Research Square

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Ozurdex Treatment for Retinal Conditions: A Systematic Review and Meta-analysis

Hui-xin Tang
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine
Yu-qin Yang
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine
Ying Yuan
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine
Jing-jing Li
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine
Zubing Mei
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine
Hong Zou (zouhong2007@shutcm.edu.cn)
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine

Research Article

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Abstract

Objectives To evaluate the clinical efficacy of Ozurdex, a dexamethasone (DEX) implant, for the treatment of macular edema (ME) caused by retinal vein occlusion (RVO) and diabetic retinopathy (DR) through a systematic review and meta-analysis.

Methods The PubMed, Embase and Cochrane Library databases were comprehensively searched from inception to July 11, 2021 for studies evaluating the clinical efficacy of Ozurdex for patients with retinal vein occlusion macular edema (RVO-ME) or diabetic macular edema (DME). Eligible studies were published in English and were randomized controlled trials (RCTs). The Cochrane Collaboration's tool was applied to assess the risk of bias in each study. Effect estimates with 95% confidence intervals (CIs) were pooled using the random effects model. We also conducted subgroup analyses to explore sources of heterogeneity and the stability of the results.

Results This meta-analysis included 7 RCTs (RVO-ME [n=2] and DME [n=5]) assessing a total of 251 eyes. Compared with anti-VEGF therapy, Ozurdex treatment achieved superior outcomes in terms of best corrected visual acuity (BCVA) (mean difference [MD] =-2.83 ([95% CI, -5.60 to -0.05], P=0.05), while no heterogeneity was found (P=0.49, I2=0%). Ozurdex treatment also significantly reduced central macular thickness (CMT) compared with anti-VEGF treatment (MD =-31.32 [95% CI, -57.92 to -4.72], P=0.02) and showed high between-trial heterogeneity (P=0.04, I2=54%). In terms of severe adverse events, Ozurdex treatment had a higher risk of elevated intraocular pressure than anti-VEGF therapy (RR=5.14; 95% CI: 1.42 to 18.66; P□0.05), and there was no significant difference in cataract progression between the two groups (RR=1.83; 95% CI: 0.63 to 5.27, P=0.31).

Conclusions Compared with anti-VEGF therapy, Ozurdex treatment is more effective in improving BCVA and reducing ME. Additionally, Ozurdex treatment has a higher risk of elevated intraocular pressure. Due to the small number of studies and the short follow-up period, the results should be interpreted with caution. The long-term effects of the two treatments need to be further determined.

Introduction

Macular edema (ME) is an important cause of serious visual impairment. Due to changes in living habits, the number of diabetic macular edema (DME) caused by diabetic retinopathy (DR) increases annually. The global prevalence of diabetes, estimated at 463 million in 2019, is expected to increase to 578 million by 2030 and to 700 million by 2045[1]. DR is the most common complication of diabetes, with an up to 27% incidence rate, and is the leading cause of preventable blindness in the working-age population; DME has an incidence rate of 4.6%[2-3]. On the one hand, with an incidence rate of 0.5%, RVO is the second most common cause of blindness in retinopathy, coming second only to DR. At present, there are approximately 16 million RVO patients worldwide[4]. On the other hand, ME is the most common complication of RVO[5-6]. Long-term ME can lead to permanent damage to the retinal structure, resulting in persistent vision loss[7]. Therefore, reducing macular edema is the key to saving the patient's vision. Current studies on macular edema indicate that overexpression of vascular endothelial growth factor (VEGF) and inflammatory mechanisms play an important role in the formation of ME[7]. Both anti-VEGF drugs and dexamethasone implants are currently effective in reducing ME and improving BCVA[8-9]. The importance of anti-inflammatory treatment for RVO-ME has also been emphasized in the 2019 Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA) [10].

Laser and anti-VEGF drugs and steroid drugs are widely used in the treatment of RVO-ME and DME. Laser photocoagulation of microaneurysms and diffuse leakage regions via local and grid lasers can reduce exudation and thus reduce the development of macula, but its treatment will inevitably cause permanent damage to the retinal structure, visual field defects, subretinal fibrosis and choroidal neovascularization and other side effects[11]. At present, except for subconjunctival hemorrhage caused by vitreous injection, other side effects caused by anti-VEGF drugs have not been found. In addition, the clinical effect of anti-VEGF drugs is remarkable, so it is the first choice currently in the treatment of DME and RVO-ME[12-18].

Current research suggests that macular edema is driven by a number of factors. The mechanism of RVO-ME is as follows: damage to RPE cell structure and function induced by retinal ischemia and hypoxia and damage to its junction complex[19-20]. Retinal ischemia induces the expression of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MCP-1α) to recruit and activate circulating macrophages[21], which in turn activate microglial macrophages to release tumor necrosis factor (TNF-α). TNF-α stimulates the production of IL-8, VEGF, basic fibroblast factor (BFGF), MCP-1 and other cytokines[22] by retinal endothelial cells and glial cells, promotes the adhesion of glial cells to microvessels, and induces retinal neovascularization. The overexpression of VEGF and occludin increased the permeability of the vascular endothelium, destroyed the inner barrier[23-25], decreased the expression of occludin tight junction protein [26] and induced the expression of a series of inflammatory factors[25] to destroy the blood retinal barrier. The main mechanism of DME is the change in blood-retinal barrier (BRB) permeability induced by hyperglycemia[23], such as the increase in endothelial and pericyte apoptosis[27]. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), immunoglobulin superfamily molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), arachidonic acid and their metabolites, and transcription factors. Inflammatory cells such as leukocytes and neutrophils can destroy the BRB, and fluid and molecules of sizes can leak through damaged BRB rupture, causing macular edema[28]. Because of

multiple factors involved, anti-VEGF drugs are not currently effective in all patients with macular edema. Studies have shown that approximately 40% of patients with DME[29] and approximately 30% of patients with RVO-ME[30] have no efficacy or response. With the development of molecular mechanisms, increasing attention has been devoted to the anti-inflammatory mechanism. Steroids, such as the anti-inflammatory drug dexamethasone, may cause elevated intraocular pressure and cataract progression[31], which restrict the treatment of ME. Dexamethasone implants are becoming more widely used in clinical practice, as their development addresses problems such as frequent injections, short duration and poor compliance. However, due to the small number of samples in clinical trials, its safety and effectiveness have yet to be considered.

To comprehensively evaluate the efficacy and safety of anti-VEGF and Ozurdex in the treatment of RVO-ME and DME, we conducted a systematic review since both anti-VEGF drugs, such as ranibizumab, bevacizumab, and dexamethasone, such as Ozurdex, can be used to treat RVO-ME and DME in the clinic.

Methods

The study was conducted in accordance with the Cochrane Handbook for Systematic Reviews and reported using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021243185).

Search strategy

The PubMed, Embase and Cochrane Library databases were systematically searched from inception to July 11, 2021, by two independent investigators. We used MeSH (for PubMed and Cochrane)/Emtree (for Embase) terms combined with free-text words (including synonyms and closely related words) that were associated with RVO-ME, DME, dexamethasone and anti-VEGF. The detailed search strategy and specific terms used in the search are shown in the **Supplementary Methods**. We also manually checked the references of relevant articles, meta-analyses, reviews, and meeting abstracts. We performed study selection in a series of consecutive stages, including duplicate checking using Endnote software, title and abstract screening, and full-text article selection according to the eligibility criteria. These processes were conducted independently by two investigators. Conflicts were resolved by consensus, and an adjudicator was consulted when necessary. If different opinions were encountered, a senior expert was consulted.

Inclusion and exclusion criteria

Studies were regarded as eligible if they met the following criteria: 1. studies were randomized controlled trials (RCTs); 2. studies included patients with RVO-ME or DME; 3. studies directly compared the clinical efficacy of intravitreal injection of Ozurdex with that of anti-VEGF. We determined the following primary outcomes: 1) best-corrected visual acuity (BCVA), 2) central macular thickness (CMT); 3) cataract; and 4) intraocular pressure (IOP). Additional outcomes collected included the mean number of intravitreal injections. Patients taking bevacizumab and ranibizumab were assigned to the anti-VEGF group. The corresponding authors had to be contacted, and necessary data were unavailable. The exclusion criteria included studies with insufficient data, non-RCTs, case reports, and review articles. RCTs were excluded if patients in the trial group were given nonsimple Ozurdex injections, including Ozurdex combined with pseudoinjection. RCTs were also excluded if patients in the control group were not simply given anti-VEGF, such as anti-VEGF combined with pseudoinjection or anti-VEGF combined with laser photocoagulation.

Study selection, data collection, and data extraction

Two investigators independently screened and extracted data from the included studies and filled in the predesigned data extraction forms. If there were any discrepancies, we consulted a senior investigator until a consensus was reached. The following study characteristics were extracted: study author, publication year, study design, study period, blinding method, the number of eyes of the trial group and the control group, the frequency of drug administration, main results with estimates of the effect of Ozurdex and anti-VEGF in improving BCVA and reducing CMT, and the incidence of IOP and cataracts in the two groups.

Quality assessment

The quality of evidence for all included outcomes was evaluated based on Cochrane Collaboration's Tool, which includes representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, comparability of cohorts on the basis of the design or analysis, assessment of outcome, follow-up long enough for outcomes to occur, and adequacy of follow-up of cohorts.

Outcomes of interest

Primary outcomes include 1) improvement in BCVA (letters) from baseline and 2) decrease in CMT (micrometers; μm) from baseline. In RCTs, visual acuity (VA) was frequently quantified and reported as an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. When the logarithm of the minimum angle of resolution (logMAR) or Snellen chart scores was used to measure VA outcome, the score was converted to approximate ETDRS letter scores using the method proposed by Gregori et al. [32], which was used in quantitative analysis.

logMAR = -1 x log (Snellen fraction)

Approximate ETDRS letter scores = 85 + 50 x log (Snellen fraction)

The secondary outcome indicators included 1) progression of cataracts compared with baseline and 2) intraocular pressure (IOP) compared with baseline.

Statistical analysis

All statistical analyses were performed using data statistics software Review Manager (RevMan) version 5.3.

The primary outcome measures were improvement in BCVA from baseline and decrease in CMT from baseline. The secondary outcomes included progression of cataracts compared with baseline and IOP compared with baseline.

The random effects model was selected to account for outcome assessment due to the anticipated substantial heterogeneity, mainly in terms of the varied enrolled populations. Pooled mean differences (MDs) of BCVA and CMT with 95% CIs were calculated for the primary outcomes. The secondary outcomes were the pooled RR with 95% CIs of IOP and cataracts.

Between-study heterogeneity was calculated by the I2 statistic when I2 ≥ 50% considering substantial heterogeneity[33]. P values < 0.05 were considered statistically significant. To explore the sources of heterogeneity, we carried out a series of subgroup analyses based on the main courses for ME (RVO or DR), different drugs in the control group (bevacizumab or ranibizumab), and follow-up period (≤6 months or >6 months). Sensitivity analysis was performed by applying the leave-one-out method.

Data availability

Data were deposited locally but are not publicly available. Most of the relevant data are included in the main article and the supplementary materials. Unpublished data will be shared upon request from any qualified investigator.

Results

Literature search and study characteristics

The initial electronic-based literature search identified a total of 1034 studies, which were from the Cochrane Library (n=46), PubMed (n=191) and Embase (n=796). After removing duplicates, a total of 871 potentially eligible studies were retrieved. During this process, we excluded 772 studies after reading the title and abstract. After reading the full text, we further excluded 17 studies because no test results or raw test data were released. Seven studies were excluded since they only released abstracts. After looking through all eligible studies, 57 studies did not compare Ozurdex VS. anti-VEGF, and 11 studies released irrelevant outcomes. Finally, 7 studies comprising 251 study eyes satisfied the inclusion criteria and were eligible to be included in the final meta-analysis (**Figure 1**).

Table 1 presents the baseline characteristics of the included studies. Studies were published between 2012 and 2020 with an average follow-up duration of 8.7 months (range: 6–24 months). The sample size of the included studies ranged from 36 to 209 months. In all included studies, 5 studies focused on ME caused by RVO, and 2 studies focused on DME. Four of these studies reported side effects, including increased IOP and cataract progression. All of the included studies used Ozurdex as the treatment group drug and chose anti-VEGF as the control group drug. Among the control groups, 4 used bevacizumab, while 2 used ranibizumab. However, in the study by Sharma et al. that defined only anti-VEGF injection of the control group as bevacizumab or ranibizumab, the authors did not specify the drugs clearly.

Methodological quality (risk of bias)

The Cochrane Collaboration's tool was applied to assess the risk of bias in each study based on the Cochrane Handbook. Random sequence generation and allocation concealment were clear for 7/7 (100%). The RCTs had a low risk of bias with respect to blinding of participants and trial personnel 3/7 (42.86%), blinding of outcome assessment 2/7 (28.57%), incomplete outcome data 6/7 (85.71%) and selective reporting 7/7 (100%). Three of the 7 RCTs (42.86%) had an unclear risk of bias with regard to the other criteria. We present the assessment of individual studies in **Figure 2**.

Comparison of the effectiveness of Ozurdex and anti-VEGF in DME and RVO-ME

When we meta-analyzed the 7 studies, the results showed that the pooled MD of BCVA reached -2.83 ([95% CI, -5.60 to -0.05], P=0.05) in the Ozurdex treatment groups compared with the anti-VEGF treatment groups. No heterogeneity was found (P=0.49, I2=0%) (**Figure 3**). Data from the included studies reported that the reduction in central macular thickness (CMT) was significantly greater in the Ozurdex group (MD =-31.32 [95% CI, -57.92 to -4.72], P=0.02). Heterogeneity among studies was high (P=0.04, I2=54%) (**Figure 5**).

Meta-analysis results

1. BCVA

1.1 The effect of ME on BCVA

Data from the 7 RCTs assessing 209 eyes (109 eyes with Ozurdex treatment, 100 eyes with anti-VEGF treatment) showed BCVA in patients with RVO-ME or DME. The treatment effect of Ozurdex is better than that of anti-VEGF. The MD in visual acuity of the 7 trials was -2.83 ([95% CI, -5.60 to -0.05], P=0.05). No statistical heterogeneity was found (P=0.49, I2=0%) (**Figure 3**).

1.2 Subgroup analysis for the effect of ME on BCVA

Data from the 2 RCTs of RVO-ME assessing 37 eyes (21 eyes with Ozurdex treatment, 16 eyes with anti-VEGF treatment) reported an improvement in BCVA from baseline. The Ozurdex group reported a similar mean change in BCVA from baseline compared with the anti-VEGF group (MD = 6.59; 95% CI, −4.64 to 17.82; P = 0.25), and no heterogeneity was found (P = 0.72; I2=0%) (**Table 2**). A meta-analysis on DME was conducted based on 5 RCTs, including 172 eyes (88 eyes with Ozurdex treatment, 84 eyes with anti-VEGF treatment). There were statistically significant differences between the Ozurdex and anti-VEGF groups in favor of the Ozurdex groups (MD =-3.44;[95% CI, -6.30 to -0.58], P=0.02). No statistical heterogeneity was found (P=0.66, I2=0%) (**Table 2**).

Data from the 4 RCTs assessing 133 eyes (70 eyes with Ozurdex treatment, 63 eyes with bevacizumab treatment) reported an improvement in BCVA from baseline. There were no statistically significant differences between the Ozurdex and bevacizumab groups (MD =-2.18 [95% CI, -5.09 to 0.72], P=0.14), and no significant heterogeneity was found (P=0.41, I2=0%) (**Table2**). Data from the 2 studies assessing 36 eyes (19 eyes with Ozurdex treatment, 17 eyes with ranibizumab treatment) reported an improvement in BCVA from baseline. Compared with ranibizumab, the Ozurdex treatment showed superiority (MD =-10.22 [95% CI, -19.88 to -0.55], P=0.04). No statistical heterogeneity was found (P=0.92, I2=0%) (**Table 2**).

Data from the 5 RCTs with a follow-up period ≤ 6 months assessing 115 eyes (60 eyes with Ozurdex treatment, 55 eyes with anti-VEGF treatment) reported an improvement in BCVA from baseline. There were no statistically significant differences between the Ozurdex and anti-VEGF groups (MD =-2.99 [95% CI, -8.34 to 2.36], P=0.27). Low heterogeneity was found (P=0.27, I2=22%) (**Table 2**). Data from the 2 studies with a follow-up period > 6 months assessing 94 eyes (49 eyes with Ozurdex treatment, 45 eyes with anti-VEGF treatment) reported an improvement in BCVA from baseline. There were no statistically significant differences between the Ozurdex and anti-VEGF groups (MD =-1.80 [95% CI, -7.09 to 3.50], P=0.51). No statistical heterogeneity was found (P=0.78, I2=0%) (**Table 2**).

1.3 Subgroup analysis of different follow-up periods on BCVA in DME

Data from the 3 RCTs with a follow-up period ≤ 6 months assessing 78 eyes (39 eyes with Ozurdex treatment, 39 eyes with anti-VEGF treatment) reported an improvement in BCVA from baseline in DME. The treatment effect of Ozurdex is better than that of anti-VEGF. The MD in visual acuity of the 3 trials was -4.12 ([95% CI, -7.52 to -0.71], P=0.02) (**Figure 4**). No statistical heterogeneity was found (P=0.40, I2=0%). Two studies of 94 eyes (49 eyes with Ozurdex treatment, 45 eyes with anti-VEGF treatment) included data on the change in BCVA. No difference was found in the two studies (MD =-1.80 [95% CI, -7.09 to 3.50], P=5.01). No statistical heterogeneity was found (P=0.78, I2=0%) (**Figure 4**).

2. CMT

2.1 The effect of ME on CMT

Data from the 7 RCTs assessing 209 eyes (109 eyes with Ozurdex treatment, 100 eyes with anti-VEGF treatment) reported a reduction in CMT from baseline. Meta-analysis demonstrated that the Ozurdex group showed a remarkable reduction in CMT from baseline in the Ozurdex group. The MD for all studies was statistically significant (MD=-31.32 [95% CI, -57.92 to -4.72], P=0.02) in favor of Ozurdex treatment over anti-VEGF treatment and showed high heterogeneity (P=0.04, I2=54%) (**Figure 5**).

2.2 Subgroup analysis for the effect of ME on CMT

Data from the 2 RCTs of RVO-ME assessing 37 eyes (21 eyes with Ozurdex treatment, 16 eyes with anti-VEGF treatment) reported a reduction in CMT from baseline. The Ozurdex group reported a similar mean change in CMT from baseline compared with the anti-VEGF group (MD=-3.35 ([95% CI, -45.68 to 38.98], P=0.88), and no heterogeneity was found (P=0.41, I2=0%) **(Table 2**). A meta-analysis on DME was conducted based on 5 RCTs, including 172 eyes (88 eyes with Ozurdex treatment, 84 eyes with anti-VEGF treatment). There were statistically significant differences between the Ozurdex and anti-VEGF groups in favor of the Ozurdex groups (MD=-42.36 [95% CI, -77.99 to -6.72], P=0.02). High statistical heterogeneity was found (P=0.02, I2=65%) (**Table 2**).

Data from the 4 RCTs assessing 133 eyes (70 eyes with Ozurdex treatment, 63 eyes with bevacizumab treatment) reported a reduction in CMT from baseline. There were no statistically significant differences between the Ozurdex and bevacizumab groups (MD=-45.54 [95% CI, -92.18 to

1.10], P=0.06)), and high statistical heterogeneity was found (P=0.02, I2=69%) (**Table 2**). Data from the 2 studies assessing 36 eyes (19 eyes with Ozurdex treatment, 17 eyes with ranibizumab treatment) reported a reduction in CMT from baseline. No statistically significant differences between the Ozurdex and bevacizumab groups were found (MD=11.51 [95% CI, -39.03 to 62.06], P=0.66), and no statistical heterogeneity was found (P=0.93, I2=0%) (**Table 2**).

Data from the 5 RCTs with a follow-up period ≤6 months assessing 115 eyes (60 eyes with Ozurdex treatment, 55 eyes with anti-VEGF treatment) reported a reduction in CMT from baseline. The MD for the 5 studies was statistically significant (MD =-19.43 [95% CI, -27.80 to -11.06], P<0.00001) in favor of Ozurdex treatment over anti-VEGF treatment and showed no heterogeneity (P=0.50, I2=0%) (**Table 2**). Data from the 2 studies with a follow-up period > 6 months assessing 94 eyes (49 eyes with Ozurdex treatment, 45 eyes with anti-VEGF treatment) reported a reduction in CMT from baseline. There was no statistically significant difference between the Ozurdex and anti-VEGF groups (MD =-83.78 [95% CI, -184.82 to 17.25], P=0.10). High statistical heterogeneity was found (P=0.05, I2=74%) (**Table 2**).

2.3 Subgroup analysis of different follow-up periods on CMT in DME

Data from the 3 RCTs with a follow-up period ≤6 months assessing 78 eyes (39 eyes with Ozurdex treatment, 39 eyes with anti-VEGF treatment) reported a reduction in CMT from baseline in DME. The treatment effect of Ozurdex is better than that of anti-VEGF. The MD in visual acuity of the 3 trials was -20.08 ([95% CI, -28.62 to -11.54], P<0.00001) (**Figure 6**). No statistical heterogeneity was found (P=0.38, I2=0%). Two studies of 94 eyes (49 eyes with Ozurdex treatment, 45 eyes with anti-VEGF treatment) included data on the change in CMT. No difference was found in the two studies (MD =-83.78 [95% CI, -184.82 to 17.25], P=0.10). High statistical heterogeneity was found (P=0.05, I2=74%) (**Figure 6**).

Adverse Events

IOP

Four RCTs demonstrated increased IOP after injection of Ozurdex/anti-VEGF, which was mostly controllable by medication or surgery. Low heterogeneity was detected between studies (I2= 0%, P=0.92). A random effects model demonstrated a statistically significant difference between Ozurdex and anti-VEGF treatment (RR=5.14; 95% CI: 1.42 to 18.66; P□0.05) (**Figure 7**).

Progression of cataracts

Three studies involving 101 eyes reported postoperative cataracts. A statistically significant difference was found between the Ozurdex and anti-VEGF groups (RR=1.83; 95% CI: 0.63 to 5.27, P=0.31), without heterogeneity (P=0.26, I2=2%) (**Figure 8**).

Sensitivity analyses and publication bias

Sensitivity analyses were performed using the leave-one-out method to further examine the stability of the result. We found that no individual study significantly altered the summary MDs of BCVA (lowest MD=-2.16, 95% CI, -6.64 to 2.33; highest MD=-3.44, 95% CI, -6.31 to -0.58) and CMT (lowest MD=-19.98, 95% CI, -27.90 to -11.12; highest MD=-38.43, 95% CI, -68.13 to -8.74). Due to the small number of trials included in each meta-analysis, we did not conduct a publication bias test.

Discussion

Principal findings

The results of this meta-analysis by pooling data from 7 RCTs suggest that in the treatment of macular edema (ME) caused by retinal vein occlusion (RVO) and diabetic macular edema (DR), compared with anti-VEGF (vascular endothelial growth factor), Ozurdex is effective in enhancing best corrected visual acuity (BCVA) and reducing central macular thickness (CMT). The results remained consistent after adjustment for potential publication bias. Through subgroup analysis, Ozurdex played a better role in improving BCVA and reducing CMT than ranibizumab. Moreover, the anti-inflammatory treatment effect of Ozurdex is better than that of anti-VEGF drugs in DR, and the results in retinal vein occlusion macular edema (RVO-ME) of the two treatments were not different. Ozurdex was more effective in reducing ME than the anti-VEGF group when the follow-up period was ≤6 months than when the follow-up period was >6 months, regardless of whether ME was caused by DR, RVO or DR alone. Through data analysis, the incidence of IOP (intraocular pressure) in the Ozurdex group was higher than that in the anti-VEGF drug group, and there was no significant difference between the two in terms of cataract progression.

Comparisons With Previous Studies

Our findings are different from the result of a last year published meta-analysis which suggested that dexamethasone (DEX) implant compared with anti- vascular endothelial growth factor (VEGF) agents, had inferior functional efficacy and safety but required fewer injections in RVO patients after analyzed 4 RCTs and 12 real-world studies[34]. In contrast, we found that as a DEX implant, Ozurdex treatment is more effective than anti-VEGF therapy in improving best corrected visual acuity (BCVA) and reducing macular edema. On the other hand, Ozurdex treatment leads to a

higher risk of elevated intraocular pressure. This meta-analysis included 7 RCTs (Retinal Vein Occlusion Macular Edema [n=2] and Diabetic Macular Edema [n=5]) assessing a total of 251 eyes from PubMed, Embase and the Cochrane Library. However, our study included diabetic macular edema (DME)-related studies compared with the pooled analysis of Ming, S.'s studies in the general analysis[34]. Furthermore, we further compared the difference between anti-VEGF drugs and conducted subgroup studies of study times in the effect of macular edema on best corrected visual acuity (BCVA) and central macular thickness (CMT) to perform a comprehensive systematic review and meta-analysis.

Potential mechanisms

Current studies have shown that after retinal vein occlusion (RVO), increased capillary pressure leads to increased vascular leakage, local blood formation turbulence damages the vascular endothelium, thrombosis forms, and inflammation[35]. After the inflammatory reaction, retinal pigment epithelium (RPE) was degranulated by mast cells and expressed Toll-like receptors. After Toll-like receptors (TLR-4) are expressed, lipase (LPS) induces nuclear factor kappa-B (NF-KB) activation, which activates the downstream inflammatory pathway[36]. Retinal ischemia induced by retinal vein occlusion induces the expression of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 α (MIP-1 α) and the recruitment and activation of circulating macrophages[21]. Activated macrophages release tumor necrosis factor (rumor microglia factor α, TNF-α), TNF-α stimulates the synthesis of interleukin 8 (IL-8), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), monocyte chemoattractant protein-1 (MCP-1) and other cytokines in retinal endothelial cells and glial cells[22], and activates the downstream inflammatory pathway. Inflammatory mechanisms have also been shown to be activated in diabetic macular edema (DME) by multiple pathways. For example, retinal hypoxia-activating cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [27] in diabetic patients with long-term hyperglycemia and tumor necrosis factor can induce the expression of intercellular adhesion molecule 1 (ICAM-1) [37] and increase the expression of ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1), which can induce leukocyte stasis, microthrombosis and endothelial cell apoptosis. On the other hand, the aggregation of leukocytes on the surface of the retinal capillary can lead to the upregulation of ICAM-1, which mediates the attraction of endothelium to monocytes and neutrophils[38-39].

As an implant of dexamethasone, Ozurdex can block the production of its inflammatory mechanism through a variety of mechanisms, including reducing the synthesis of inflammatory mediators, reducing the synthesis of vascular endothelial growth factor (VEGF) [40], downregulating selectin and integrin to prevent leukocyte arrest[41], and preventing the occurrence of an inflammatory cascade reaction from multiple links. Ozurdex directly affects the expression of tight junction proteins and enhances the barrier integrity of retinal endothelial cells by upregulating the expression of Claudin-5 and occludin[42], thus reducing the increase in paracellular permeability caused by protein phosphorylation of endothelial molecules, IL-6, etc. Ozurdex inhibited the expression of intercellular adhesion molecule 1 (ICAM-1) in the retina[43], blocked the attraction of ICAM-1-mediated endothelium to monocytes and neutrophil cells, and reduced leukocyte arrest and endothelial cell injury. Ozurdex can inhibit the leakage of blood vessels, prevent the osmotic expansion of Müller cells[44], protect their water transport function and reduce edema.

We found that although some of the inflammatory pathways of retinal vein occlusion macular edema (RVO-ME) and diabetic macular edema (DME) were blocked by Ozurdex, in our meta-analysis, the Ozurdex group achieved better efficacy than the anti-vascular endothelial growth factor (VEGF) group in treating DME. Combined with previous studies by Arroba, Valverde, Roy and Yu[45-47], oxidative stress and inflammation in the retina induced by chronic hyperglycemia constitute an early stage in the development of diabetic macular edema. We hypothesized that the inflammatory reaction mechanism plays a more important role in diabetic macular edema than vascular endothelial growth factor and that the anti-inflammatory mechanism plays a more important role in the treatment of diabetic macular edema than anti-VEGF drugs. However, more robust clinical evidence should be provided before confirming this hypothesis. Therefore, future studies on diabetic macular edema inflammation mechanisms are of great importance in the prevention and treatment of diabetic macular edema.

Strengths and limitations

The current study has several strengths in terms of the following aspects. First, we included RCTs in the meta-analysis instead of studies with other designs, as they were regarded as high-quality evidence for the estimation of study effects. Second, we developed systematic and comprehensive database search strategies for major online databases (PubMed, Embase and Cochrane Library) with no search date restriction to avoid the impact of publication bias on the pooled findings and improve the repeatability of the results. Third, the evidence quality of all included outcomes was evaluated based on the Cochrane Collaboration's tool. Fourth, several approaches, including subgroup analyses and sensitivity analyses, have been applied to thoroughly determine sources of heterogeneity based on the abstracted study-level baseline characteristics.

Our study is limited by the following factors. First, there were only 7 RCTs (251 eyes) included, and the number of retinal vein occlusion macular edema (RVO-ME) studies was relatively small (n=2), which was less than that in diabetic macular edema (DME) studies (n=5). Second, in some clinical trials, the follow-up period of the study was short, which may understate the adverse events caused by the drug, and some of the studies did not document the group of adverse events in detail, which affected our assessment of the incidence of adverse events. Third, because the anti-VEGF group had different kinds of drugs and different injection frequencies, Ozurdex also had different application frequencies, the heterogeneity of the study was inevitable. Therefore, more experimental studies are needed to confirm the efficacy and safety of these two treatment strategies.

Conclusion

In summary, this systematic review and meta-analysis shows that despite some ocular adverse events, Ozurdex-treated eyes have relatively superior anatomic outcomes compared with anti-VEGF-treated eyes: Ozurdex treatment improves the best corrected visual acuity (BCVA) and reduces central macular thickness (CMT) significantly in diabetic macular edema (DME). Ozurdex also elevates the occurrence of intraocular pressure (IOP). In addition, because of the short study period, the long-term effects of the two drug treatments cannot be more clearly identified.

Abbreviations

DEX = dexamethasone; ME = macular edema; RVO-ME = retinal vein occlusion macular edema; DME = diabetic macular edema; DR = diabetic retinopathy; BCVA = best corrected visual acuity; CMT = central macular thickness; RCTs = randomized controlled trials; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CI = confidence interval; MD = mean difference; RR = relative risk.

Declarations

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Competing interests None declared.

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Tables

Table 1 Summary of the characteristics of the included studies

Study (year)	Conditions	Blinding methods	Subject	Period (months)	Participants numbers		Types		Number of doses	
					anti-VEGF group	Ozurdex	anti-VEGF group	Ozurdex	anti-VEGF group	Ozurdex
NCT 2012	RCT	Single blind	DME	6	10 eyes	10 eyes	bevacizumab	Ozurdex	5	2
Guignier 2013	RCT	Not mentioned	BRVO-ME	6	8 eyes	11 eyes	bevacizumab	Ozurdex	3	1
Shah 2016	RCT	Single blind	DME	7	23 eyes	27 eyes	bevacizumab	Ozurdex	7.0±0.5	2.7±0.5
Wickremasinghe 2017	RCT	Single blind	DME	24	22 eyes	22 eyes	bevacizumab	Ozurdex	14.2±7.9	14.2±7.9
Kumar 2019	RCT	Not mentioned	BRVO-ME	6	30 eyes	30 eyes	ranibizumab	Ozurdex	3	1
Podkowinski 2020	RCT	Double blind	DME	6	9 eyes	9 eyes	ranibizumab	Ozurdex	2	2
Sharma 2020	RCT	Not mentioned	DME	6	20 eyes	20 eyes	bevacizumab or ranibizumab	Ozurdex	4.04	1.15

Table 2 Subgroup analysis for the effect of ME on BCVA and CMT

Subgroup analyses for the effect of ME on BCVA

Variables	MD	95%CI	I^2,%	No.studies
ME type				
RVO-ME	6.59	-4.64,17.82	0	2
DME	-3.44	-6.30,-0.58	0	5
Different drugs				
Ranibizumab	-10.22	-19.88,-0.55	0	2
Bevacizumab	-2.18	-5.09,0.72	0	4
Study time				
≤6month	-2.99	-8.34,2.36	22	5
6month	-1.80	-7.09,3.50	0	2

Abbreviations:CI=confidence interval;MD=mean difference

Subgroup analyses for the effect of ME on CMT

Variables	MD	95%CI	I^2,%	No.studies
ME type				
RVO-ME	-3.35	-45.68,38.98	0	2
DME	-42.36	-77.99,-6.72	65	5
Different drugs				
Ranibizumab	11.51	-39.03,62.06	0	2
Bevacizumab	-45.54	-92.18,1.10	69	4
Study time				
≤6month	-19.43	-27.80,-11.06	0	5
6month	-83.78	-184.82,17.25	74	2

Abbreviations:CI=confidence interval;MD=mean difference

Figures

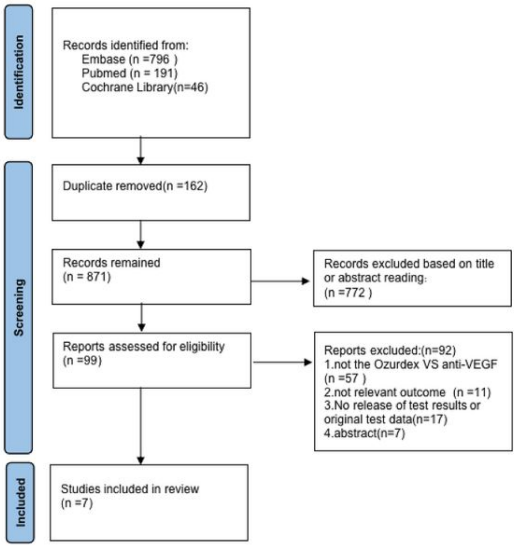

Figure 1 Flow chart of the literature search

Figure 1

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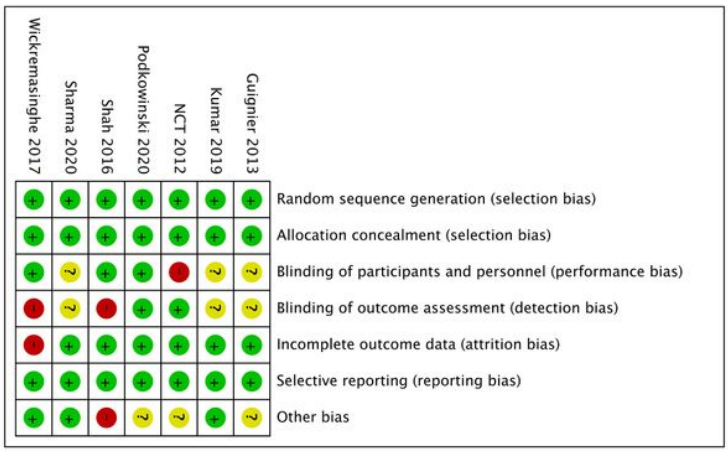

Figure 2.1 Risk of bias summary: review authors' judgements about each risk of bias item for each included study. +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.

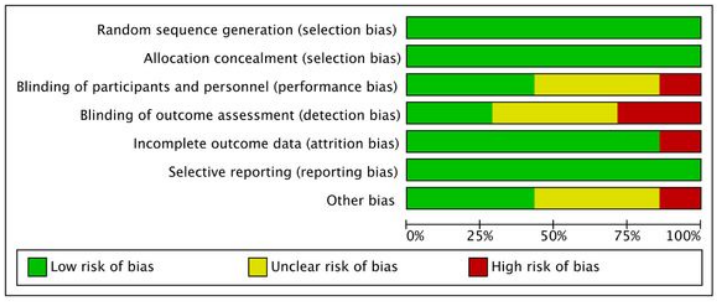

Figure 2.2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 2

See image above for figure legend

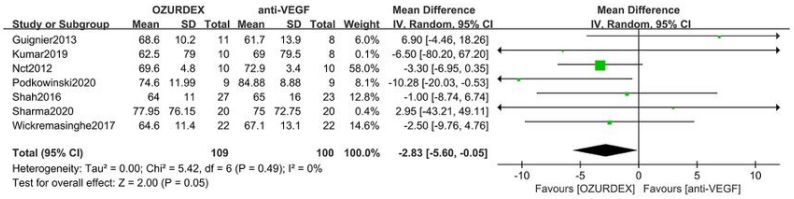

Figure 3 A forest plot diagram showing the mean BCVA and the associated 95% CI, comparing Ozurdex with Anti-VEGF treatment in ME

Figure 3

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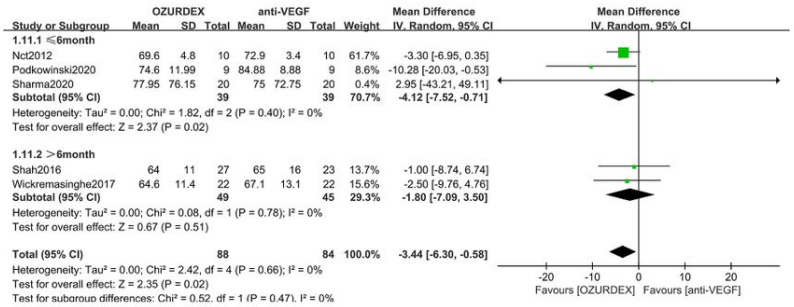

Figure 4 A forest plot diagram showing subgroup analysis of different follow-up periods on BCVA and the associated 95% CI, comparing Ozurdex with Anti-VEGF treatment in DME

Figure 4

See image above for figure legend

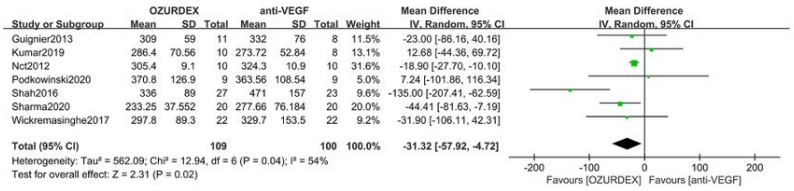

Figure 5 A forest plot diagram showing the mean CMT and the associated 95% CI, comparing Ozurdex with Anti-VEGF treatment in ME

Figure 5

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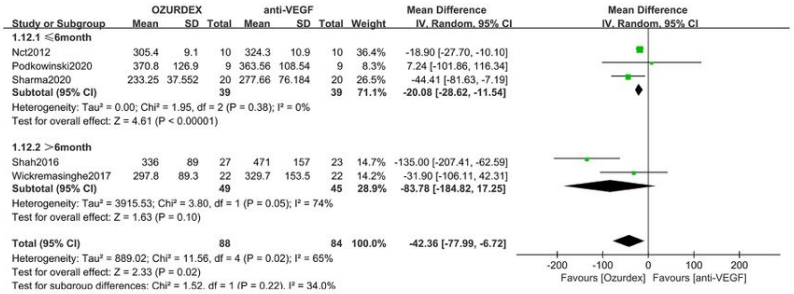

Figure 6 A forest plot diagram showing subgroup analysis of different follow-up periods on CMT and the associated 95% CI, comparing Ozurdex with Anti-VEGF treatment in DME

Figure 6

See image above for figure legend

Figure 7 A forest plot diagram showing adverse events of IOP and the associated 95% CI, comparing Ozurdex with Anti-VEGF treatment in ME

Figure 7

See image above for figure legend

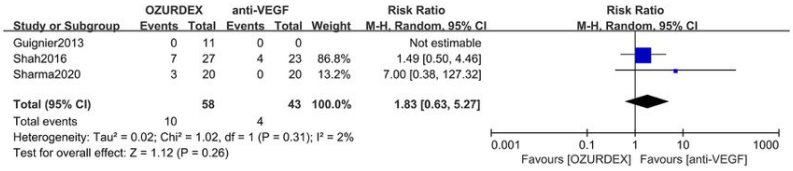

Figure 8 A forest plot diagram showing adverse events of progression of cataracts and the associated 95% CI, comparing Ozurdex with Anti-VEGF treatment in ME

Figure 8

See image above for figure legend