

# Intravitreal Dexamethasone Implant versus Ranibizumab versus Ranibizumab Combined with Dexamethasone Implant for Macular Edema Secondary to Retinal Vein Occlusion

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## Research Article

**Keywords:** dexamethasone implant, efficacy, macular edema, ranibizumab, retinal vein occlusion

**Posted Date:** October 18th, 2026

**DOI:** <https://doi.org/10.21203/rs.3.rs-11024170/v1>

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**Additional Declarations:** No competing interests reported.

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## Abstract

## Background

To compare the efficacy of intravitreal injections (IVI) of ranibizumab, ranibizumab plus dexamethasone implants (R + DEX), and DEX alone for macular edema secondary to retinal vein occlusion (RVO-ME).

## Methods

This was a double-blind, randomized, comparative study registered in the Chinese Clinical Trial Registry. Two hundred sixty eyes with a first diagnosis of RVO-ME were randomized into one of five groups based on treatment assignment. Best-corrected visual acuity (BCVA), central retinal thickness (CRT), number of injections (NOI), intraocular pressure (IOP), and cataract progression were compared at 1, 2, 3, 4, 5, 6, 9, and 12 months post-injection.

## Results

At each follow-up, BCVA significantly increased in all five groups compared with baseline, and there was a significant difference between the groups at the last follow-up ( $p = 0.009$ ). DEX, R + DEX, and ranibizumab successfully reduced CRT at each follow-up. There was a significant difference in the mean decrease in CRT between the five groups at the last follow-up ( $p = 0.03$ ). Both CRVO and BRVO patients had significant between-group differences in mean NOI (both  $p < 0.01$ ). The incidences of elevated IOP and cataract progression were significantly higher in the IVI R + DEX and DEX groups than in the ranibizumab group (both  $p < 0.01$ ).

## Conclusions

Early IVI administration of DEX + ranibizumab significantly improved BCVA and reduced CRT in patients with RVO-ME. The advantages of DEX include fewer injections and longer duration of efficacy, whereas the advantages of ranibizumab include fewer adverse effects.

## Trial Registration

The trial was registered on January 5, 2021. The trial registration number was ChiCTR2100042682.

## Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. It is estimated to affect 16 million adults worldwide, with a reported prevalence of 4.6% in those aged  $\geq 80$  years<sup>[1]</sup>. Although clinical classification can be challenging, RVO has traditionally been subdivided into two main types: central (CRVO), with a prevalence of 0.1%–0.4%, and branch (BRVO), affecting 0.6%–1.2% of individuals<sup>[2, 3]</sup>. Retinal vein occlusion–macular edema (RVO-ME) is the most common cause of visual impairment in affected patients. The pathogenesis of RVO involves upregulation of vascular endothelial growth factor (VEGF) and an increase in inflammatory mediators, which contribute to vascular leakage, breakdown of the blood–retinal barrier, and macular edema (ME)<sup>[4, 5]</sup>. Antiangiogenic and anti-inflammatory agents have been developed for the treatment of ME. Since 2010, intravitreal injections (IVI) of anti-VEGF agents, such as ranibizumab (Lucentis R, Genentech Inc., San Francisco, CA, USA), have been approved for the treatment of RVO-related ME and are widely applicable. Recently,

dexamethasone (DEX; Ozurdex R; Allergan Inc., Irvine, CA, USA) intravitreal implants have gained popularity and are increasingly used to treat RVO-related ME. This therapy has been shown to be highly effective in treating RVO-related ocular disorders and demonstrates favorable long-term safety<sup>[6, 7]</sup>. However, these treatment strategies are not suitable for all patient groups and have limitations in clinical practice. Ranibizumab is a rapid-onset anti-vascular endothelial growth factor (VEGF) agent that provides short-term effects and requires frequent injections. This places a significant burden on patients and increases the risk of complications<sup>[8, 9]</sup>. As a sustained-release drug, DEX implants release low doses of DEX into the vitreous cavity for 3–6 months. However, this therapy carries the risk of glaucoma and cataract formation<sup>[6]</sup>. Given the limitations of single-drug therapy, the combination of DEX implants and anti-VEGF agents may address the multifactorial pathophysiology of RVO and provide rapid-onset and favorable long-term functional and anatomical improvements. There is no consensus regarding the optimal timing of combination therapy.

This study investigated the efficacy and number of injections (NOI) of anti-VEGF monotherapy, DEX implant monotherapy, and combination therapy with an anti-VEGF agent and a DEX implant for RVO-related macular edema (ME). This study aimed to determine whether combination therapy with anti-VEGF and dexamethasone (DEX) implants is synergistic and provides additional improvements in best-corrected visual acuity (BCVA) and central macular thickness (CRT) compared with anti-VEGF or DEX monotherapy. To standardize and optimize local RVO therapy strategies, we present 12-month follow-up data focusing on real-world efficacy and safety.

## Methods

### Design and Population

This double-blind, randomized, comparative study was approved by the Ethics Committee of the Qingdao Eye Hospital of Shandong First Medical University and registered in the Chinese Clinical Trial Registry (ChiCTR2100042682). The trial was registered on January 5, 2021. Our reporting adheres to CONSORT guidelines for reporting clinical trials. Written informed consent was obtained from each participant prior to enrollment in accordance with the principles of the Declaration of Helsinki. To achieve a power of 90% at an alpha level of 0.05, a sample size of 51 patients per group was required, totaling 255 patients across five groups. This study included 260 consecutive eyes enrolled between January 2021 and December 2023. Each eye was enrolled only once. Patients were randomly assigned to one of the five IVI agent groups using a random number table generated by a statistician (S.X.J.). Group 1 received ranibizumab with three consecutive monthly loading doses of ranibizumab + pro re nata (three + PRN), with ranibizumab continued upon recurrence of ME. Group 2 received ranibizumab and DEX implants, with ranibizumab and DEX implants injected successively for the first month and continued upon recurrence of ME. Group 3 received ranibizumab 2 and DEX implants, with ranibizumab injected in the first month, and ranibizumab and DEX implants injected successively in the second month and continued upon ME recurrence. Group 4 received ranibizumab and DEX implants, with ranibizumab injected in the first and second months, and ranibizumab and DEX implants injected successively for the third month and continued upon ME recurrence. Group 5 received DEX implants which were injected for the first month and continued upon recurrence of ME. The researchers, surgeons, and patients were blinded to details of the IVI agents. To list in detail the treatment methods used for each arm segment/lanes and the re-administration time points for each arm segment/lanes, a "lane diagram" was shown in Fig. 1. The inclusion criteria were as follows: (1) age > 18 years; (2) according to RVO-ME diagnostic criteria and (3) first diagnosis and treatment. The exclusion criteria were as follows: (1) previous IVI of anti-VEGF agents or DEX; (2) history of glaucoma or intraocular pressure (IOP) greater than 21 mmHg; (3) diabetic retinopathy, uveitis, macular anterior membrane, or other fundus diseases affecting vision or causing ME; (4) aphakia or posterior capsule defects; (5) refractive interstitial opacity affecting fundus examination or optical coherence tomography (OCT); (6) cardiovascular and cerebrovascular events or serious systemic diseases within the previous 6 months; (7) poor follow-up compliance or incomplete case data. Patients with BRVO or CRVO

without neovascularization or ischemia on fundus fluorescein angiography (FFA) were eligible for treatment or retreatment if CRT  $\geq 250$   $\mu\text{m}$ .

## Injection Procedure

IVI was administered in a laminar-flow operating room under sterile conditions. Before the procedure, the ocular surface was prepared by a nurse (L.Y) and sterilized with 5% povidone-iodine eye drops by a retinal specialist (D.Q). An eyelid speculum was inserted and 5% povidone-iodine eye drops were applied to the injection site. The injection was performed using a 30-gauge needle containing ranibizumab (0.5 mg/0.05 mL), administered in the superotemporal quadrant of the right eye or the superonasal quadrant of the left eye, or a 27-gauge needle was used to administer a DEX implant (0.7 mg) in the inferotemporal (right eye) or inferonasal (left eye) quadrant, and the entry site of the needle was 3.5 mm from the limbus in pseudophakic patients and 4.0 mm from the limbus in phakic patients. The sclera was penetrated obliquely, and the drug was injected intravitreally. After needle withdrawal, sterile cotton swabs were applied to the injection site to prevent reflux. The eyelid speculum was removed, and tobramycin–dexamethasone eye ointment (Akorn, Inc.) approximately 1–1.5 cm in length was applied to the injection site. Patients were routinely examined 1 d postoperatively. Follow-up visits were scheduled monthly post-injection.

## Outcome Measures

The systemic and ophthalmic histories of all patients were recorded before injection. Detailed ophthalmic examinations, including BCVA, IOP, slit-lamp examination, OCT, and fundus photography, were performed at baseline and every month after injection. Optical coherence tomography angiography (OCTA) was performed at baseline and at 1, 2, 3, 4, 5, 6, 9, and 12 months after injection. BCVA, anterior segment, and fundus examinations with slit-lamp biomicroscopy, IOP measurement using a Goldmann applanation tonometer, OCT scan, OCTA scan, and fundus photography were recorded at each visit.

## Statistical Analysis

Statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA). General patient characteristics were analyzed using the chi-square test. Preoperative and postoperative BCVA, CRT, number of IVIs, and incidence of adverse events were compared using the Wilcoxon rank-sum test. Changes in BCVA and CRT between the groups were compared using the Wilcoxon rank-sum test. Statistical significance was defined as  $p < 0.05$ . Snellen visual acuity measurements were converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis.

## Results

### Patient Characteristics

A total of 260 eyes from 260 patients were randomly allocated to five groups, with each group including 52 eyes. The participants consisted of 132 (50.76%) male and 128 (49.24%) female patients, with 137 (52.69%) right and 123 (47.31%) left eyes. The mean age was  $66.2 \pm 8.5$  years (range 39–88 years), and there were 171 (65.77%) patients with hypertension and 89 (34.23%) patients without hypertension. The enrolled patients included 98 eyes (37.69%) with CRVO and 162 (62.31%) with BRVO. The participants comprised 27 (10.38%) eyes with intraocular lenses and 233 (89.60%) with phakic lenses. The five groups were comparable in terms of age, sex, eye, type of RVO, high blood pressure, and phakic status. The characteristics of the five groups are presented in Table 1.

Table 1  
Demographic, clinical, and ocular characteristics of the patients

| Clinical category                                                                                                                                         | Total data      | Ranibizumab   | Ranibizumab 1 + DEX | Ranibizumab 2 + DEX | Ranibizumab 3 + DEX | DEX           | p-value |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------|---------------------|---------------------|---------------------|---------------|---------|
| Number                                                                                                                                                    | 260             | 52            | 52                  | 52                  | 52                  | 52            |         |
| Sex (M:F)                                                                                                                                                 | 132/128 (50.8%) | 28:24 (53.8%) | 23:29 (44.2%)       | 25:27 (48.1%)       | 27:25 (51.9%)       | 24:28 (46.2%) | 0.356   |
| Average age                                                                                                                                               | 66.2 ± 8.5      | 61.7 ± 13.6   | 60.8 ± 12.2         | 69.3 ± 5.2          | 65.3 ± 7.2          | 66.3 ± 8.2    | 0.573   |
| Eye (R:L)                                                                                                                                                 | 137/123         | 30/22         | 27/25               | 24/28               | 25/27               | 23/29         | 0.075   |
| CRVO                                                                                                                                                      | 98              | 20            | 22                  | 17                  | 21                  | 19            | 0.211   |
| BRVO                                                                                                                                                      | 162             | 32            | 30                  | 35                  | 31                  | 33            | 0.317   |
| HBP                                                                                                                                                       | 171 (65.7)      | 32 (61.5%)    | 35 (67.3%)          | 36 (69.2%)          | 33 (63.5%)          | 35 (67.3%)    | 0.251   |
| IOL                                                                                                                                                       | 27              | 6             | 5                   | 3                   | 7                   | 6             | 0.073   |
| Phakic                                                                                                                                                    | 233             | 46            | 47                  | 49                  | 45                  | 46            | 0.129   |
| M: male, F: female, R: right, L: left, CRVO: central retinal vein occlusion, BRVO: branch retinal vein occlusion, HBP: hypertension;IOL: Intraocular lens |                 |               |                     |                     |                     |               |         |

## Best-Corrected Visual Acuity

For 260 eyes, the mean BCVA was 53.4 ± 21.8 ETDRS letters at baseline and 69.7 ± 25.6 ETDRS letters at follow-up, and the mean improvement was 16.5 ± 7.9 ETDRS letters. Patients in Groups 1–5 at baseline reported mean BCVA of 53.4 ± 25.6 ETDRS letters, 52.8 ± 23.3 ETDRS letters, 53.1 ± 19.0 ETDRS letters, 52.7 ± 21.5 ETDRS letters, and 51.6 ± 22.7 ETDRS letters, respectively. There were no statistically significant differences in baseline BCVA among the five groups ( $p = 0.63$ ). The mean BCVA after the treatment of Groups 1–5 was 67.4 ± 26.7 ETDRS letters, 73.5 ± 30.0 ETDRS letters, 70.7 ± 33.5 ETDRS letters, 69.0 ± 22.3 ETDRS letters, and 63.1 ± 23.6 ETDRS letters, respectively. There was a statistically significant difference in BCVA among the five groups ( $p = 0.009$ ). The mean improvement was 14.2 ± 6.8 ETDRS letters, 20.9 ± 10.4 ETDRS letters, 17.8 ± 8.1 ETDRS letters, 16.3 ± 9.7 ETDRS letters, and 13.5 ± 7.3 ETDRS letters, respectively. Comparisons between groups indicated statistically significant differences between Group 2 and Groups 1, 4, and 5 (adjusted  $p = 0.024$ ,  $0.038$ , and  $0.011$ , respectively). The detailed BCVA results of the five groups are presented in Table 2. In patients with CRVO, there was a statistically significant difference in BCVA at 2, 3, 4, 5, 9, and 12 months between the five groups ( $p < 0.01$ ,  $p < 0.01$ ,  $p = 0.036$ ,  $p = 0.021$ ,  $p = 0.039$ , and  $p = 0.045$ , respectively). There was no statistically significant difference in BCVA at 6 months ( $p = 0.097$ ) (Fig. 2). In patients with BRVO, there was a statistically significant difference in BCVA at 2, 3, 4, 5, 6, 9, and 12 months between the five groups ( $p < 0.01$ ,  $p < 0.01$ ,  $p = 0.017$ ,  $p = 0.029$ ,  $p = 0.040$ ,  $p = 0.012$ ,  $p = 0.039$ ) (Fig. 3).

Table 2  
BCVA (ETDRS letters) of the five groups of patients

| BCVA<br>ETDRS<br>letters | Ranibizumab    |                | Ranibizumab 1 +<br>DEX |                | Ranibizumab 2 + DEX |                | Ranibizumab 3<br>+ DEX |                | DEX            |                |
|--------------------------|----------------|----------------|------------------------|----------------|---------------------|----------------|------------------------|----------------|----------------|----------------|
|                          | CRVO           | BRVO           | CRVO                   | BRVO           | CRVO                | BRVO           | CRVO                   | BRVO           | CRVO           | BRVO           |
|                          | n = 20         | n = 32         | n = 22                 | n = 30         | n = 17              | n = 35         | n = 21                 | n = 31         | n = 19         | n = 33         |
| Base<br>line             | 51.6<br>± 23.7 | 56.3<br>± 30.8 | 50.7 ± 19.3            | 55.3<br>± 25.8 | 51.9<br>± 17.0      | 54.1<br>± 22.6 | 49.9<br>± 19.6         | 54.4<br>± 25.1 | 48.7<br>± 17.8 | 53.7<br>± 25.1 |
| 1m                       | 60.9<br>± 20.2 | 65.2<br>± 22.6 | 61.2 ± 23.7            | 67.1<br>± 32.4 | 60.1<br>± 25.4      | 62.0<br>± 26.9 | 58.3<br>± 21.7         | 63.5<br>± 18.7 | 56.5<br>± 16.9 | 61.0<br>± 17.9 |
| 2m                       | 66.4<br>± 27.5 | 67.5<br>± 26.3 | 71.0 ± 31.6            | 74.3<br>± 36.6 | 69.7<br>± 27.3      | 70.8<br>± 33.1 | 64.5<br>± 23.0         | 68.4<br>± 23.5 | 60.3<br>± 20.7 | 64.4<br>± 23.5 |
| 3m                       | 68.5<br>± 33.6 | 69.0<br>± 15.4 | 72.3 ± 25.4            | 75.1<br>± 23.8 | 71.2<br>± 35.0      | 71.5<br>± 32.3 | 68.7<br>± 25.5         | 71.7<br>± 25.0 | 54.0<br>± 21.7 | 59.7<br>± 24.2 |
| 4m                       | 62.1<br>± 19.0 | 62.9<br>± 26.2 | 63.8 ± 22.1            | 68.0<br>± 30.4 | 73.3<br>± 31.5      | 75.3<br>± 30.4 | 70.2<br>± 29.1         | 73.3<br>± 22.6 | 56.3<br>± 23.1 | 60.9<br>± 22.3 |
| 5m                       | 67.3<br>± 31.1 | 67.1<br>± 23.6 | 64.3 ± 29.8            | 67.1<br>± 35.7 | 66.7<br>± 33.1      | 70.7<br>± 28.2 | 71.8<br>± 25.8         | 75.2<br>± 26.8 | 60.0<br>± 20.5 | 64.0<br>± 23.9 |
| 6m                       | 64.4<br>± 28.3 | 65.3<br>± 19.2 | 67.7 ± 22.5            | 70.4<br>± 33.3 | 66.0<br>± 27.3      | 69.3<br>± 23.9 | 66.3<br>± 21.0         | 72.4<br>± 31.2 | 56.4<br>± 24.8 | 60.1<br>± 18.5 |
| 9m                       | 66.7<br>± 33.2 | 70.2<br>± 32.6 | 70.1 ± 26.5            | 74.5<br>± 28.2 | 67.8<br>± 36.2      | 67.4<br>± 24.5 | 64.3<br>± 32.5         | 66.5<br>± 35.9 | 58.5<br>± 19.3 | 63.4<br>± 26.6 |
| 12m                      | 65.4<br>± 23.9 | 69.3<br>± 30.7 | 71.3 ± 31.8            | 75.1<br>± 32.6 | 69.5<br>± 38.6      | 71.3<br>± 31.6 | 66.6<br>± 26.2         | 69.5<br>± 23.6 | 60.9<br>± 21.0 | 66.5<br>± 25.7 |

The older (> 65 years) patients reported a mean BCVA of  $48.6 \pm 21.3$  ETDRS letters at baseline and  $57.7 \pm 21.1$  ETDRS letters at follow-up, with a statistically significant difference ( $p = 0.027$ ). The younger ( $\leq 65$  years) patients reported a mean BCVA of  $55.7 \pm 16.3$  ETDRS letters at baseline and  $71.5 \pm 23.0$  ETDRS letters at follow-up; the difference was statistically significant ( $p = 0.019$ ). There was no significant difference ( $p = 0.071$ ) in BCVA between older (> 65 years) and younger ( $\leq 65$  years) patients at baseline, and there was a significant difference ( $p = 0.037$ ) between the older (> 65 years) and younger ( $\leq 65$  years) patients at follow-up. There was no significant difference in BCVA at baseline ( $p = 0.61$ ) or follow-up ( $p = 0.54$ ) between patients with and without hypertension. Patients with hypertension had a BCVA of  $54.2 \pm 19.8$  ETDRS letters at baseline and  $69.1 \pm 20.6$  ETDRS letters at follow-up, whereas patients without hypertension had a BCVA of  $53.0 \pm 22.8$  ETDRS letters at baseline and  $68.3 \pm 19.0$  ETDRS letters at follow-up.

## Central Retinal Thickness

For 260 eyes, the mean central retinal thickness (CRT) was  $599.3 \pm 157.4$   $\mu\text{m}$  at baseline and  $272.9 \pm 91.5$   $\mu\text{m}$  at follow-up, and the mean CRT decrease was  $314.7 \pm 117.5$   $\mu\text{m}$ . Patients in Groups 1–5 at baseline reported a mean CRT of  $617.3 \pm 267.8$   $\mu\text{m}$ ,  $602.5 \pm 307.0$   $\mu\text{m}$ ,  $597.9 \pm 311.5$   $\mu\text{m}$ ,  $587.7 \pm 265.0$   $\mu\text{m}$ , and  $611.1 \pm 277.6$   $\mu\text{m}$ , respectively. There was no statistically significant difference in the mean CRT at baseline among the five groups ( $p = 0.63$ ). The mean CRT after treatment in Groups 1–5 was  $325.8 \pm 197.0$   $\mu\text{m}$ ,  $235.7 \pm 199.4$   $\mu\text{m}$ ,  $250.1 \pm 188.9$   $\mu\text{m}$ ,  $253.6 \pm 238.5$   $\mu\text{m}$ , and  $279.6 \pm 158.1$   $\mu\text{m}$ , respectively. There was a statistically significant difference in the mean CRT at follow-up among the five groups ( $p = 0.03$ ). A comparison between the groups indicated statistically significant differences between Group 2 and Groups 1, 4, and 5 (adjusted  $p = 0.012$ ,  $p = 0.029$ , and  $p = 0.033$ , respectively). The detailed CRT results for the five

groups are shown in Table 3. In patients with CRVO, there was a statistically significant difference in CRT at 2, 3, 4, 5, 6, 9, and 12 months between the five groups ( $p < 0.01$ ,  $p < 0.01$ ,  $p = 0.011$ ,  $p = 0.025$ ,  $p = 0.029$ ,  $p = 0.037$ , and  $p = 0.023$ , respectively) (Fig. 4). In patients with BRVO, there was a statistically significant difference in CRT decreases at 2, 3, 4, 5, 6, 9, and 12 months between the five groups ( $p < 0.01$ ,  $p < 0.01$ ,  $p < 0.01$ ,  $p = 0.020$ ,  $p = 0.031$ ,  $p = 0.039$ , and  $p = 0.043$ , respectively) (Fig. 5).

Table 3  
The CRT of the five groups of patients

| CRT<br>( $\mu\text{m}$ ) | Ranibizumab          | Ranibizumab 1 +<br>DEX  |                         | Ranibizumab 2 +<br>DEX  |                         | Ranibizumab 3 + DEX     |                         | DEX                     |                         |                         |
|--------------------------|----------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                          | CRVO                 | BRVO                    | CRVO                    | BRVO                    | CRVO                    | BRVO                    | CRVO                    | BRVO                    | CRVO                    | BRVO                    |
|                          | n = 20               | n = 32                  | n = 22                  | n = 30                  | n = 17                  | n = 35                  | n = 21                  | n = 31                  | n = 19                  | n = 33                  |
| Base<br>line             | 607.5 $\pm$<br>233.7 | 625.3<br>$\pm$<br>328.6 | 598.6<br>$\pm$<br>313.3 | 610.7<br>$\pm$<br>371.0 | 570.6<br>$\pm$<br>328.4 | 633.6<br>$\pm$<br>297.3 | 557.5<br>$\pm$<br>287.3 | 599.1<br>$\pm$<br>210.3 | 622.0<br>$\pm$<br>281.5 | 601.2<br>$\pm$<br>299.5 |
| 1m                       | 303.0 $\pm$ 93.4     | 330.6<br>$\pm$<br>122.7 | 289.0<br>$\pm$<br>118.8 | 300.5<br>$\pm$<br>129.8 | 328.5<br>$\pm$<br>129.5 | 320.9<br>$\pm$<br>169.0 | 320.7<br>$\pm$<br>187.0 | 329.9<br>$\pm$<br>177.0 | 312.4<br>$\pm$<br>136.8 | 340.0<br>$\pm$<br>167.5 |
| 2m                       | 333.8 $\pm$<br>136.3 | 309.0<br>$\pm$<br>145.3 | 227.1<br>$\pm$<br>193.6 | 250.5<br>$\pm$<br>201.2 | 308.9<br>$\pm$<br>219.3 | 290.3<br>$\pm$<br>233.9 | 311.3<br>$\pm$<br>199.6 | 313.6<br>$\pm$<br>178.2 | 272.9<br>$\pm$<br>133.3 | 259.3<br>$\pm$<br>151.7 |
| 3m                       | 349.2 $\pm$<br>204.5 | 355.4<br>$\pm$<br>233.8 | 240.9<br>$\pm$<br>201.3 | 255.3<br>$\pm$<br>182.2 | 275.3<br>$\pm$<br>182.1 | 291.0<br>$\pm$<br>155.5 | 355.1<br>$\pm$<br>222.9 | 334.0<br>$\pm$<br>252.5 | 278.8<br>$\pm$<br>127.9 | 269.6<br>$\pm$<br>189.2 |
| 4m                       | 379.6 $\pm$<br>321.1 | 400.7<br>$\pm$<br>297.2 | 252.5<br>$\pm$<br>166.7 | 244.0<br>$\pm$<br>130.9 | 221.7<br>$\pm$<br>233.5 | 199.2<br>$\pm$<br>179.8 | 310.5<br>$\pm$<br>159.6 | 300.9<br>$\pm$<br>211.7 | 331.2<br>$\pm$<br>155.0 | 337.8<br>$\pm$<br>307.0 |
| 5m                       | 369.9 $\pm$<br>222.5 | 381.0<br>$\pm$<br>266.2 | 217.3<br>$\pm$<br>238.5 | 208.7<br>$\pm$<br>199.9 | 289.8<br>$\pm$<br>175.4 | 277.3<br>$\pm$<br>188.0 | 253.7<br>$\pm$<br>140.9 | 231.4<br>$\pm$<br>200.9 | 270.4<br>$\pm$<br>191.9 | 244.6<br>$\pm$<br>229.3 |
| 6m                       | 401.5 $\pm$<br>244.3 | 394.9<br>$\pm$<br>215.3 | 300.8<br>$\pm$<br>144.0 | 302.8<br>$\pm$<br>248.1 | 300.9<br>$\pm$<br>244.3 | 301.6<br>$\pm$<br>202.5 | 281.3<br>$\pm$<br>188.0 | 266.5<br>$\pm$<br>187.9 | 301.3<br>$\pm$<br>207.0 | 317.6<br>$\pm$<br>205.7 |
| 9m                       | 349.0 $\pm$<br>298.6 | 343.9<br>$\pm$<br>266.5 | 287.1<br>$\pm$<br>138.9 | 299.0<br>$\pm$<br>185.6 | 270.7<br>$\pm$<br>292.0 | 289.0<br>$\pm$<br>261.7 | 258.6<br>$\pm$<br>164.0 | 279.2<br>$\pm$<br>152.0 | 283.6<br>$\pm$<br>223.5 | 296.0<br>$\pm$<br>192.3 |
| 12m                      | 336.7 $\pm$<br>199.5 | 321.5<br>$\pm$<br>233.9 | 229.3<br>$\pm$<br>149.7 | 239.7<br>$\pm$<br>201.1 | 250.5<br>$\pm$<br>243.1 | 249.4<br>$\pm$<br>252.9 | 256.5<br>$\pm$<br>267.6 | 251.6<br>$\pm$<br>231.7 | 279.2<br>$\pm$<br>179.8 | 281.5<br>$\pm$<br>155.6 |

The older ( $> 65$  years) patients reported a mean CRT of  $592.8 \pm 166.5 \mu\text{m}$  at baseline and  $293.9 \pm 102.5 \mu\text{m}$  at follow-up, with a statistically significant difference ( $p = 0.012$ ). The younger ( $\leq 65$  years) patients reported a mean CRT of  $607.2 \pm 216.6 \mu\text{m}$  at baseline and  $263 \pm 209 \mu\text{m}$  at follow-up, with a statistically significant difference ( $p = 0.019$ ). There was no significant difference ( $p = 0.095$ ) in CRT between older ( $> 65$  years) and younger ( $\leq 65$  years) patients at baseline, and there was a significant difference ( $p = 0.037$ ) between older ( $> 65$  years) and younger ( $\leq 65$  years) patients at follow-up. There was no significant difference in CRT at baseline ( $p = 0.721$ ) and follow-up ( $p = 0.665$ ) between patients with and without hypertension. Patients with hypertension had a CRT of  $603.9 \pm 187.1 \mu\text{m}$  at baseline

and  $281.3 \pm 190.5 \mu\text{m}$  at follow-up, whereas patients without hypertension reported a CRT of  $594.7 \pm 201.9 \mu\text{m}$  at baseline and  $267.3 \pm 159.0 \mu\text{m}$  at follow-up.

## Intravitreal Injections

During the 12-month follow-up, among patients with CRVO, the mean NOI was  $6.8 \pm 1.4$ ,  $3.1 \pm 1.5$ ,  $4.7 \pm 1.4$ ,  $5.6 \pm 1.6$ , and  $3.1 \pm 1.3$  in Groups 1–5, respectively. There were statistically significant differences among the five groups ( $p < 0.01$ ). For patients with BRVO, the mean NOI was  $6.3 \pm 1.6$ ,  $3.3 \pm 1.8$ ,  $4.5 \pm 1.6$ ,  $5.3 \pm 1.6$ , and  $3.4 \pm 1.6$  in Groups 1–5, respectively. There were statistically significant differences among the five groups ( $p < 0.01$ ). The detailed data for the five groups are presented in Table 4.

Table 4  
Intravitreal injections and adverse events of the patients

| adverse events                                       | Ranibizumab   |               | Ranibizumab 1 + DEX |               | Ranibizumab 2 + DEX |               | Ranibizumab 3 + DEX |               | DEX           |               |
|------------------------------------------------------|---------------|---------------|---------------------|---------------|---------------------|---------------|---------------------|---------------|---------------|---------------|
|                                                      | CRVO          | BRVO          | CRVO                | BRVO          | CRVO                | BRVO          | CRVO                | BRVO          | CRVO          | BRVO          |
|                                                      | n = 20        | n = 32        | n = 22              | n = 30        | n = 17              | n = 35        | n = 21              | n = 31        | n = 19        | n = 33        |
| NOI                                                  | $6.8 \pm 1.4$ | $6.3 \pm 1.6$ | $3.1 \pm 1.5$       | $3.3 \pm 1.8$ | $4.7 \pm 1.4$       | $4.5 \pm 1.6$ | $5.6 \pm 1.6$       | $5.3 \pm 1.6$ | $3.1 \pm 1.3$ | $3.4 \pm 1.6$ |
| IOP↑                                                 | 0             | 0             | 3<br>(13.6%)        | 4<br>(13.3%)  | 2<br>(11.8%)        | 4<br>(11.4%)  | 3<br>(14.3%)        | 5<br>(16.1%)  | 4<br>(21.1%)  | 6<br>(18.2%)  |
| Cataract                                             | 0             | 0             | 2<br>(10.0%)        | 3<br>(11.1%)  | 1<br>(6.2%)         | 3<br>(9.1%)   | 1<br>(5.3%)         | 2<br>(7.7%)   | 2<br>(11.8%)  | 4<br>(13.8%)  |
| NOI: number of injections, IOP: intraocular pressure |               |               |                     |               |                     |               |                     |               |               |               |

## Adverse Events

### IOP change

A significant increase in IOP was observed from 1 to 12 months post-injection ( $p < 0.01$ ) in the DEX group. The incidences of elevated IOP in Groups 1–5 were 0%, 13.5%, 11.5%, 15.4%, and 19.2%, respectively. There was a statistically significant difference in the incidence of elevated IOP among the five groups ( $p < 0.01$ ). The mean IOP reached its peak at 2 months post-injection, measuring  $24.1 \pm 8.7 \text{ mmHg}$ , with an increase of  $8.7 \pm 6.9 \text{ mmHg}$ . At the 12-month follow-up, there was no statistically significant difference in IOP compared with baseline ( $p > 0.05$ ). IOP remained stable in patients receiving ranibizumab. There were no statistically significant differences at any scheduled visit, and the mean change in IOP was less than 1 mm Hg. There was a statistically significant difference in IOP changes in the combined DEX treatment groups throughout the follow-up period. All patients with elevated IOP were successfully managed with a single application of topical IOP-lowering medication. The detailed data for the five groups are presented in Table 4.

### Cataract occurrence

However, the incidence of postoperative cataracts varied among the groups. There were no cases of postoperative cataracts in patients receiving ranibizumab, whereas cataracts occurred in patients receiving DEX. The incidence of cataracts in Groups 1–5 was 0%, 10.64% (5/47 eyes), 8.16% (4/49 eyes), 6.67% (3/45 eyes), and 13.0% (6/46 eyes),

respectively. There was a statistically significant difference in the incidence of cataracts among the five groups ( $p < 0.01$ ). The detailed data for the five groups are presented in Table 4.

## Discussion

RVO-ME has diverse pathological mechanisms that involve increased vascular permeability, neovascular leakage, and chronic inflammation<sup>[4]</sup>. The European Society of Retina Specialists<sup>[10]</sup> recommends anti-VEGF therapy as first-line treatment for RVO-ME. However, suboptimal visual and anatomical outcomes may be observed in some patients and may persist despite anti-VEGF therapy<sup>[11]</sup>. Recent studies have shown that inflammatory factors play an important role in the pathogenesis of RVO-ME<sup>[12]</sup>. Therefore, inhibition of the inflammatory response is an important component of RVO-ME management. Corticosteroids exert strong anti-inflammatory effects. DEX is the only corticosteroid approved for the treatment of RVO-ME by drug regulatory authorities in the United States and the European Union. The GENEVA study demonstrated that Ozurdex significantly improves visual function and anatomical outcomes in patients with RVO-ME<sup>[13]</sup>. DEX is a sustained-release system that allows continuous delivery of therapeutic concentrations of dexamethasone in the vitreous cavity. Therefore, it may offer advantages over anti-VEGF drugs by prolonging the retreatment interval. Its clinical efficacy is comparable to that of anti-VEGF agents<sup>[13]</sup>. However, the optimal timing for initiating DEX to maximize visual improvement, has not been clearly established. The present study demonstrated that successive injections of ranibizumab and DEX implants in the first month improved the vision of patients with RVO-ME. However, DEX may cause adverse effects including elevated IOP and cataract formation.

Previous research by Harb et al<sup>[14]</sup> evaluated the efficacy of combination therapy with intravitreal aflibercept and DEX implant 2 weeks later versus DEX alone and found that aflibercept with a DEX implant achieved better visual outcomes than DEX alone. However, RVO typing was not performed in this study. Patients with CRVO are more likely to have extensive ischemia, and their natural history is poorer than that of patients with BRVO<sup>[15]</sup>. Therefore, it is necessary to investigate RVO types in studies involving intravitreal injection. In our study, RVO was analyzed by classifying CRVO and BRVO at different time points in combination with DEX treatment.

In this study, we compared the efficacy of intravitreal DEX implants with that of intravitreal ranibizumab for the treatment of ME secondary to RVO. In both patients with CRVO and BRVO, BCVA improved within 1 month after IVI R, IVI R + DEX, and IVI DEX treatment. Therefore, both anti-VEGF agents and DEX act rapidly and IVI R can rapidly improve BCVA. This finding is consistent with previous studies on intraocular injections of RVO-ME<sup>[16, 17]</sup>. We found significant improvement in visual acuity and decreased CRT at each scheduled visit in the five groups compared with baseline, indicating that patients treated with ranibizumab or DEX had vision benefits. In patients with CRVO, there was a statistically significant difference in BCVA between the groups at 2, 3, 4, 5, 9, and 12 months. There was no statistically significant difference in BCVA at 6 months. In patients with BRVO, there was a statistically significant difference in BCVA at 3, 4, 5, 6, 9, and 12 months among the five groups. There was a statistically significant difference CRT reduction at 3, 4, 5, 6, 9, and 12 months between the groups. At 6 months, in the CRVO group, we observed no statistically significant difference in visual acuity between the groups, although there was a difference in CRT reduction. This finding is consistent with clinical observations that macular edema may decrease, but visual acuity may not show obvious improvement after combined dexamethasone treatment in later stages. Post-injection combined treatment with DEX following ranibizumab improved visual acuity and reduced CRT. In our study, in the second month of combined treatment, there was a statistically significant difference in visual acuity improvement and reduced CRT. The difference became more pronounced between the groups at 2 months post-injection with the combined treatment, indicating that DEX following ranibizumab performed better in improving visual acuity and reducing CRT at this time point. The analysis suggested that combined treatment targeting inflammatory factors and VEGF plays a synergistic role in interrupting the pathological cycle of RVO-ME. Two months after treatment, maximum

visual function and anatomical benefits were observed, which is consistent with the pharmacokinetic profile of DEX. This is consistent with data from Menke et al<sup>[18]</sup> data, which showed that CRT remained greater than 300  $\mu$ m in 30% of patients 1 month after anti-VEGF treatment, suggesting that anti-inflammatory hormone therapy for RVO-ME is important. A comparison between groups indicated statistically significant differences between Group 2 and Groups 1, 4, and 5. This indicates that, compared with monotherapy with ranibizumab, monotherapy with DEX, and treatment with two doses of ranibizumab followed by combination therapy results in greater visual benefit. The proposed strategy of combining DEX with ranibizumab as the initial treatment for RVO-ME aims to leverage the advantages of DEX's long half-life and the rapid onset of action of ranibizumab<sup>[19]</sup> to compensate for the pharmacokinetic limitations of each drug when used alone. However, the mechanisms of action of anti-VEGF agents and corticosteroids in treating RVO-ME are different<sup>[12, 13]</sup>, and their combined use can more comprehensively target pathogenic factors and improve ME through multiple pathways. Moreover, drug tolerance should also be considered. Given the limitations of single-drug treatments, combined therapies have potential clinical value. Currently, there are several studies on combined drug therapy for RVO-ME; however, drug regimens vary. The main difference lies in the interval between administration of the two drugs. In the study by Maturi et al<sup>[20]</sup>, the interval between bevacizumab and DEX injections was one week, whereas in the study by Singer et al<sup>[21]</sup>, the interval between anti-VEGF agents and DEX administration was two weeks. These studies suggest that the combined strategy can provide significant visual and anatomical benefits and are consistent with the findings of our study.

As predicted, a significant between-group difference was observed in the number of injections administered. Patients received  $6.8 \pm 1.4$ ,  $3.1 \pm 1.5$ ,  $4.7 \pm 1.4$ ,  $5.6 \pm 1.6$ , and  $3.1 \pm 1.3$  injections in the five CRVO groups. For the patients with BRVO, the mean NOI was  $6.3 \pm 1.6$ ,  $3.3 \pm 1.8$ ,  $4.5 \pm 1.6$ ,  $5.3 \pm 1.6$ , and  $3.4 \pm 1.6$  in Groups 1–5, respectively. Our results show that DEX provided a longer therapeutic duration. Moreover, DEX therapy reduces the burden of intensive injection regimens, frequent hospital visits, and examination costs for patients<sup>[22]</sup>. Meanwhile, fewer injections may reduce the incidence of adverse events associated with the IV procedure, such as endophthalmitis, and lessen the financial burden on patients. This finding is consistent with previous research<sup>[16, 17]</sup>.

In terms of safety, DEX may increase IOP and the risk of cataract formation<sup>[23]</sup>. In the present study, increases in IOP were observed in the DEX group after treatment. This finding is consistent with previous studies<sup>[16, 17]</sup>. A significant increase in IOP from 1 to 12 months post-injection ( $p < 0.01$ ) was observed in the DEX group. The mean IOP peaked at 2 months post-injection ( $24.1 \pm 8.7$  mm Hg), with an elevation of  $8.7 \pm 6.9$  mm Hg. At the 12-month follow-up, IOP was not significantly different from baseline ( $p > 0.05$ ). IOP remained stable in patients receiving ranibizumab. After DEX treatment, the increase in IOP was mainly due to the corticosteroid-induced changes in the extracellular matrix of trabecular meshwork cells, resulting in reduced aqueous humor outflow<sup>[24]</sup>. Although it can be controlled with local IOP-lowering drugs, IOP remains an important focus of clinical attention, and regular follow-up should be conducted after treatment. In addition, because DEX reaches its peak concentration approximately 2 months after injection, special attention should be paid to changes in patients' IOP. The GENEVA trial<sup>[25]</sup>, consisting of two identical multicenter prospective studies, reported that over 12 months, DEX intravitreal implants caused cataract progression in 29.8% of patients with macular edema related to branch or central retinal vein occlusion. However, 6.67%–13.0% of eyes in the four DEX groups developed cataracts after treatment. This rate is lower than that reported in previous studies<sup>[25]</sup> and may be related to the short observation period and relatively small sample size in our study.

The limitations of this study include a small sample size, short follow-up time, and a single observation index. These results should be verified by clinical studies with larger sample sizes, long cycles consistent with the course of RVO-ME, and multiple observational indicators, including the ischemia index and inner retinal structural disorders.

## Conclusions

In patients with RVO-ME, IVI DEX or ranibizumab resulted in significant visual improvement. Moreover, early use of ranibizumab combined with DEX yielded better results in improving vision and reducing ME. Additional benefits of DEX include fewer injections and prolonged therapeutic effect. It can also increase intraocular pressure and the risk of cataract development. However, ranibizumab is associated with fewer adverse effects. Future studies should determine the optimal timing for reinjection, and further research is needed to compare these two treatments over longer follow-up periods.

## Declarations

### **Ethics approval and consent to participate:**

This double-blind, randomized, comparative study was approved by the Ethics Committee of the Qingdao Eye Hospital of Shandong First Medical University and registered in the Chinese Clinical Trial Registry (ChiCTR2100042682). Written informed consent was obtained from each participant prior to enrollment in accordance with the principles of the Declaration of Helsinki.

### **Consent for publication:**

Not applicable.

## Competing interests:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Funding:

This study was supported by the Natural Science Foundation of Shandong Province (ZK2022MH277) and Shandong Province Medicine and Health Science and Technology Development Plan Project (202207020714).

## Author Contribution

YQ performed data collection, data organization, figure generation, and drafted the original manuscript. YRW conducted data collection and organization. XIX, KkZ and HYY were responsible for data collection and verification. XBM conceived the study and revised the manuscript. All authors reviewed the manuscript.

## Acknowledgement

Xiujing Shi

## Data Availability

All data supporting the findings of this study are available within the paper Information.

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## Figures

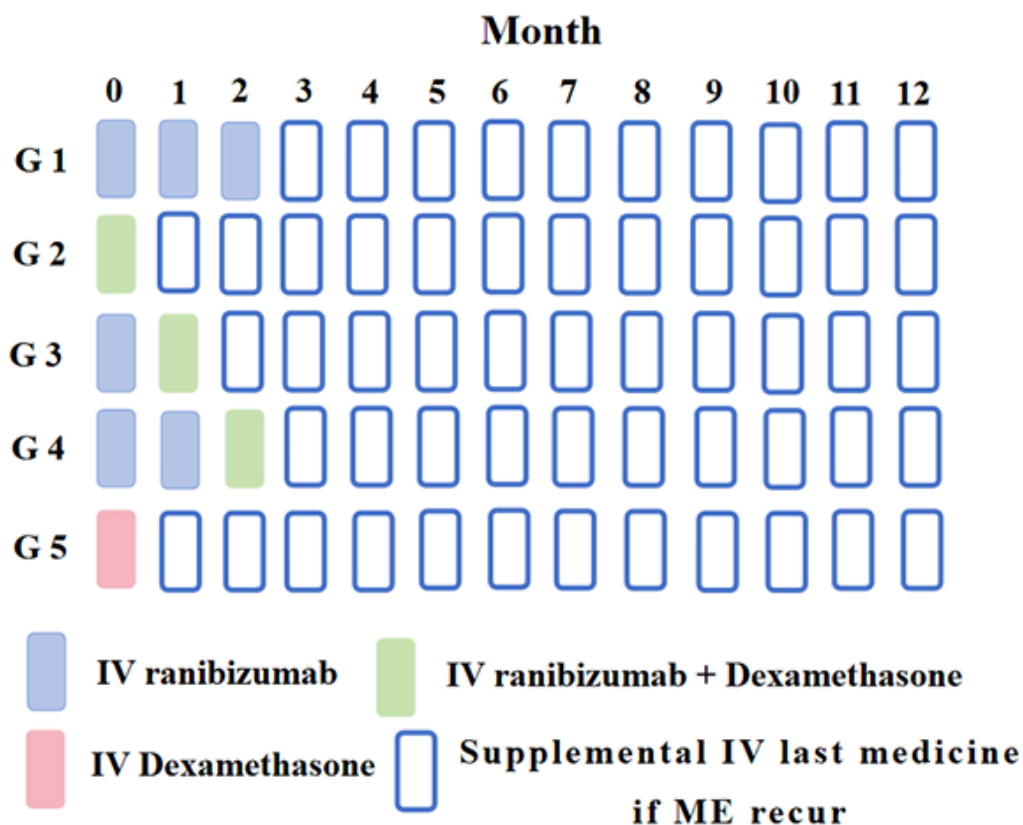


Figure 1

The "lane diagram" to list in detail the treatment methods.

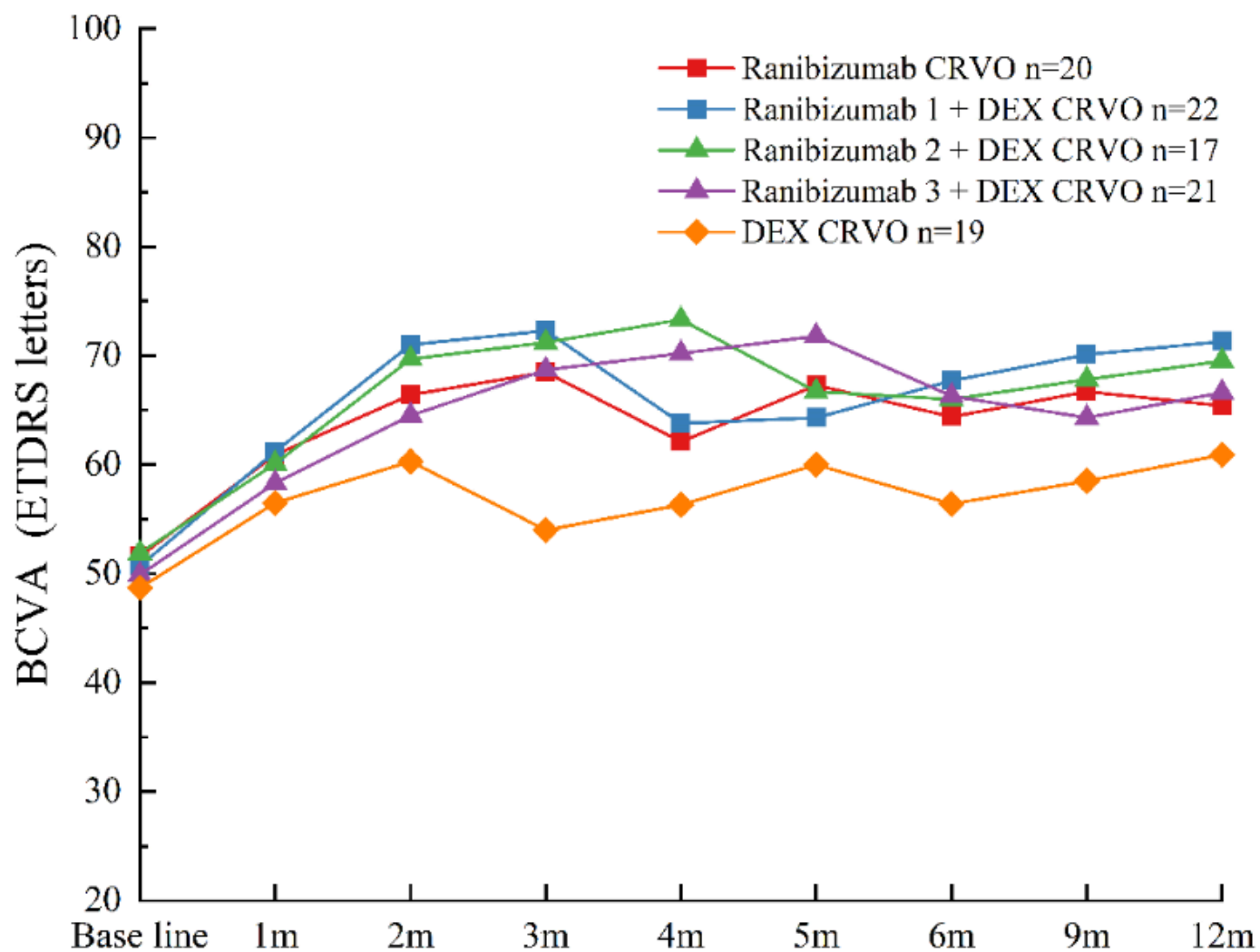


**Figure 2**

Mean BCVA improvement over time compared to baseline: 12-month follow-up in five treatment groups after initial therapy in patients with CRVO.

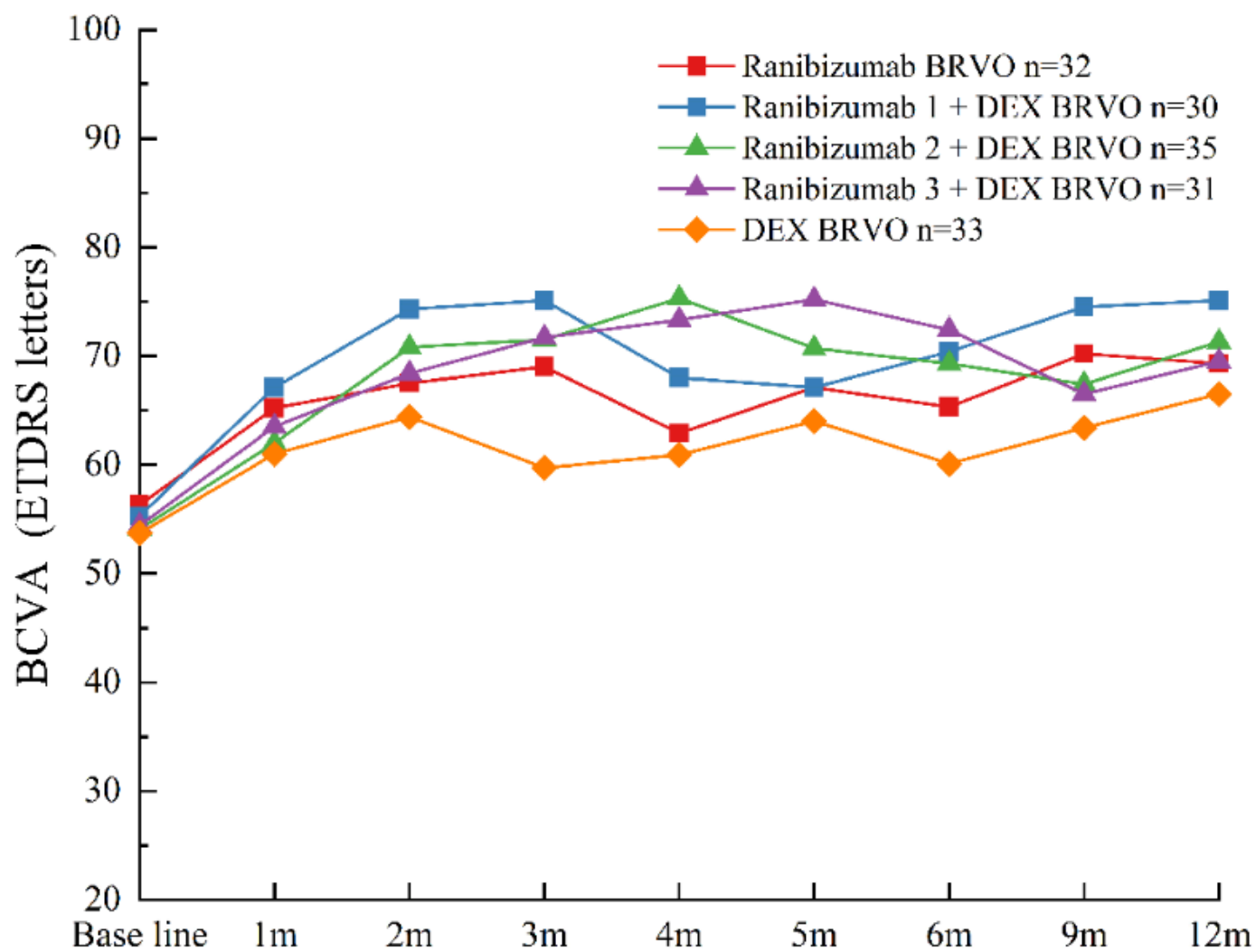


**Figure 3**

Mean BCVA improvement over time compared to baseline: 12-month follow-up in five treatment groups after initial therapy in patients with BRVO.

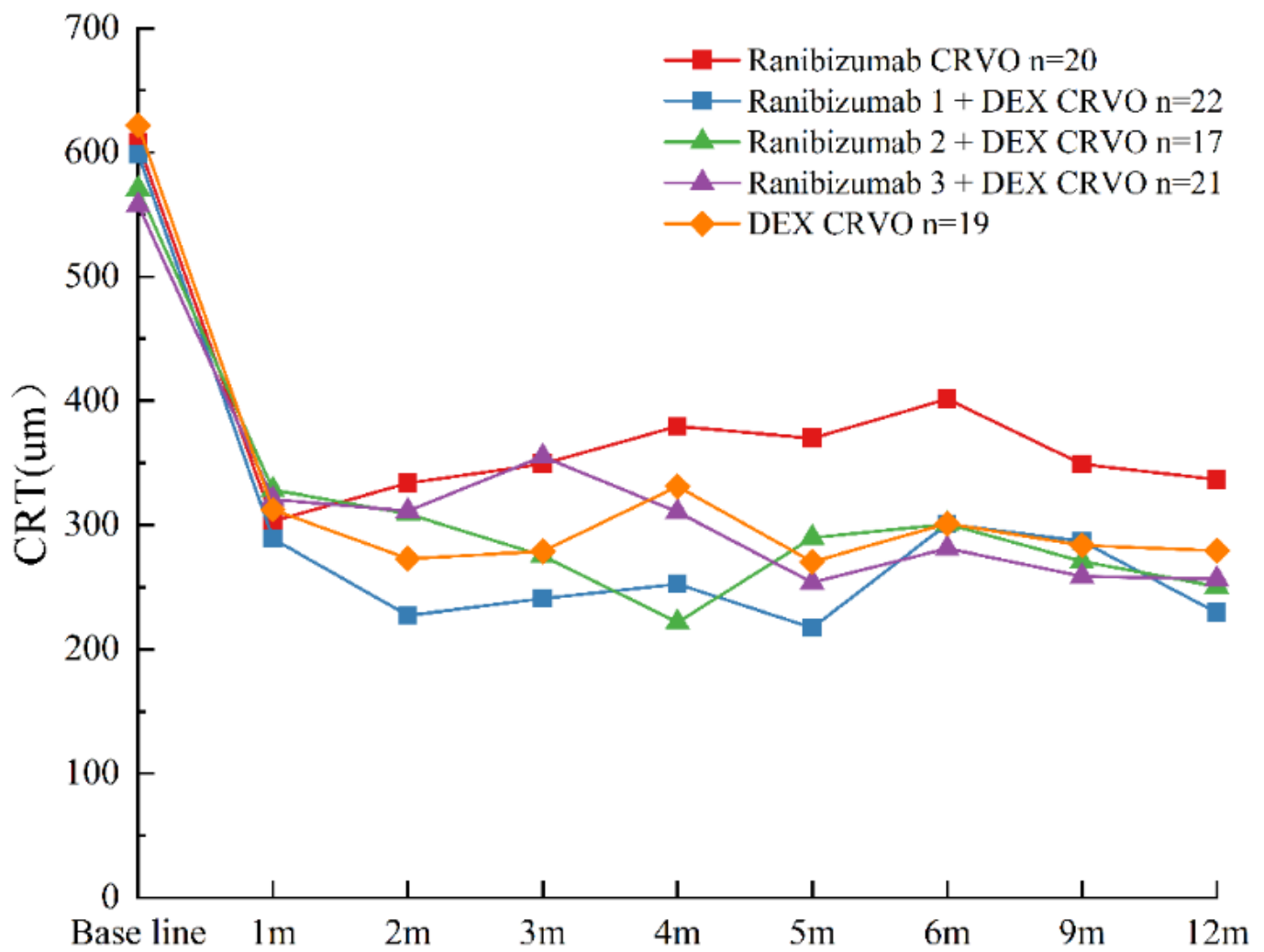


**Figure 4**

The CRT over time compared to baseline: 12-month follow-up in five treatment groups after initial therapy in patients with CRVO.

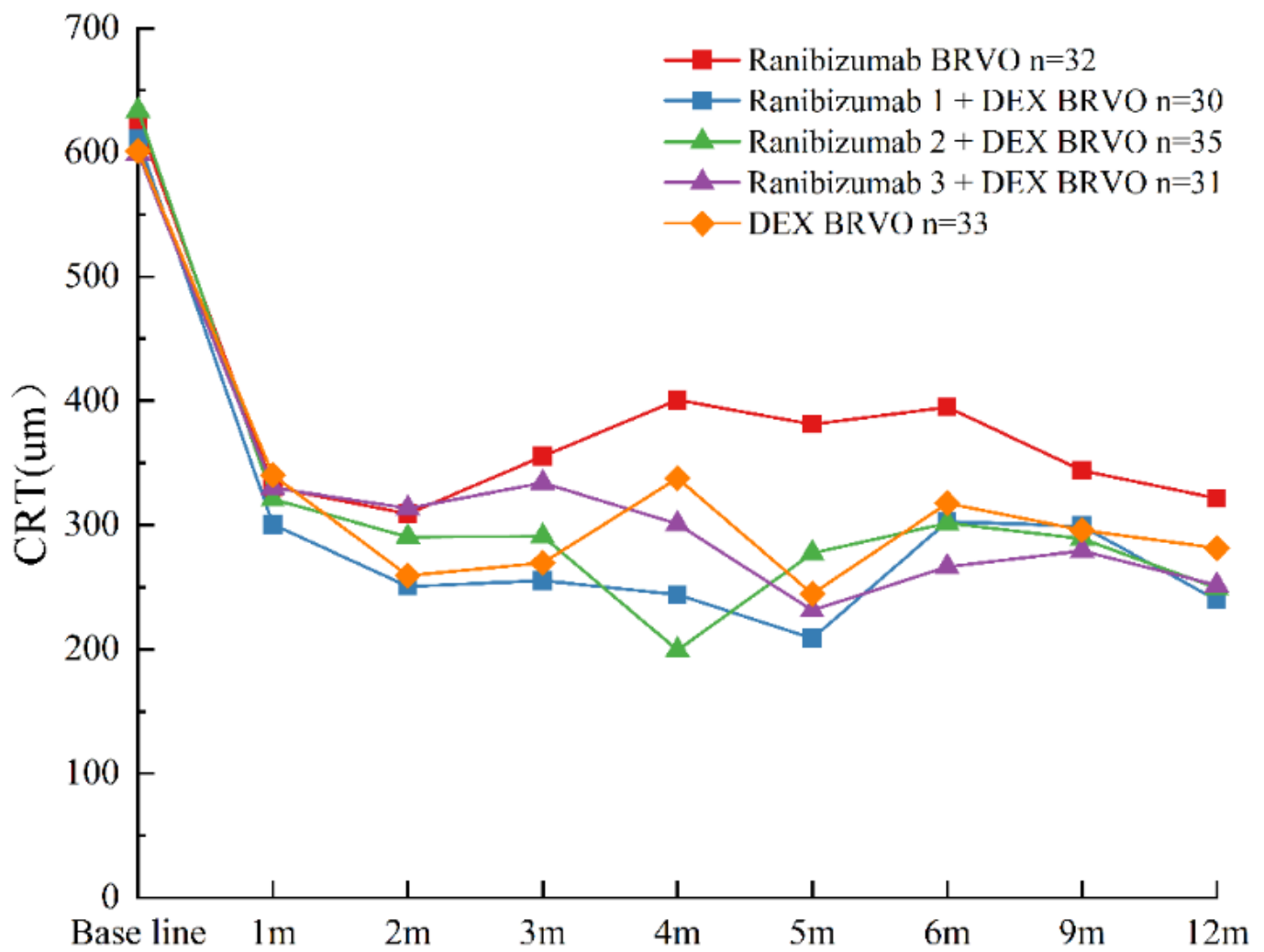


**Figure 5**

The CRT over time compared to baseline: 12-month follow-up in five treatment groups after initial therapy in patients with BRVO.