• Clinical Research •

Effect of simultaneous intravitreal ranibizumab and extended-release dexamethasone injection on patients with naïve versus refractory retinal vein occlusion macular edema: a prospective, multicenter, and interventional open-label study

Yao-Yao Sun[1,2], Jie Meng[3], Shan-Shan Li[4], Qin Xiao[5], Tian-Zi Zhang[5], Heng Miao[1,2], Ming-Wei Zhao[1,2], Hui-Jun Qi[1,2]

[1]Department of Ophthalmology, Peking University People's Hospital, Beijing 100034, China
[2]Beijing Key Laboratory of Ocular Disease and Optometry Science, Beijing100034, China
[3]Eye Institute of Shandong, State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao 266000, Shandong Province, China
[4]Department of Ophthalmology, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China
[5]Department of Ophthalmology, Affiliated Hospital of Inner Mongolia University for the Nationalities, Tongliao 028000, Inner Mongolia Autonomous Region, China
Correspondence to: Hui-Jun Qi. Department of Ophthalmology, Peking University People's Hospital, Beijing 100034, China. drqihuijun@126.com
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Abstract

● **AIM:** To evaluate the efficacy and safety of concurrent intravitreal ranibizumab (IVR) and extended-release dexamethasone injections (Dex-I) in naïve and refractory patients with retinal vein occlusion macular edema (RVO-ME).

● **METHODS:** This was a prospective, interventional, and open-label clinical trial. There were two groups: naïve and refractory patients (received ≥5 times of previous IVR within one year prior to enrollment) enrolled. Patients received IVR and Dex-I concurrently and re-combination therapy was required if one or more retreatment criteria were met. IVR and Dex-I were given pro re nata (PRN). The mean changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) were measured as main outcomes.

● **RESULTS:** Totally 63 patients (63 eyes) completed the entire follow-up (31 naïve and 32 refractory patients). At month 12, the change in BCVA was greater in the naïve group than in the refractory group [19.67±11.7 (95%CI: 15.03, 24.31) letters *vs* 11.74±11.18 (95%CI: 7.32, 16.16) letters, *P*=0.014). There was no difference between the two groups of mean macular thickness reduction [364.26±215.29 (95%CI: 279.09, 449.43) μm *vs* 410.19±204.34 (95%CI: 329.35, 491.02) μm, *P*=0.43). The mean co-injection numbers were 2.52±0.58 (95%CI: 2.29, 2.75) and 2.33±0.55 (95%CI: 2.11, 2.55) in both groups (*P*=0.24), respectively. The retreatment interval was 115.81±13.79 d (95%CI: 110.36, 121.27) and 122.74±14.06 d (95%CI: 119.93, 133.56) in both groups (*P*=0.073). There was no significant difference in the incidence of glaucoma or the progression of cataracts between the two groups.

● **CONCLUSION:** In both naïve and refractory RVO-ME patients, IVR combined with Dex-I is effective. The initial combination therapy for naïve patients demonstrates more efficient improvement in BCVA and may reduce total injection numbers compared to refractory patients.

● **KEYWORDS:** retinal vein occlusion; macular edema; prospective clinical trial; anti-vascular endothelial growth factor; dexamethasone implant

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INTRODUCTION

Retinal vein occlusion (RVO), defined as an obstruction of the normal retinal venous system, is the second most common retinal vascular disorder after diabetic retinopathy.

RVO affects patients over the age of 40 at a rate of 1% to 2% and contributes significantly to vision loss and visual handicaps[1-2]. RVO is classified into two types: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). RVO frequently causes retinal ischemia and macular edema (ME), both of which are challenging to treat[3].

RVO is characterized by mechanical damage to the retinal vascular walls, followed by thrombosis, hypercoagulation, and blood stagnation. In this process, vascular endothelial growth factor (VEGF), as well as inflammation and oxidative stress, participated in the disruption of the inner blood-retinal barrier, increasing vascular permeability, retinal ischemia, and neovascularization[4-5]. Based on the above pathogenesis, the current treatment strategy for retinal vein occlusion macular edema (RVO-ME) primarily consists of anti-VEGF and anti-inflammatory therapy. Most current guidelines recommend anti-VEGF therapy as the first-line treatment for RVO-ME[6]. Extended-release steroids (0.7 mg dexamethasone, Ozurdex®, USA), have gained popularity in recent years and are now recommended as a first- or second-line approach to RVO-ME treatment[7-8]. Despite the fact that all of these treatments have been shown in randomized clinical trials to significantly improve best-corrected visual acuity (BCVA) and decrease central macular thickness (CMT) in patients with RVO-ME, there is still treatment non-response in either approach, and both treatments have some limitations. Anti-VEGF therapy, for example, increases the risk of intraocular injection complications and the treatment burden for patients. In real-world studies, patients' average number of injections is much lower than expected, indicating lower treatment efficacy[9-11]. Furthermore, when Ozurdex® (Dex-I) is injected more than three times intravitreally, the risk of cataract and glaucoma increases significantly[12].

The current treatment modality for combining anti-VEGF with Dex-I has yet to be investigated. According to various guidelines, Dex-I is frequently used as second-line therapy for refractory patients; thus, even when combined with anti-VEGF therapy, it is still a delayed combination therapy modality, and treatment efficacy is not always met. Since the upregulation and pathological changes brought on by the action of several inflammatory and vasogenic mediators are the cause of the development of RVO-ME, according to previous reported, the combination of corticosteroids and anti-VEGF agents may have synergistic effects in the treatment of RVO-ME[13-14]. However, few studies have been conducted to assess the effects of initial anti-VEGF and Dex-I combination therapy[15-17] and there are currently no widely acknowledged guidelines for combination therapy[18]. Even so, there have been several studies demonstrated that the combination therapy achieved good BCVA improvement and exhibited a significantly longer treatment interval with limited side effects, not only for refractor patients, but also for naïve patients. The pattern and timing of combination therapy varies among different studies and naïve patients can receive combination therapy initially or alternate between combination therapy and anti-VEGF alone[13,15,19]. Besides, there are more studies focusing on macular edema secondary to diabetic retinopathy than on RVO-ME. Thus, comparing the effect of combination treatment on naïve patients and refractory patients is critical in the search for appropriate treatment modalities and to help to explore the time of combination therapy. We conducted a prospective study to compare the effect of combined intravitreal anti-VEGF treatment and DEX-I in naïve RVO-ME patients with that in refractory patients.

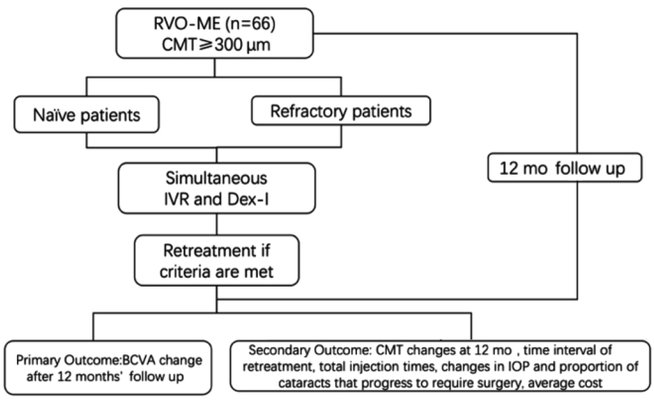

Figure 1 The study design is demonstrated RVO-ME: Retinal vein occlusion macular edema; CMT: Central macular thickness; IVR: Intravitreal ranibizumab; Dex-I: Dexamethasone injections; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure.

PARTICIPANTS AND METHODS

Ethical Approval The study design is demonstrated in Figure 1 and this study was registered with the identifier ChiCTR-INR-17011877 at https://www.chictr.org.cn/ and the date of first trial registration was (05/07/2017). The Medical Ethics Committee of Peking University People's Hospital approved this study (2016PHA008). All patients provided written informed consent to participate in accordance with the Helsinki Declaration guidelines.

Patients The design of our study was prospective, multicenter, interventional, and open-label case series. From October 2020 to October 2021, patients with RVO-ME were enrolled in this study at Peking University People's Hospital; Eye Institute of Shandong, Qilu Hospital of Shandong University and Affiliated Hospital of Inner Mongolia University for the Nationalities. A 12-month follow-up was performed on all patients. Patients were divided into two groups as 1:1 ratio: naïve patients and refractory patients. Refractory patients were defined as patients who had received more than 5 anti-VEGF treatments in the previous year with consistent subretinal or intraretinal fluid, or failure to gain 5 ETDRS letters[20]. Other inclusion criteria

Table 1 Demographic information for the two group

Group	Patients/eyes (*n*)	Male/female (*n*)	Age (mean±SD)	BRVO/CRVO (*n*)	IOP (mm Hg)
Naïve patients' group	31/31	18/13	63.15±11.32	11/20	16.0±11.79
Refractory patients' group	32/32	16/16	63.26±10.88	17/15	13.83±2.71
P		0.62	0.97	0.12	0.14

BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; IOP: Intraocular pressure.

for both groups are: 1) age >18 years old patients; 2) patients with a primary diagnosis of RVO confirmed by color fundus photography (CFP) and fundus fluorescein angiography (FFA); 3) CMT≥300 μm on spectral domain optical coherence tomography (SD-OCT). Patients with various ocular disorders such as uncontrolled glaucoma (defined as progressive visual field impairment despite receiving the most effective treatment to reduce intraocular pressure (IOP), uveitis, rhegmatogenous retinal detachment, age-related macular degeneration, epiretinal membrane, high myopia fundus changes, and ocular tumors were excluded. Any patient who had received intraocular steroid therapy within 6mo prior to enrolling was excluded.

Treatment and Follow-up Each patient had a comprehensive ocular examination which included disease duration, BCVA (as defined by the ETDRS protocol), IOP, anterior segment examination with a slit lamp, posterior segment examination, and CFP, FFA (both from Optos PLC, Dunfermline, United Kingdom), and SD-OCT (optical coherence tomography angiography, OCTA, both from Carl Zeiss Meditec AG, Jena, Germany). Patients were checked on a monthly basis. The study eyes were subjected to a standard ophthalmological examination at each visit, which included all of the above examinations except FFA. The intraocular injection was performed in accordance with the previously stated protocol[21]. Intravitreal ranibizumab (IVR, 0.5 mg, Lucentis®, Genentech/Roche, San Francisco, USA) was used as an anti-VEGF agent, and Dex-I (0.7 mg Ozurdex®, Allergan plc, Dublin, Ireland) and IVR were performed on the same day in the same surgical procedure.

If one or more of the following criteria are met, re-combination treatment is required: 1) BCVA decrease ≥5 letters compared to the previous visit; 2) CMT ≥ 250 μm; 3) macular edema threatening fovea or CMT increase≥ 50 μm compared to the previous visit; 4) new retinal cystic changes. Each injection was a combination IVR+Dex-I, and Dex-I and IVR were performed on the same day in the same surgical procedure.

FFA were performed every three months. The capillary nonperfusion area on FFA was used to assess retinal ischemia. Laser photocoagulation was performed on BRVO patients with nonperfusion area ≥5 disk areas and CRVO patients with nonperfusion area ≥10 disk areas. The primary outcome was the change in BCVA 12mo after the first treatment. As a secondary efficacy analysis, CMT changes at 12mo, time intervals between retreatments, total injection times, and the proportion of elevated IOP cataracts that progress to require surgery were investigated. For the sake of the subjects' safety, the researchers believe that the subjects should withdraw from the study.

Statistical Analysis For the primary objectives (BCVA improved at month 12), a power of 90%, a two-sided alpha level of 0.05, and a dropout rate of 10% were calculated using the PASS software version 15.0. According to previous reported, at the 12-month follow-up time point after combined treatment with Dex-I and intravitreal IVR, BCVA improved by a mean of 21.3 letters in naïve patients[22] and by a mean of 9.8 letters in refractory patients[15], with a maximum standard deviation of 13.3 letters. Therefore, the final sample size was determined to be 33 cases per group.

SPSS software was used to analyze the data (version 22.0, USA). A 2-sided independent-sample *t*-test was used to test the primary efficacy analysis (BCVA and CMT changes). Besides, multiple linear regression analysis was used to explore the potential confounders of BCVA changes.

RESULTS

Demographic Information From October 2020 to October 2021, 63 patients completed the entire follow-up, and 3 patients were excluded due to missing follow-up, for a total enrolled rate of 95.45%, with 34 men and 29 women having an overall mean age of 63.20±11.00 years old, respectively. Demographic information for the two groups were listed in Table 1. The study was terminated due to the predicted sample size being reached.

BCVA Changes Between Two Groups BCVA improved in both groups at the end of month 12. In the naïve patients' group, the average BCVA improved by 19.67±11.7 [95% confidence interval (CI): 15.03, 24.31] letters compared to 11.74±11.18 (95%CI: 7.32, 16.16) letters in the refractory patients' group. The difference in BCVA change between the two groups was significant (*P*=0.014; Figure 2A). Figure 2B depicted the change in BCVA at each visit. At each visit, the average BCVA was higher in the naïve patients' group than in the refractory patients' group. The percentage of BCVA improvement greater than 15 letters in the naïve patients' group and refractory patients' group were 70.97% and 34.38%, respectively, and the difference was statistically significant (*P*=0.005; Figure 2C).

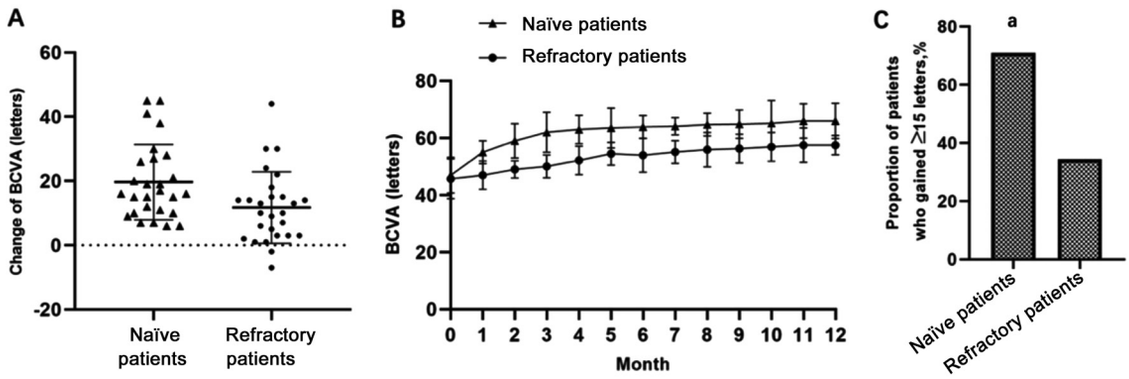

Figure 2 BCVA changes of two groups A: The difference in BCVA change between the two groups was significant at the end of month 12 (*P*=0.014). B: The change in BCVA at each visit in both groups. At each visit, the average BCVA was higher in the naïve patients group (*n*=31) than in the refractory patients' group (*n*=32). Error bars represent the standard error of the mean. C: There was statistically significant difference in the percentage of BCVA improvement greater than 15 letters in the naïve patients group and refractory patients' group (*P*=0.005, [a]Statistically significant difference). BCVA: Best-corrected visual acuity.

We also performed further statistical analyses to analyze the coeffect of gender, age, disease type (CRVO/BRVO), whether the disease was ischemic, whether the cataract progressed, and whether the glaucoma progressed, on the final BCVA change. It was found that none of the factors had an effect on the BCVA change except for group (naïve and refractory patients).

CMT Changes Between Two Groups CMT decreased in both groups at the end of month 12. The average CMT in the naïve patients' group was 364.26±215.29 (95%CI: 279.09, 449.43) μm compared to 410.19±204.34 (95%CI: 329.35, 491.02) μm in the refractory patients' group. The difference in CMT change between the two groups was not significant (*P*=0.43; Figure 3A). Figure 3B depicted the average CMT change at each visit. Typical case of the naive group in Figure 4 showed significant improvement in CMT.

We also performed further statistical analyses to analyze the coeffect of gender, age, disease type (CRVO/BRVO), whether the disease was ischemic, whether the cataract progressed, and whether the glaucoma progressed, on the final CMT change. It was found that none of the factors had an effect on the CMT change.

Other Outcomes Since patients received IVR as well as Dex-I for each administration in the operating room, there was a mean co-injection number of 2.52±0.58 (95%CI: 2.29, 2.75) in the naïve patients' group and 2.33±0.55 (95%CI: 2.11, 2.55) in the refractory patients' group at month 12 (*P*=0.24). Patients in the refractory group received an average of 6.30±1.64 (95%CI: 5.72, 6.87) anti-VEGF injections prior to enrollment and 8.63±1.57 (95%CI: 8.01, 9.25) total injections after enrollment. There were significant differences in total injection times between the two groups (2.52±0.58 *vs* 8.63±1.57, *P*=0.000). The time interval between retreatments was 115.81±13.79d (95%CI: 110.36, 121.27) in naïve patients and 122.74±14.06d (95%CI: 119.93, 133.56) in patients

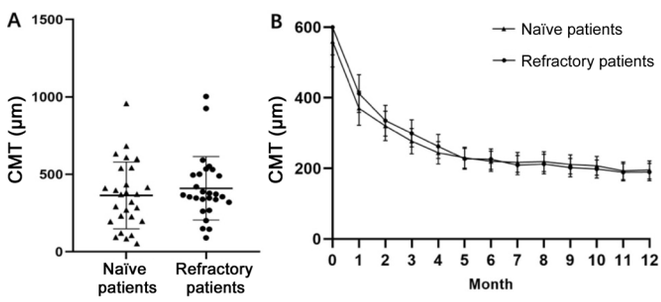

Figure 3 CMT changes of two groups A: The difference in CMT change between the two groups was not significant at the end of month 12 (*P*=0.43). *n*=31 in the naïve patients' group and *n*=32 in the refractory patients' group. B: The average CMT change at each visit in both groups. Error bars represent the standard error of the mean. CMT: Central macular thickness.

(*P*=0.073). In the naïve patient groups, 3 BRVO patients and 1 CRVO patient received photocoagulation based on the photocoagulation criteria mentioned above. In the refractory group, 1 BRVO and 4 CRVO patients had photocoagulation prior to enrollment, while 2 BRVO and 3 CRVO patients had photocoagulation during follow-up (Case 2; Figure 5).

Safety At 12mo, 4 eyes (12.90%) in the naïve patients' group had elevated IOP, including 1 eye with IOP ≥ 30 mm Hg; and 4 eyes (12.50%) in the refractory patients' group had elevated IOP, including 2 patients with IOP ≥ 30 mm Hg. The incidence of elevated IOP did not differ statistically between the two groups (*P*=0.43). All patients with elevated IOP had their IOP normalized by using topical IOP-lowering medications, and none required anti-glaucoma surgery. During the follow-up period, 1 eye (3.23%) in the naïve patients' group and 4 eyes (12.5%) in the refractory patients' group experienced cataract progression (*P*=0.355), and all received cataract surgery. Other ocular complications such as vitreous hemorrhage, endophthalmitis, or retinal detachment did not occur in either group nor did systemic complications.

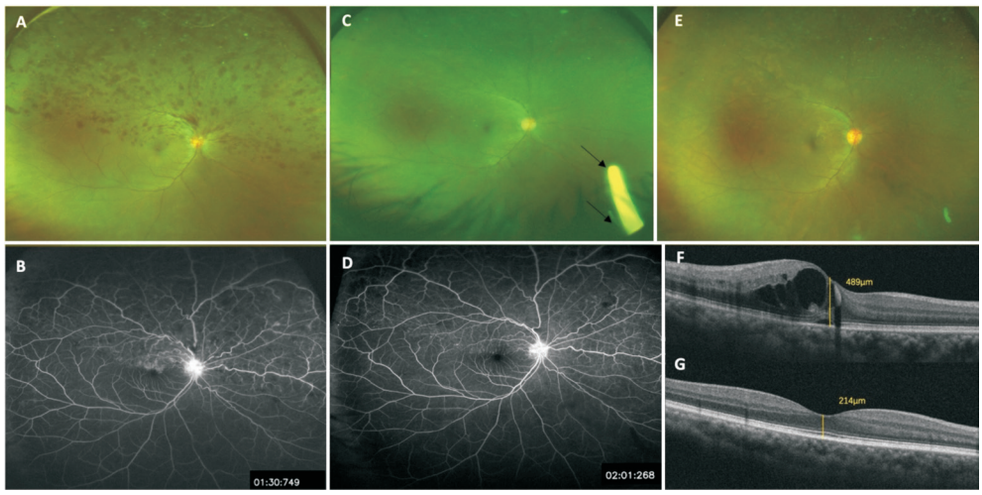

Figure 4 Case 1: a 60-year-old woman with 2wk of right eye blur and BCVA of 65 letters was diagnosed with BRVO She received combined IVR and Dex-I, with a second injection at 5mo, improving BCVA to 85 letters. Pre-treatment CFP (A) and FFA (B) confirmed BRVO. Post-injection CFP showed Dex residue (arrow, C). At 12mo, CFP and FFA revealed a clear retina without non-perfusion (D, E). OCT showed macular edema resolution and full recovery with an intact ellipsoidal zone (F, G). CFP: Color fundus photo; FFA: Fundus fluorescing angiography; BRVO: Branch retinal vein occlusion; Dex: Dexamethasone; OCT: Optical coherence tomography; BCVA: Best-corrected visual acuity; Dex-I: Dexamethasone injections; IVR: Intravitreal ranibizumab.

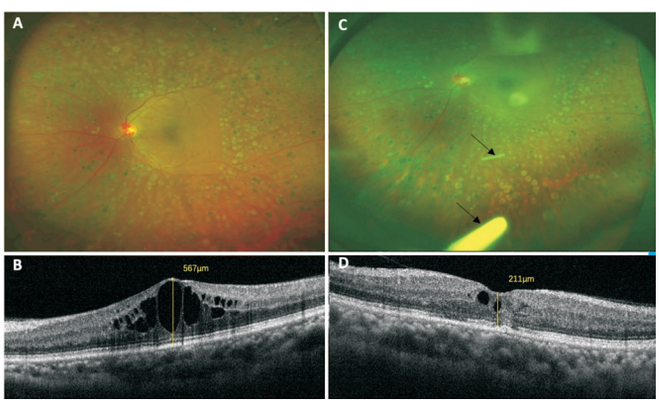

Figure 5 Case 2: a 55-year-old woman with a month of left eye blurred vision and BCVA of 55 letters was diagnosed with CRVO She received 7 IVR and panretinal photocoagulation for severe ischemia before enrollment but had persistent macular edema. During follow-up, she received two combined IVR and Dex-I, improving BCVA to 65 letters. CFP showed laser spots (A), and OCT revealed macular edema at enrollment (B). Post-injection CFP displayed Dex residue (C, arrow). At 12mo, OCT showed reduced central macular thickness but residual cystic structures with irregular ellipsoidal zone and RPE (D). CFP: Color fundus photo; FFA: Fundus fluorescing angiography; CRVO: Central retinal vein occlusion; Dex: Dexamethasone; OCT: Optical coherence tomography; BCVA: Best-corrected visual acuity; Dex-I: Dexamethasone injections; RPE: Retinal pigment epithelium; IVR: Intravitreal ranibizumab.

DISCUSSION

In this study, we discovered that the combination treatment improved BCVA and decreased CMT in both the naïve and refractory patient groups, with the naïve group showing greater improvement in BCVA and no increase in complications. With the growing emphasis on anti-VEGF and anti-inflammatory combination therapy for RVO-ME, the treatment modality proposed in this study is an excellent addition to the investigation of combination treatment strategies. This study compared the treatment effects in patients with naïve and refractory patients, which provides new evidence for exploring the timing of intervention of combination therapy.

Pathological processes in RVO-ME suggest that anti-inflammatory therapy, in addition to anti-VEGF therapy, is important. The results of clinical trials heavily influence the treatment modality chosen for RVO-ME. Anti-VEGF therapy is commonly used in the treatment of RVO-ME. Ranibizumab has been shown in clinical trials, whether randomized controlled trials (*e.g.*, BRAVO study)[23] or real-world studies (*e.g.*, LUMINOUS study)[10], to improve patients' vision while reducing macular edema. Simultaneously, the GENEVA study demonstrated the efficacy of Dex-I on RVO-ME[12]. According to a recent expert consensus, intravitreal anti-VEGF should be used as first-line therapy, followed by other anti-VEGF agents or Dex in cases of persistent or recurrent ME[24]. However, there have been reports of patients who did not respond to either treatment. Despite being the first-line treatment, anti-VEGF has a high rate of non-response. The rate of non-response to anti-VEGF treatment in randomized controlled trials was 15%-20%[25], and in the real world, the rate of non-response to anti-VEGF treatment for vision was up to 27.9% at 4mo and 30.2% at 12mo. In addition, 75% remained nonresponsive after one year in patients who did not respond to early treatment[26]. In other words, persistence does not guarantee success. The results of previous studies that switched from Dex-I to anti-VEGF or vice versa were not ideal. Failure to respond to anti-VEGF or

Dex-I monotherapy may be due to a variety of factors. On the one hand, a single molecule may only partially address the pathogenesis of ME, especially when many components have been implicated. Tachyphylaxis or tolerance may develop after repeated administration of the same medicine[17,27]. Therefore, combined anti-VEGF and anti-inflammatory treatment modalities have been investigated in recent years.

The use of anti-VEGF combined with Dex-I in RVO-ME eyes has been reported less frequently[16-17,28-29]. For example, Mayer *et al*[15] conducted a prospective study and found that the combined treatment of bevacizumab and dexamethasone implant demonstrated slightly better functional result compared to bevacizumab alone. Also, for treatment-naïve ME patients secondary to RVO, Bae *et al*[13] found that contrary to intravitreal anti-VEGF monotherapy, treatment with intravitreal corticosteroid and anti-VEGF injections alternately had a better visual outcome. In addition, for patients with ME secondary to diabetic retinopathy, combination therapy has also been shown to have a significant effect on both BCVA and CMT[19,30-31]. The few available studies of RVO-ME, however, did not use the same treatment paradigm as ours. The investigation of RVO-ME treatment options is ongoing, and combination therapy is being tried more frequently, but the timing of combination therapy is not yet conclusive. Unlike previous studies, our study not only focused on the efficacy and safety of combination therapy, but also wanted to explore the timing of combination therapy intervention. Previous research has shown that when compared to anti-VEGF monotherapy, combination therapy significantly prolongs treatment duration, restores the anatomy and improves visual acuity, and reduces the number of anti-VEGF treatments[32]. After one year of combination therapy, Giuffrè *et al*[17] discovered refractory RVO-ME patients with significant improvement in CMT but not in BCVA. Therefore, we conducted this prospective study to determine whether initial combination therapy was superior to delayed combination therapy in terms of functional and anatomical improvement and whether naïve patients had better BCVA outcomes. The benefit of BCVA was lower in the refractory group, which could be attributed to irreversible photoreceptor and retinal pigment epithelium (RPE) damage caused by prolonged macular edema. According to the studies, sudden ischemia can cause a surge of VEGF and inflammatory factors in a short period of time, so an initial combined treatment can rapidly inhibit the release of VEGF and inflammatory factors, slow the progression of the disease, and maintain better visual outcomes. On the contrary, as the ME disease course was prolonged in refractory patients, the macular structure appeared to be continuously damaged, and patients' visual prognosis remained poorer even after the combination treatment was administered.

IVR was performed concurrently as Dex-I in this study, which simplified the treatment process and reduced the treatment burden on patients. Patients in this study were admitted to the operating room less frequently when compared to alternate or sequential treatments. The mean number of co-injections during the follow-up period was 2.52±0.58 in the naïve patients' group and 2.33±0.55 in the refractory patients' group, which is lower than previously reported. Retreatment occurred around every 4mo in either group, which is much longer than monthly injection. Approximately 42% of patients, according to previous reports, expect to reduce the number of injections while maintaining efficacy[33]. The reduction in the number of injections in this study, compared to the refractory patients' group, not only reduced the incidence of injection-related complications such as vitreous hemorrhage and retinal detachment objectively but also reduced the financial burden on patients in the context of the COVID-19 pneumonia epidemic.

The most common side effects of Dex-I treatment were increased IOP and cataract risk[12]. This study also demonstrated that the initial combination treatment was safe, with cataract and high IOP side effects roughly comparable to previously reported results[34]. In this study, IOP elevation was generally moderate, and no patients required surgery to control IOP. Our study found that improvements in BCVA were not consistent with changes in CMT. As mentioned in the literature, an extreme macula thinning falling below normal thresholds may result in a drop in BCVA as a result of intravitreal therapy[35], further analyze it in future post hoc analysis is necessary to assess this effect.

There several limitation of this study. First, the small sample size is the study's main limitation, and longer follow-up clinical studies with larger sample sizes are expected in the future. Second, we did not set up a separate experimental group to compare the effects of Dex-I monotherapy; our findings would have been better grounded if we had set up this control group. In addition, we failed to explore other treatment modalities. These include, as previously reported in the literature, alternative treatment modalities, or initial combination therapy with subsequent monotherapy, and so on.

Overall, this study showed that the initial combination of IVR and Dex-I treatment contributed to the recovery of visual acuity and the resolution of ME in naïve patients, but long-term visual improvement must be confirmed in the future.

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Authors' Contributions: Qi HJ was responsible for designing the protocol, writing the protocol and report, conducting the search, treating the patients, extracting, analyzing data and

writing the manuscript. Sun YY, Xiao Q and Zhang TZ were responsible for conducting the research, treating the patients, analyzing data and writing the manuscript. Meng J and Li SS were responsible for the registration, design and statistics of this study. Zhao MW and Miao H was responsible for conducting the research, treating the patients and writing the manuscript.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Please contact Sun YY, sunyaoyao11@126.com for the raw data.

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Conflicts of Interest: Sun YY, None; **Meng J,** None; **Li SS,** None; **Xiao Q,** None; **Zhang TZ,** None; **Miao H,** None; **Zhao MW,** None; **Qi HJ,** None.

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