Results of Intravitreal Dexamethasone Implant and Anti-VEGF Treatment in Treatment of Macular Edema Secondary to Branch Retinal vein Occlusion

Ayşe Balıkçı[1], Hafize Gökben Ulutaş[2], Mehmet Emin Aslancı[3]

ABSTRACT

Purpose: To evaluate the changes in best corrected visual acuity (BCVA) and central macular thickness (CMT) in patients who received intravitreal dexamethasone implant (DEX-implant) and anti-vascular endothelial growth factor (VEGF) in the treatment of macular edema secondary Branch Retinal Vein Occlusion (BRVO).

Materials and Methods: In this interventional, retrospective, single-center study, BCVA and CMT at baseline and on months 6, 9, 12 and 24 as well as mean number of injections and adverse effects were evaluated in 91 eyes with macular edema secondary to BRVO which were treated via intravitreal route.

Results: In our study, 24 patients received intravitreal DEX-implant (group 1) and 46 patients received intravitreal anti-VEGF (group 2). The treatment was switched in 21 patients who were resistant to treatment (group 3). The mean number of injections was 2.13 (± 1.2) in group 1, 4 (± 1.8) in group 2 and 5.6 (± 3) in group 3. In all three groups, the percent change in BCVA and CMT was found to be significant on months 6, 9, 12 and 24 when compared to baseline ($p < 0.05$). Laser photocoagulation was added to drug therapy in 33% of patients. The intraocular pressure elevation was observed in 8.8% whereas cataract in 6.6% and epiretinal membrane in 9.9% of the patients.

Conclusion: Both DEX-implant and intravitreal anti-VEGF agents are effective treatments in the treatment of macular edema associated with BRVO. In resistant BRVO cases, visual gain and reduction in CMT can be achieved when the treatment is switched. Laser photocoagulation may be added to intravitreal treatment when needed.

Keywords: Retinal vein branch occlusion, macular edema, dexamethasone implant, anti-vascular endothelial growth factor.

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common cause of retinal vascular diseases after diabetic retinopathy. It may occur as central vein occlusion (CRVO) or branch retinal vein occlusion (BRVO). Compression at arteriovenous junction, degenerative changes and hyper-coagulation play an important in the role of branch retinal vein occlusion. The ischemia resulting from vascular occlusion increases vascular endothelial growth factor (VGEF), leading macular edema[1, 2]. Macular edema is the major cause of vision loss secondary to branch vein occlusion[3]. In BRVO, current therapeutic options include laser photocoagulation, intravitreal corticosteroid and anti-VGEF agents[4]. The anti-VGEF agents (ranibizumab, bevacizumab and aflibercept) have become first-line treatment in the treatment of macular edema secondary to BRVO. The ranibizumab was assessed regarding safety and efficacy in the treatment of macular edema secondary to BRVO in BRAVO[5], HORIZON[6], BRIGHTER[7] and BLOSSOM[8] studies while aflibercept in VIBRANT study[9,10] and dexamethasone intravitreal implant (DEX implant) in GENEVA study[11]. Anti-VGEF agents was investigated regarding superiority to sham injections or laser photocoagulation in some study while they were compared with DEX implant regarding efficacy in other studies.

1- Ophthalmologist, Bursa Yüksek Ihtisas Education and Research Hospital, Department of Ophthalmology, Bursa, Turkey

2- Ophthalmologist, Bursa Yüksek Ihtisas Education and Research Hospital, Department of Ophthalmology, Bursa, Turkey

3- Ophthalmologist, Department of Ophthalmology, Bursa City Hospital, Bursa, Turkey

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Correspondence Adress:
Ayşe Balıkçı
Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Göz Kliniği, Bursa, Türkiye

Phone: +90 505 573 5482
E-mail: drtufekciayse@yahoo.com

In this study, it was aimed to assess effects of DEX implant and anti-VGEF agents on best-corrected visual acuity BCVA) and central macular thickness (CMT) in patients treated in our clinic; thus, present real-world data in the treatment of macular edema secondary to BRVO.

MATERIAL AND METHOD:

In this interventional, retrospective, single-center case series, we assessed 91 eyes of 91 patients received intravitreal treatment for macular edema secondary to BRVO between January, 2017 and December, 2019. The study was approved by Institutional Ethics Committee. The study was conducted in accordance to tenets of Helsinki Declaration. The patients gave written informed consent before injection. Patient data were extracted from patient files at retina unit. In addition, fundus fluorescein angiography (FFA) and optic coherence tomography (OCT) images were also extracted. All injections were performed at operating room under sterile conditions. After topical administration 0.5% proparacaine eye drop, eye was prepared using 10% povidone iodine. 5% povidone iodine was administered to conjunctival sac over 2 minutes; then, it was removed by flushing normal saline. Intravitreal injection was performed at 4 mm distal to limbus in phakic eyes and at 3.5 mm distal to limbus in pseudophakic eyes. 2. Moxifloxacin (4 drops daily, over one week) was prescribed to all patients after injection. Since anti-VGEF agents was initially approved for treatment of age-related macular degeneration and diabetic macular edema in Turkey, we initially used DEX implant, the only approved agent, in the treatment of retinal vascular occlusions. Both treatments were administered after abolishment of limitation of reimbursement and approval of anti-VGEF agents in the treatment of retinal vascular disorders. DEX implant was preferred if the patient had cardiac risk, incompliance to month regimen, pseudophakia or if there was no avascular area in the involved area on FFA. Anti-VGEF agents were preferred if above-mentioned risks were lacking or if there was avascular areas in the occluded area on FFA. The patients with macular ischemia were excluded.

The patients received monthly injections during first 3 months; followed by pro re nata (PRN) regimen. Repeated injection was scheduled if there was one order loss in BCVA (Snellen charts) compared to prior visit or CMT was ≥250 µm. For Dex implant, repeated injection was scheduled if CMT was ≥250 µm or there was one order loss in BCVA (Snellen charts) compared to prior visit on month 4 after first injection. The treatment was switched in cases in which CMT showed no change or worsened despite injections in prior two visits between Dex implant and anti-VGEF groups. The patients with incompliance to the treatment were excluded due to retrospective nature of the study. Thus, no reason other than medical treatment (patient-related, social, transportation difficulty, off-label use etc.) was detected for switch.

The exclusion criteria wee ischemic maculopathy, previous intravitreal treatment, epiretinal membrane on pretreatment OCT, presence of other causes of retinopathy and maculopathy, previous history of vitreoretinal surgery and history of macular photocoagulation prior to intravitreal treatment. BCVA and CMT as measured by OCT were assessed at baseline and on months 6, 9, 12 and 24 in 91 patients fulfilling inclusion criteria and having at least 6 months of follow-up. The presence of ischemia was assessed using angiographic images. The data regarding age, gender, vision, eye with vein occlusion, complications and surgery during follow-up, laser photocoagulation during follow-up, systemic diseases, number of injections, duration of follow-up and switch were assessed based on patient files. Visual acuity was measured using Snellen charts and transformed to logMAR (Logarithm of the Minimum Angle of Resolution) units for statistical analysis. The OCT was performed using RTVue-100, Optovue. The BCVA and CMT measurements at baseline and on months 6, 9, 12 and 24 were assessed in patients received Dex implant and switched treatment.

STATISTICAL ANALYSIS

The normal distribution of data was assessed using Shapiro-Wilk test. Repeated measurements were compared between groups were performed by calculation of percent change than baseline value [percent change=(final measurement-baseline measurement)/baseline measurement]. Bonferroni correction was used to analyze repeated measurements. Wicoxon signed rank test was used for intra-group analysis of percent changes in BCVA and CMT on months 6, 9, 12 and 24. Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp., released 2015); IBM SPSS for Windows, version 23.0, Armonk, NY, IBM Corp).

FINDINGS

In this study, 24 patients received DEX implant while 46 patients received intravitreal anti-VGEF treatment. The switch between DEX implant and anti-VGEF agent was performed in 21 patients due to treatment failure. These patients were included as switch group. Of 24 patients in DEX implant group, 16 patients completed 12-months followed while 11 patients completed 24-months follow-up. Of 46 patients in anti-VGEF group 29 patients completed 12-months follow-up while 15 patients completed

24-months follow-up. Of the 21 patients in the switch group, 14 patients completed 12-months follow-up while 12 patients completed 24-months follow-up. In anti-VGEF group, 23 patients (50%) received ranibizumab while 20 patients (43.5%) received aflibercept, one patient (2.2%) received bevacizumab and 2 patients (4.3%) received both ranibizumab and bevacizumab.

There were 12 men and 12 women with mean age of 68.5±8.9 years in the DEX implant group (group 1). There were 26 men and 20 women with mean age of 61.4±9.6 years in the anti-VGEF group (group 2). There were 13 men and 8 women with mean age of 63.3±8.7 years in the switch group (group 3). In all 3 groups, BRVO involvement was more common in upper quadrants (78.1%). Again, it was more common in right eye (57.2%). Laser photocoagulation was performed in 7 patients (29.2%) from group 1, 9 patients (19.6%) from group 2 and14 patients (66.7%) in group 3. Laser photocoagulation rate was higher in the switch group.

The most common systemic disease was hypertension in the etiology (58.2%). There was diabetes mellitus in 2.2%, coronary artery disease in 1.1% and hypertension plus diabetes mellitus in 1.1% of the patients.

In the switch group, 10 patient (41.6%) switched to anti-VGEF treatment from DEX implant while 11 patients (23.9%) switched to DEX implant from anti-VGEF therapy. The switch was performed after 1.6 injection in average in DEX-implant group and after 3.6 injection in anti-VGEF group. Mean BCVA was 0.85±1.42 at time of switch while it was 0.5±1.41 after treatment. Mean CMT was 448.6±159.5 µ at time of switch while it was 270±114.6 µ after treatment.

During treatment, intraocular pressure (IOP) elevation (≥10 mmHg compared to baseline) was observed in 4 patients (16.7%), cataract in 4 patients (16.7%), and epiretinal membrane (ERM) in 2 patients (8.3%) in group 1. IOP elevation was observed in 2 patients (4.3%%), cataract in 1 patient (2.2%), and ERM in 3 patients (6.5%) in group 2. IOP elevation was observed in 2 patients (9.5%%), cataract in 1 patient (4.8%), and ERM in 4 patients (19.1%) in group 3.

Macular and peripheral ischemia was assessed on FFA images. The patients with ischemic maculopathy, those with neovascularization at occlusion area due to peripheral ischemia or at high risk for neovascularization with retinal capillary occlusion larger than 5 disc area were excluded. During follow-up, peripheral laser photocoagulation was added to areas with no retinal perfusion which had distance more than 2 disk diameter from macular center in patients with retinal capillary occlusion smaller than 5 disc area. In our study, no macular laser therapy was given to the patients.

The number of pseudophakic patients were 7 (29.2%), 4 (8.7%) and 5 (23.8%) in three groups, respectively. Mean follow-up duration was 12.6±5.5 months in group 1, 12.4±5.9 months in group 2 and 18.1±7.2 months in group 3. Mean number of injections was 2.13±1.2 in group 1, 4±1.8 in group 2 and 5.6±3 in group 3. Table 1 presents demographic characteristics of the patients.

At baseline, mean BCVA (logMAR) was 0.98±1.4 in group 1, 9.85±1.4 in group 2 and 0.85±1.42 in group 3. Table 2 presents mean BVCA values on months 6, 9, 12 and 24. In group 1, percent BCVA change was 0.84±1.6 on month 6, 0.41±0.5 on month 9, 0.55±0.7 on month 12 and 0.42±0.2 on month 24. In group 2, percent BCVA change was 0.4±2.3 on month 6, 0.79±1.1 on month 9, 1.17±2..7 on month 12 and 0.67±0.8 on month 24. In group 3, percent BCVA change was 0.41±0.7on month 6, 0.54±1 on month 9, 0.76±1..2 on month 12 and 0.30±0.2 on month 24. There significant differences in percent BCVA changes on months 6, 9, 12 and 24 in all groups ($p<0.05$) (Table 4, 5, 6).

Mean CMT was 427 ±125.4µm in group 1, 448.8 ±153.3 µm in group 2 and 448.6 ±159.5 µm in group 3. Table 3 presents CMT values on months 6, 9, 12 and24. In group 1, CMT reduction (compared to baseline) was -69.4µm on month 6, -119.2 µm on month 9, -88.8µm on month 12 and -260µm on month 24. . In group 2, it was -192.9 µm on month 6, -81.3 µm on month 9, -209.7 µm on month 12 and -241.2 µm on month 24 whereas -144.1 µm on month 6, -134.6 µm on month 9, -223.9 µm on month 12 and -178.6 µm on month 24. There significant differences in percent BCVA changes on months 6, 9, 12 and 24 in all group ($p<0.05$) (Table 4, 5, 6).

DISCUSSION

In many studies, efficacy of intravitreal anti-VGEF and DEX implant therapies are shown in the treatment of macular edema secondary to branch retinal vein occlusion. In BRAVO and CRUISE studies, ranibizumab and sham injection were compared in macular edema secondary to BRVO and CRVO, respectively; marked visual gain was achieved on months 6 and 12 in ranibizumab group when compared to baseline[5, 12]. In HORIZON study, it was shown that visual gain achieved by ranibizumab injection using PRN protocol (control visits every 3 months) was maintained over 2 years[6]. In BRIGHTER study, the long-term efficacy and safety of 0.5 mg ranibizumab with PRN regimen were shown in patients with BRVO at the end

Table 1: *Demographic characteristic of patients.*

	DEX-IMPLANT (n=24)	ANTI-VEGF (n=46)	SWITCH (n=21)	TOTAL (n=91)
GENDER n (%)				
Male	12 (50)	26 (56.5)	13 (61.9)	51 (56)
Female	12 (50)	20 (43.5)	8 (38.1)	40 (44)
AGE. MID-YEAR (±SS)	68.5 (8.9)	61.4 (9.6)	63.3 (8.7)	63.7 (9.6)
LATERALITY n (%)				
RIGHT SBVO	11 (45.8)	21 (45.7)	8 (38.1)	40 (44)
RIGHT IBVO	5 (20.8)	5 (10.9)	2 (9.5)	12 (13.2)
LEFT SBVO	5 (20.8)	16 (34.8)	10 (47.6)	31 (34.1)
LEFT IBVO	3 (12.5)	4 (8.7)	1 (4.8)	8 (8.8)
SWITCH n (%)	10 (41.6)	11 (23.9)		21 (23)
SYSTEMIC DISEASE n (%) +	14 (58.4)	33 (71.7)	10 (47.7)	57 (62.6)
COMPLICATION n (%)				
GLAUCOMA	4 (16.7)	2 (4.3)	2 (9.5)	8 (8.8)
CATARACT	4 (16.7)	1 (2.2)	1 (4.8)	6 (6.6)
ERM	2 (8.3)	3 (6.5)	4 (19.1)	9 (9.9)
PATIENTS RECEIVED LPC n (%)	7 (29.2)	9 (19.6)	14 (66.7)	30 (33)
PSEUDOPHAKIA n (%)	7 (29.2)	4 (8.7)	5 (23.8)	16 (17.6)
NUMBER OF INJECTION MEAN (±SD)	2.13 (1.2)	4 (1.8)	5.6 (3)	3.8 (2.3)
FOLLOW-UP. MONTH MEAN (±SD)	12.6 (5.5)	12.4 (5.6)	18.1 (7.2)	13.8 (6.4)

DEX: dexamethasone; **ANTI-VEGF:** anti-vascular endothelial growth factor; **BRVO:** retinal branch vein occlusion; **SD:** standard deviation; **SBRVO:** superior branch vein occlusion; **IBVO:** inferior branch vein occlusion; **ERM:** epiretinal membrane; **LPC:** laser photocoagulation

Table 2: *BCVA change over months in all 3 groups (LogMAR).*

	BASELINE BCVA	BCVA on month 6	BCVA on month 9	BCVA on month 12	BCVA on month 24
DEX-IMPL	0.98±1.4	0.68±1.4	0.5±1.45	0.81±1.42	0.55±1.59
Anti-VEGF	0.85±1.4	0.39±1.45	0.38±1.52	0.28±1.47	0.21±1.58
Switch	0.85± 1.42	0.61±1.36	0.5±1.38	0.34±1.41	0.5±1.41

BCVA: Best-corrected visual acuity; **DEX:** dexamethasone; **ANTI-VEGF:** anti-vascular endothelial growth factor.

Table 3: *CMT change over months in 3 groups.*

	Baseline CMT	CMT on month 6	CMT on month 9	CMT on month 12	CMT on month 24
DEX-IMPL	427±125.4	357.6±141.1	307.8±152.5	338.2±156.5	167±32.5
Anti-VEGF	448.8±153.3	255.9±91.7	267.5±128	239.1±72.9	207.6±58.7
Switch	448.6±159.5	304.5±147	314±180.3	224.7±95.3	270±114.6

DEX: dexamethasone; **ANTI-VEGF:** anti-vascular endothelial growth factor; **CMT:** central macular thickness.

Table 4: *Percent change in BCVA and CMT compared to baseline in DEX implant group.*

	BCVA (LogMAR)	p*	CMT (µ)	p*
Month 6 -% change	0,84±1,6	0,001[a]	-0,13±0,3	0,014[a]
Month 9-% change	0,41±0,5	0,007[a]	-0,27±0,3	0,015[a]
Month 12-% change	0,55±0,7	0,001[a]	-0,21±0,3	0,003[a]
Month 24 -% change	0,42±0,2	0,004[a]	-0,65±0	0,018[a]

BCVA: Best-corrected visual acuity; **CMT:** central macular hickness; [a]Wilcoxon Signed Ranks Test; *p<0,05

Table 5: *Percent change in BCVA and CMT compared to baseline in Anti-VEGF group.*				
	BCVA (LogMAR)	**p***	**CMT (µ)**	**p***
Month 6 -% change	0,94±2,3	<0,001[a]	-0,33±0,3	<0,001[a]
Month 9-% change	0,79±1,1	<0,001[a]	-0,23±0,6	<0,001[a]
Month 12-% change	1,17±2,7	<0,001[a]	-0,43±0,2	<0,001[a]
Month 24 -% change	0,67±0,8	0,004[a]	-0,38±0,3	0,006[a]
BCVA: Best-corrected visual acuity; **CMT:** central macular hickness; [a] Wilcoxon Signed Ranks Test; *p<0,05				

Table 6: *Percent change in BCVA and CMT compared to baseline in switch group.*				
	BCVA LogMAR)	**p***	**CMT (µ)**	**p***
Month 6 -% change	0,41±0,7	0,004[a]	-0,28±0,4	0,015[a]
Month 9-% change	0,54±1	0,001[a]	-0,32±0,3	0,001[a]
Month 12-% change	0,76±1,2	<0,001[a]	-0,43±0,3	<0,001[a]
Month 24 -% change	0,20±0,2	0,044[a]	-0,39±0,2	0,006[a]
BCVA: Best-corrected visual acuity; **CMT:** central macular hickness; [a] Wilcoxon Signed Ranks Test; *p<0,05				

of 24-months follow-up[7]. In BLOSSOM study on Asian patients, it was shown that 0.5 mg intravitreal ranibizumab treatment was superior to sham injection on month 6 in the treatment of macular edema secondary to BRVO and that visual gain was maintained up to 12 months[8]. In VIBRANT study, aflibercept injection was compared to laser photocoagulation, showing that aflibercept was more effective[9, 10]. In a randomized, controlled, phase III study (GENEVA), it was shown that single injection of intravitreal DEX implant decreased macular edema and improved vision over 6 months[11]. In a real-world study, Kanra et al. evaluated repeated DEX implant injection in eyes with macular edema secondary to RVO and showed significant improvement in BCVA and CMT during mean follow-up of 17 months[13]. In a short-term study using single dose of bevacizumab, Ayyildiz et al. showed that intravitreal bevacizumab injection was safe and effective at early phases in the treatment of macular edema secondary to BRVO but the efficacy was insufficient in CRVO[14]. Recently, many studies have been conducted, indicating efficacy and safety of anti-VGEF agents in the treatment of macular edema secondary to BRVO[15-24].

In many studies, anti-VGEF agents were compared to each other and DEX implant therapy regarding efficacy in BRVO[25-28]. In a multicenter study by Bandello et al., it was shown that there was 7.4 letters gain in BCVA compared to baseline in 154 eyes received DEX implant injection whereas 17.4 letters gain in 153 patients received ranibizumab after 12 months of follow-up (p<0.0006). Again, there was a reduction in CMT by 227 µm in patients received DEX implant whereas reduction by 252µm in patients received ranibizumab on month 12 (p=0.0839). In a meta-analysis including 3 studies, DEX implant and ranibizumab achieved significant functional and anatomic improvement at short-term; however, ranibizumab group achieved greater improvement when compared to DEX implant group (p<0.00001). In ranibizumab group, higher CMT reduction was detected when compared to DEX implant group (p<0.0001)[28]. In recent studies, it has been emphasized that DEX implant is a better alternative to anti-VGEF treatment in vascular occlusions[29, 30]. In our study, we assessed DEX implant and anti-VGEF agents as well as switching therapy. When changes in BCVA and CMT values on months 6, 9 12 and 24 were assessed according to baseline, significant differences were detected in all time points in all groups. The switch between treatments in case of failure in intravitreal therapy provided visual gain and CMT reduction in our study. In our study, DEX implant intervals shorter than 6 months and switch in refractory eyes allowed us to achieve significant improvement in group 3. In some studies, it was reported that DEX implant efficacy was increased up to 3 months; decreased about month 6 and injections every 6 months caused reduction in efficacy[31, 34].

Underlying reasons such as age, hypertension, diabetic retinopathy o hyper-coagulopathy play role in the etiology of branch retinal vein occlusion[35]. In recent years, it has been proposed that high neutrophil: lymphocyte rate, high platelet: lymphocyte rate and high monocyte: HDL rate may be important markers to determine risk for BRVO[36,37]. In our study, there was a comorbid systemic disease in 62.6% of the patients including hypertension in 58.2%, diabetes mellitus in 2.2%, coronary artery disease in 1.1% and hypertension plus diabetes mellitus in 1.1%.

In the study by Bandello et al., the IOP elevation ≥10 mmHg compared to baseline was found to be more common in DEX implant group than ranibizumab group (38.6% vs. 5.3%). Again, cataract formation and cataract surgery were also found to be more common in DEX implant group (cataract: 59.8% vs.30.9%; cataract surgery: 3.1% vs. 0%)[26]. Similar outcomes were found in the meta-analysis by Wei et al.[28]. In a study analyzed real-world data from patients received intravitreal DEX implant injection, International Ozurdex Study Group reported IOP elevation in 26.5% and cataract development requiring surgery in 32.5% of the patients[38]. In our study, mean number of injection was greater in anti-VGEF group than DEX implant group in agreement with literature[26, 29].

The Branch Vein Occlusion Study (BVOS) group determined macular laser as standard treatment for BRVO in 1984[39]. In the study by Clarkson et al., it was shown that 2-orders visual gain was achieved in patients underwent macular laser therapy when compared to controls. In their subsequent study, authors found that peripheral laser photocoagulation was effective in the treatment of neovascularization and the for vitreal hemorrhage was decreased from 60% to 30% in patients with BRVO[40-42]. Some recent studies showed that laser therapy added to anti-VGEF agents can provide additional benefit in the patients[43, 44]. One of the reasons of less need for peripheral laser in anti-VGEF group may be the fact that anti-VGEF agents are more effective in reducing ischemia as reported in previous studies. In the post hoc analysis of COMBRADE study, it was found that less peripheral laser therapy was performed in CRVO treated with dexamethasone than those treated with ranibizumab over 6 months while no significant difference was found in the number of peripheral laser therapy between BRVO groups. It was also found that ranibizumab was associated with less ischemia in CRVO[45].

In previous studies, effect of DEX implant and anti-VGEF agents were assessed as monotherapy in the treatment of BRVO and two treatment modalities were compared. In our study, we aimed to present real-world data in patients with BRVO. For this purpose, we also assessed patients received switched therapy due to failure of monotherapy with these treatment modalities. Our study showed that both DEX implant and anti-VGEF agents decreased macular edema and improved vision in eyes with BRVO; however, additional visual gain and CMT reduction could be achieved when switching between treatments in cases in which no change or worsening was noted in CMT after two injections. The laser photocoagulation added to medical therapy in 33% of patients showed the need for planning BRVO treatment according to treatment response of macular edema.

LIMITATIONS

This study has some limitations including retrospective design and small sample size. In addition, lacking of assessment regarding difference in the efficacy of anti-VGEF agents (bevacizumab, ranibizumab and aflibercept) is also an important limitation.

CONCLUSION

Both intravitreal DEX implant and anti-VGEF agents are effective in the treatment of macular edema secondary to BRVO. In refractory cases, switching treatment may provide visual gain and CMT reduction. Laser photocoagulation can be added to intravitreal treatment when needed.

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