intravitreal injections frequently while IVC monotherapy may be recommended as a first choice for patients who have a history of cardiovascular and cerebrovascular diseases. However, the IVC/IVA seems to have a limited value to anti-VEGF-resistant eyes according to our results. Although Rezar-Dreindl *et al*[22] have proposed that co-administration of IVC/IVA at early stage may have potential benefits for nvAMD patients, our subgroup analysis showed that at the 6-month, patients with or without prior treatment who received IVC/IVA treatment both demonstrated no statistical significance compared with IVA group (Figures 7 and 8). Future studies focusing on the cost-effectiveness of the two therapies seem significantly valuable.

In recent years, aflibercept and conbercept have shown promising effects on nvAMD, but so far there are few comparisons when combining with intraocular corticosteroids[35-37]. In addition, looking for reliable marker to predict the prognosis or even screen out the patients suitable for various treatment plans is necessary as well.

To conclude, our research shows that corticoid combined with anti-VEGF therapy is difficult to improve patients' BCVA and CMT in the short-term, but it has the potential value of reducing the thickness of patients' CMT and reducing the number of anti-VEGF injections in the long-term. Meanwhile,

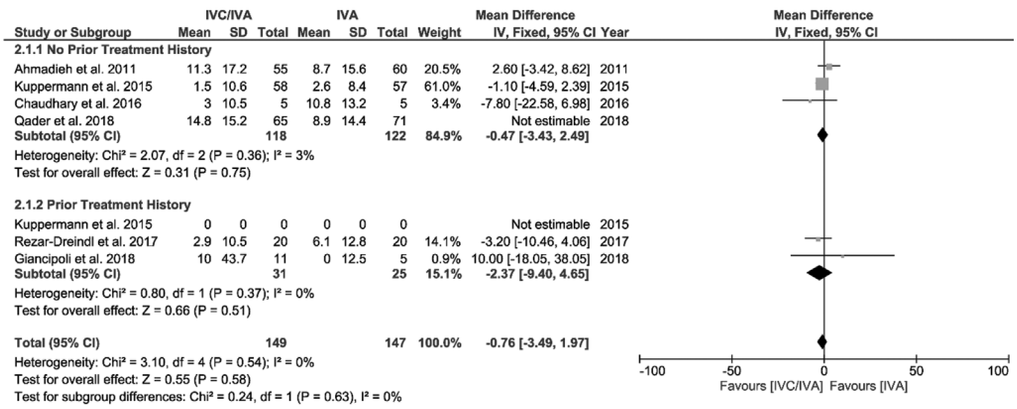

Figure 7 A forest plot assessing the BCVA changes at 6mo in patients with/without prior treatment.

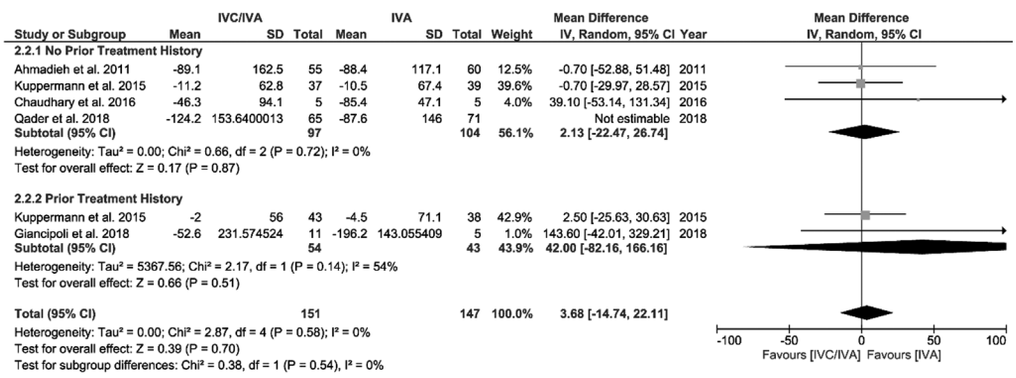

Figure 8 A forest plot assessing the CMT changes at 6mo in patients with/without prior treatment.

monitoring and controlling IOP during the combined treatment is significant as well.

This Meta-analysis aimed to evaluate the efficacy and safety of intraocular corticoid as adjunctive therapy to anti-VEGF in nvAMD. Heterogeneity was inevitable due to different types of intraocular corticoids and anti-VEGF regimens. However, there has been several reports illustrated that intravitreal triamcinolone and DEX implant had similar curative effect, although DEX implant is more tolerated and safer than TA[38-39]. In addition, bevacizumab and ranibizumab also showed equivalent effects on visual acuity when administered according to the same schedule in nvAMD[40-41]. In order to find an optimal solution, it is necessary to further clarify the interaction mechanism between glucocorticoids and different kinds of anti-VEGF drugs.

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Authors' contributions: Cui BH and Yan H participated in designing the study. Cui BH, Zhou W, and Wang WW participated in literature search. Yang H, Dong YL, and Liu YY participated in assessing the quality of the included studies and analyzing the data. Cui BH, Zhou W, and Wang WW participated in preparing figures and tables and authoring drafts of the paper. Yan H supervised the study, reviewed drafts of the paper and approved the final draft.

Conflicts of Interest: Cui BH, None; **Zhou W,** None; **Wang WW,** None; **Yang H,** None; **Dong YL,** None; **Liu YY,** None; **Yan H,** None.

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