DOI:10.14744/bej.2023.42243
Beyoglu Eye J 2023; 8(1): 21-25

Original Article

Comparison of Intravitreal Dexamethasone Implant and Intravitreal Ranibizumab Efficacy in Younger Patients with Branch Retinal Vein Occlusion

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Abstract

Objectives: This study aimed to compare the effects of dexamethasone (DEX) implants and ranibizumab (RAN) injections in younger patients with macular edema due to branch retinal vein occlusion (RVO) in a 6-month follow-up.

Methods: The treatment-naive patients with macular edema secondary to branch RVO were included retrospectively. Medical records of patients who were treated with intravitreal RAN or DEX implant were evaluated before and at the 1st, 3rd, and 6th months after the injection. Primary outcome measures were the change in best-corrected visual acuity (BCVA) and central retinal thickness. The level of statistical significance was set at 0.05/3=0.016, according to the Bonferroni correction.

Results: Thirty-nine eyes of 39 patients were included in the study. The mean age of the study population was 53.82±5.08 years. Median BCVA in the DEX group (n=23) at baseline, 1st, 3rd, and 6th month was 1.1, 0.80 (p=0.002), 0.70 (p=0.003), and 1 (p=0.018) logarithm of the minimum angle of resolution (log-MAR), respectively (p<0.05). Median BCVA in the RAN group (n=16) at baseline, 1st, 3rd, and 6th months was 0.90, 0.61, 0.52, and 0.46 logMAR, respectively (p<0.016 for all comparisons). Median central macular thickness (CMT) in the DEX group at baseline, 1st, 3rd, and 6th months was 515, 260, 248, and 367 µm, respectively (p<0.016 for all comparisons). Median CMT in the RAN group at baseline, 1st, 3rd, and 6th months was 432.5 (p<0.016), 275 (p<0.016), 246 (p<0.016), and 338 (p=0.148) µm.

Conclusion: There is no significant difference in treatment efficacies in both visual and anatomical outcomes at the end of the 6th month. However, RAN can be considered the first choice in younger patients with macular edema secondary to branch RVO because of the lower side effect profile.

Keywords: Branch retinal vein occlusion, dexamethasone implant, macular edema, ranibizumab

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease that causes visual loss after diabetic retinopathy (1). It is known that increased hypoxia-induced vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines in branch RVO (BRVO) induce vascular permeability and macular edema (2). Macular edema is the most common cause of low vision in BRVO. Untreated macular edema causes irreversible structural changes in the macula and, as a result, permanent visual loss (3). The main purpose of the treatment in macular edema due to BRVO is to reduce the duration of edema, prevent neovascularization, and minimize photoreceptor damage (4). The effectiveness of laser photocoagulation, anti-VEGF therapy (ranibizumab [RAN], aflibercept, and bevacizumab), and corticosteroids (triamcinolone and dexamethasone [DEX]) have been shown in several studies in reducing BRVO-related edema (5).

How to cite this article: Gurakar Ozcift S, Aydin E, Egrilmez ED, Koc F, Eris E. Comparison of Intravitreal Dexamethasone Implant and Intravitreal Ranibizumab Efficacy in Younger Patients with Branch Retinal Vein Occlusion. Beyoglu Eye J 2023; 8(1): 21-25.

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Submitted Date: August 07, 2022 **Revised Date:** December 26, 2022 **Accepted Date:** January 06, 2023 **Available Online Date:** March 01, 2023

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

Although BRVO has seen frequently in patients over 60 years of age, it is a vascular pathology that can be seen at early ages and threatens vision (6). However, there are many studies on RVO in the literature, there are not enough studies on the group of age ≤60 years, considered as a low-risk group. Therefore, we aimed to compare the effects of DEX implants and RAN injections on the best-corrected visual acuity (BCVA) and central macular thickness (CMT) in treatment-naive younger patients with macular edema due to BRVO in a 6-month follow-up.

Methods

In this study, the medical records of patients with intravitreal injection treatment who were followed up with the diagnosis of macular edema due to BRVO were evaluated retrospectively. The study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee at Izmir Katip Celebi University (2021-KAEK-40). Informed consent was obtained from all patients.

Intravitreal injections were applied in Izmir Katip Celebi University Atatürk Training and Research Hospital, Ophthalmology Clinic between 2012 and 2016. BRVO diagnoses were confirmed with fundus examination, optical coherence tomography (OCT) (Cirrus HD OCT 4000, software version 6.5.0.; Carl Zeiss Meditec, Inc. Dublin, CA, USA), and fundus fluorescein angiography (FFA). Patients with macular edema due to BRVO in the biomicroscopic (slit-lamp) examination and CMT >250 μm in OCT analysis, and without neovascularization or ischemia in FFA were included in the study.

Patients were excluded if they had panretinal or macular laser, intraocular surgery in the past 3 months, YAG capsulotomy in the past 1 month, an active or previous infection affecting vision, active retinal neovascularization, glaucoma, uncontrolled hypertension, and history of cerebro-vascular disease. Furthermore, patients over the age of 60 were excluded from the study. The patients who will get intravitreal injections were informed about the macular edema due to branch vein occlusion and the possible course of the disease. The patients were informed about the administration of intravitreal injections, the expected effect, and possible complications. The patients were divided into two groups according to the treatment agent: the DEX (n=23) group and the RAN (n=16) group. A single DEX intravitreal implant or anti-VEGF injections (following a pro re nata (PRN) regimen) were performed with monthly monitoring.

The systemic and ophthalmic histories of all patients were recorded before the injection. Detailed ophthalmic examinations of the patients were performed before and at the 1st, 3rd, and 6th months after the injection. The BCVA using the Snellen chart, anterior segment, and fundus examinations with slit-lamp biomicroscopy, intraocular pressures (IOP) with Goldmann applanation tonometer, and OCT scan were recorded at each visit.

BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR) unit to make a statistical evaluation. Topical antiglaucoma treatment was started in patients with IOP above 21 mmHg.

Injection Technique

All injections were performed in the operating room. The standard injection technique applied to all patients is as follows: Eyelids and around the eyes were wiped with a 10% sterile gauze pad impregnated with povidone-iodine. Proparacaine hydrochloride (Alcaine) was dropped for topical anesthesia. After placing the sterile eyelid retractor, 5% povidone-iodine was added to the eye surface and left for 3 min and then washed with a sterile isotonic solution. Four mm from the limbus in phakic eyes and 3.5 mm from the limbus in pseudophakic eyes were marked with compasses. Superotemporal quadrant was tried to be preferred as the entry point. 0.1 mL (0.5 mg) RAN was injected from the point determined by the compass with the 30 gauge needle toward the center of the vitreous cavity. The same procedure was followed in the DEX group, but additionally, subconjunctival anesthesia was applied and the DEX implant was injected into the vitreous with a 22 gauge applicator.

A short-term gentle pressure was applied to the injection site with a cotton-tipped applicator immediately after the injection to prevent the drug or vitreous from leaking back and bleeding from the conjunctiva. The tone of the eye was controlled digitally. Whether there was a sense of light was questioned. Antibiotic drops were given to all patients for one week and they were warned to apply to the emergency department if they have complaints such as sudden vision decrease, pain, and redness. Patients were called for control the next day and examined for infection and sudden IOP increase.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Windows (version 17.0; SPSS Inc., Chi-cago, IL, USA) package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where necessary). Chi-square test or Fisher test statistic was used to compare categorical variables. For the longitudinal comparisons regarding BCVA and CMT between baseline and each time point, the Wilcoxon matched-pairs signed-ranks test was used; given that three comparisons (baseline versus each month) were done, the level of statistical significance was set at 0.05/3=0.016, according to the Bonferroni correction. $P<0.05$ was considered as significant, apart from cases where the Bonferroni correction was adopted, as declared above.

Results

Thirty-nine eyes of 39 BRVO patients were included in the study. A total of 23 eyes (59 %) were treated with DEX whereas 16 eyes (41%) had RAN injection. The mean age

of patients in the DEX group was 54.26±5.05 (median 56) (min-max: 41–60) years and in the RAN group 53.19±5.23 (median 54.5) (min-max: 40–59) years (p=0.524). The demographic and clinical characteristics of the two groups are summarized in Table 1.

At baseline, the median BCVA was 1.1 (0.52–3.10) LogMAR in the DEX group and 0.90 (0.15–3.10) LogMAR in the RAN group (p=0.191). Figure 1 shows the median BCVA evolution over time in each group. In the DEX group, the median BCVA was significantly improved at month 1 (p=0.002) and month 3 (p=0.003) compared to baseline, while there was no significant difference at month 6 (p=0.018) in BCVA in comparison with baseline. The median BCVA showed significant improvement at all time points of examination compared to baseline in the RAN group (p<0.016 for all comparisons). There was no statistically significant difference in BCVA change between the two groups at month 6 (p=0.807).

At baseline, the median CMT was 515.00 (318–770) µm in the DEX group and 432.5 (268–845) µm in the RAN group (p=0.199). Figure 2 shows the median CMT in each group over time. The median CMT showed significant reduction from baseline at all time points of examination in the DEX group (p<0.016 regarding all comparisons). In the RAN group, the median CMT showed significant reduction from baseline at all time points of examination, except month 6 (p=0.148). The median change in CMT was −145 µm in the DEX group and −80 µm in the RAN group at month 6 and there was no statistically significant difference between the two groups (p=0.33).

At baseline the median IOP was 14 (9–20) mmHg in the DEX group and 13 (8–20) in the RAN group (p=0.518). Figure 3 shows the median IOP alteration in each group over

Table 1. Baseline study population characteristics

	DEX (n=23)	RAN (n=16)	p*
Mean age±SD (years)	54.26±5.05	53.19±5.23	0.524
Sex (female/male)	10/13	5/11	0.44
Hypertension (%)	73.9	56.3	0.25
Diabetes Mellitus (%)	52.2	37.5	0.366
Lens Status (phakic/pseudophakic)	3/20	4/12	0.34
Baseline BCVA (logMAR) (median)	1.1	0.9	0.191
Baseline CMT (µm) (median)	515.0	432.5	0.199
Baseline IOP (mmHg) (median)	14	13	0.518

DEX: Dexamethasone, RAN: Ranibizumab, BCVA: best-corrected visual acuity, logMAR: logarithm of the minimum angle of resolution, CMT: central macular thickness, IOP: intraocular pressure.

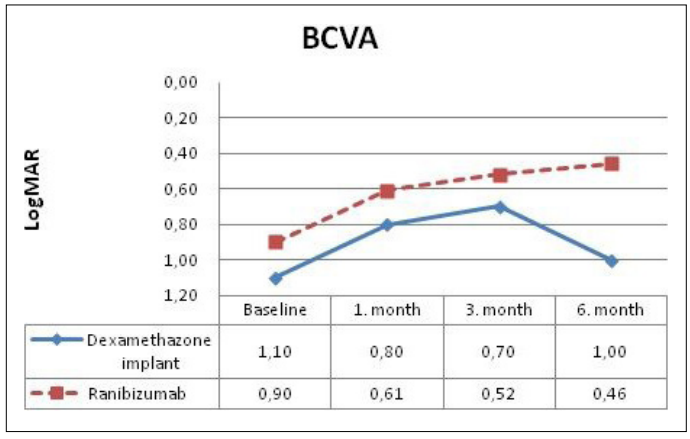

Figure 1. The changes in median best-corrected visual acuity (BCVA) in the dexamethasone implant and ranibizumab groups. The graph shows the median logarithm of the logMAR BCVA levels from baseline to month 6.

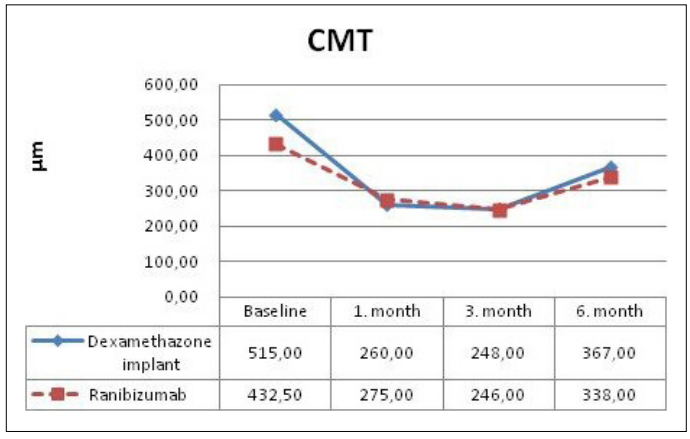

Figure 2. The changes in median central macular thickness (CMT) in the dexamethasone implant and ranibizumab groups. The graph shows the median CMT from baseline to month 6.

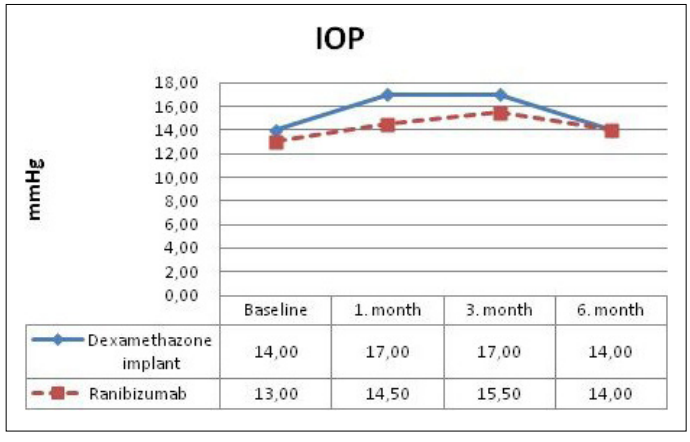

Figure 3. The changes in median intraocular pressure (IOP) in the dexamethasone implant and ranibi-zumab groups. The graph shows the median IOP from baseline to month 6.

time. There was no statistically significant difference in IOP change between the two groups at month 6 (p=0.430). The median IOP showed significant increase from baseline at all time points of examination in the DEX group except month 6 (p=0.411). In the RAN group, there was no statistically significant increase in the median IOP from baseline at all time points of examination (p>0.016 regarding all comparisons).

No serious ocular or systemic complications were reported in any of the patients in both group in the study. Three patients in the DEX group (13%) developed high IOP (>30 mmHg) at month 1, 3 patient (13%) at month 3 and were treated successfully with anti-glaucomatous drops. None of the patients required surgery. No injection related endophthalmitis, vitreous hemorrhage, retinal tear, retinal detachment, or thromboembolic events was noted. None of the patients required cataract surgery during the follow-up period.

Discussion

In our study, we compared the 6-month efficacy of DEX and RAN in patients with BRVO-related macular edema in a younger population under 60 years of age. Significant improvements were found in both the DEX-treated group and the RAN-treated group in BCVA and CMT compared to baseline. There was no statistically significant difference in BCVA changes between the two groups. However, in the DEX group compared to the RAN group, BCVA improved more in the 1st month, but this improvement could not be maintained after the 3rd month.

Intravitreal therapies including anti-VEGF agents and steroids are still used in the treatment of macular edema due to RVO (5). Although there are many studies in the literature comparing this treatment efficacy, the study evaluating the treatment results in the younger population under 60 years old, which is considered as a low-risk group, is not available to our knowledge.

According to the results of the BVOS study, focal-grid laser photocoagulation had been used as a standard in the treatment of BRVO-related macular edema for many years. However, the increase in visual acuity was limited (7). In the literature, there is no definite consensus about the intravitreal agent to be used in the treatment of BRVO (6). The effectiveness of RAN, an anti-VEGF agent in the treatment of macular edema due to RVO, has been shown in several studies. Patients who received 0.3 and 0.5 mg RAN injection were compared with the control group in the BRAVO (BRVO) and the CRUISE (Central RVO) studies. Groups with intravitreal RAN showed a significant increase in visual acuity and significant thinning in CMT after 6 months (8,9). Most of the patients in these studies are over 60 years old. In our study, especially varying from these studies, we examine a different group under the age of 60 and evaluate the responses of this group to the treatment. Although the visual prognosis is considered to be better in younger patients, studies have shown that serious vision loss or destructive complications (macular atrophy, neovascular glaucoma, etc.) may develop in young people (10-14). In our study, visual acuity started to increase from the 1st month after intravitreal RAN treatment and this increase continued until the 6th month. The maximal decrease in CMT was observed in the 1st month. However, CMT increased again at the 6th month after injection. The CMT at the 6th month appears to be higher compared to the 3rd month, but still lower, although not statistically significant compared to pre-injection. Although RAN injection is an effective treatment, it requires quite well patient compliance due to the high number of injections and requiring monthly follow-up. For this reason, intravitreal steroids, which are thought to be longer acting, can be preferred primarily in elderly aged group patients with low compliance. In the GENEVA study, patients with macular edema due to RVO were treated with intravitreal DEX injection at 6-month intervals. Haller et al. observed significant improvement in BCVA and CMT in the group treated with DEX implant compared to the sham group, but it was reported to be effective until the 6th month (15). In our study group, this effect of DEX implant decreased in the 3rd month. The maximal decrease in CMT due to DEX was observed in the 1st month. The CMT increased again after the 3rd month. This may be due to a decrease in the vitreous level of DEX.

The common complication after intravitreal DEX implant administration is increased IOP (16). In patients treated with implants containing 0.35 mg and 0.7 mg DEX, 3.9% and 4% increase in IOP have been reported, respectively (15). This result suggests that DEX administered at a higher dose does not increase the risk of increased IOP. In another study, a 9% increase in IOP was reported, which was all controlled by medical treatment (17). In the COMRADE study, although IOP values remained at about 15 mmHg with RAN, it increased to approximately 20 mmHg at the 1st and 2nd months with DEX, and returned to the baseline from the 4th month and stabilized there (p<0.0001) (18). Similarly, in the younger population in our study, IOP in the RAN group remains at approximately 15 mmHg during the follow-up; however, IOP in the DEX group rises to approximately 17 mmHg in the 3rd month and returns to baseline levels at the 6th month.

Cataract development, another complication of steroid injection, was reported in the GENEVA study as 7.3% in the 0.7 mg DEX group, 4.1% in the 0.35 mg DEX group and 4.5% in the control group (15). In our study, cataract development was not observed. This may be related to the short follow-up period of our study, the younger patient population, and the need for a longer period for the development of cataract. In the MEAD study, cataract related to a single injection did not develop, and 70% of cataracts developed after four injections

(19). Similarly, in another study, Eris et al. (20) reported that during the 6 months of follow-up after a single dose of DEX for the treatment of BRVO, no patient developed cataract. The reason for the absence of cataract in our study may be that a single DEX implant was applied. The small number of patients, the retrospective design, and the limited follow-up period are the main limitations of our study. On the other hand, the study was performed in the age group considered as the younger population, which has not been studied before.

Conclusion

A repeated DEX injections are more likely to be performed since the effect of the DEX implant decreased in the 3rd month in the younger age group. In this case, it increases the risks of diseases such as cataracts and glaucoma. Since there is no significant difference in treatment efficacies, RAN can be considered the first choice in younger patients with a higher life expectancy because of the lower side effect profile.

Disclosures

Ethics Committee Approval: The study was approved by the Izmir Katip Celebi University Clinical Trials Ethics Committee (date: 08.04.2021, no: 2021-KAEK-40).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Conception: S.G.O., E.A.; Design – S.G.O., E.A., E.E.; Supervision – S.G.O., E.A.; Resource – S.G.O.; Materials – S.G.O., E.D.E., F.K.; Data Collection and/or Processing – S.G.O., E.D.E., F.K., E.A.; Analysis and/or Interpretation – S.G.O., E.A., E.E.; Literature Search – S.G.O., E.D.E., F.K.; Writing – S.G.O., E.E.; Critical Reviews – S.G.O., E.E.

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