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Narrative Review

Intravitreal Pharmacotherapy for the Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion: A Narrative Review

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Abstract

Branch retinal vein occlusion (BRVO) is the next most common retinal vascular disorder following diabetic retinopathy, and macular edema is the most frequent cause of visual impairment in patients with BRVO. For many years, grid laser photocoagulation was the standard of care for the treatment of BRVO-associated macular edema. Grid laser photocoagulation was used for patients with macular edema secondary to BRVO longer than 3 months and visual acuity less than 20/40. Currently increasing data supports the effect of anti-vascular endothelial growth factors in the treatment of BRVO-associated macular edema. Recent studies have shown that intravitreal bevacizumab injection is a safe and effective modality for the treatment of BRVO-associated macular edema; however, the recurrence of macular edema is common following an intravitreal bevacizumab injection. Other anti-vascular endothelial growth factor (VEGF) agents such as ranibizumab, pegaptanib, and aflibercept are effective options. Combining anti-VEGFS with grid laser may be effective in refractory cases and also may prolong the interval between intravitreal injections. Switching to a different anti-VEGF or dexamethasone implant may be effective in the treatment of refractory cases; however, the efficacy of an intravitreal dexamethasone implant may diminish after a few months, and elevated intraocular pressure and cataract formation may occur.

Keywords: Branch Retinal Vein Occlusion, Macular Edema, Anti-VEGF, Intravitreal Injection

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Introduction

Branch retinal vein occlusion (BRVO) is the second most frequent disorder of the retinal vasculature after diabetic retinopathy,[1-3] affecting mostly patients over 50 years of age.[4,5] Occlusion of the venous branches of the retinal circulation results in the elevation of intraluminal pressure as well as hemorrhage and edema in the affected area of the retina.[6] Visual impairment happens because of different mechanisms, including capillary non-perfusion and ischemia and elevated hydrostatic pressure that leads to hemorrhage, exudation, and edema.[7] However, the most frequent cause of visual impairment in patients with BRVO is macular edema.[8]

In a meta-analysis using data from 11 studies, the prevalence of BRVO was estimated to be 4.42 per 1000.[9] In this study, the prevalence of BRVO was greatest in Asian and Hispanics.

The Eye Disease Case-Control Study Group identified the major risk factors of BRVO as hypertension, a history of previous cardiovascular disease, smoking, an increased level of body mass index, and a higher level of alpha 2 globolin.[10]

Anatomically, the retinal arterioles and retinal venules share a common adventitial sheath at the arterio-venous crossing; therefore, the mechanical pressure of the arterioles, especially in patients with hypertension and arteriosclerosis, results in venous lumen narrowing and leads to endothelial damage, thrombosis, and ultimately occlusion occurs.[11]

The current study reviewed the literature on intravitreal pharmacotherapy against BRVO-associated macular edema.

Laser Photocoagulation

After the publication of the Branch Vein Occlusion Study (BVOS),[12] grid laser photocoagulation became the standard of care for visual impairment following BRVO-associated macular edema for many years.[13] The BVOS included 139 eyes with BRVO-associated macular edema and visual acuity between 20/40 and 20/200 with no retinal ischemia and no hemorrhage within the fovea. Patients were randomized into the laser photocoagulation or the observation groups. After an average follow-up period of 3.1 years, the mean visual acuity was 20/40 to 20/50 in the treatment group and 20/70 in the control group ($P<0.0001$). Patients with acute manifestation (<3 months) were not included in the BVOS. The study showed that patients with a shorter time from onset

of symptoms to treatment had better visual outcomes. Shilling and Jones' study confirmed the BVOS results.[14]

Battaglia-Parodi et al evaluated the efficacy of grid laser photocoagulation in cases with acute BRVO-associated macular edema (<15 days).[15] In their study, 77 eyes with BRVO and macular edema were randomized into the treatment or the observation groups and followed-up for 12 months. They showed that visual acuity was improved in both groups without a significant difference. Therefore, it was suggested that grid laser photocoagulation be considered for the treatment of BRVO-associated macular edema after a period of 3 to 6 months after onset. In another study, Battaglia-Parodi et al evaluated 137 eyes with BRVO-associated macular edema.[16] Patients were randomized into early treatment with laser photocoagulation (3 months after diagnosis), late treatment with laser photocoagulation (6-18 months after diagnosis), or no treatment groups. Visual acuity improvement was seen in all groups without significant difference after 2 years of follow-up. In conclusion, the authors of both studies believed that macular laser photocoagulation does not significantly improve the prognosis of BRVO-associated macular edema.

Intravitreal Pharmacotherapy

Vascular endothelial growth factor (VEGF) is an important mediator of retinal neovascularization and macular edema in BRVO-affected eyes. VEGFs up-regulated secondary to retinal hypoxia.[17] Today anti-VEGFs have been used to inhibit the effects of VEGF in patients with BRVO-associated macular edema.

1. Bevacizumab

Bevacizumab (Avastin; Genentech Inc., San Francisco, California, USA) is a monoclonal antibody that inhibits VEGF. It has been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic colon cancer.[7] Since 2005, intravitreal bevacizumab has been used off-label in cases with wet-type macular degeneration.

Some studies have shown that the production of VEGF was increased in eyes with BRVO, and it may lead to long-standing vascular leakage and macular edema[18]; therefore, the use of anti-VEGFs may be an effective option for the treatment of BRVO-associated macular edema.

In their prospective randomized study, Russo et al compared the efficacy of 1.25 mg intravitreal bevacizumab (15 eyes) and grid laser photocoagulation (15 eyes).[19] They showed that visual acuity was improved and central macular thickness was reduced in both groups; however, during the 12-month follow-up period, the intravitreal bevacizumab group achieved better results. Other studies have obtained similar results. For example, Leitritz et al[20] and Parveen et al[21] reported that laser photocoagulation led to a reduction in macular thickness, but intravitreal bevacizumab injections resulted in better visual outcomes.

Donati et al,[22] Salinas-Alaman et al,[23] and Ogino et al[24] showed that, compared with intravitreal bevacizumab injection mono-therapy, combination therapy (intravitreal bevacizumab and laser photocoagulation) can reduce the number of intravitreal injections and also provide good results in the maintenance of visual acuity.

Bevacizumab is most commonly used intravitreally in doses of 1.25 mg or 2.50 mg. Wu et al evaluated 63 eyes with BRVO-associated macular edema and treated with either 1.25 mg (38 eyes) or 2.5 mg (25 eyes) intravitreal bevacizumab. They found that after 24 months of follow-up, both groups achieved significant improvement in visual acuity and central macular thickness; however, there were no significant differences between the 2 dose groups in visual acuity, central macular thickness, or the number of injections (Pan American Collaborative Retina Study).[25]

One of the potential limitations of intravitreal bevacizumab for the treatment of BRVO-associated macular edema is rebound macular edema; thus, repeated injections may be necessary to avoid recurrent macular edema.[26] Yasuda et al evaluated 65 eyes with BRVO-associated macular edema.[27] They found that 10.8% of cases showed rebound macular edema after treatment with intravitreal bevacizumab. Thinner pre-treatment fovea and a shorter interval between symptom presentation and beginning of intravitreal bevacizumab injections were significantly associated with a higher rate of rebound macular edema ($P < 0.01$). The researchers suggested that patients should wait at least 8 weeks after the presentation of symptoms to allow macular edema to reach its maximum level and then begin intravitreal bevacizumab injections. In a prospective study, Khan et al compared the efficacy of immediate versus deferred intravitreal bevacizumab treatments on BRVO-associated macular edema.[28] In their study, 40 patients with treatment-naïve BRVO who presented within one month of symptom initiation and had a BCVA equal to or less than 6/12 were randomized into 2 treatment groups (20 eyes in each group) to receive immediate or deferred (after 3 months of observation) intravitreal bevacizumab. The mean visual gain was significantly better in the immediate intervention group compared with the deferred treatment group, and fewer injections were required in the early treatment group.

2. Ranibizumab

Ranibizumab (Lucentis) is an anti-VEGF drug used in the treatment of BRVO-associated macular edema. In a prospective study, Campochiaro et al evaluated the efficacy of doses of 0.3 mg and 0.5 mg of ranibizumab in the treatment of BRVO-associated macular edema and found that visual acuity was improved in both dose groups (10 letters in the 0.3 mg group and 18 letters in the 0.5 mg groups).[29] In another prospective study, Campochiaro et al randomized 397 eyes with BRVO-associated macular edema into 3 groups that received monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab or sham injections.[30] After a 6-month follow-up period, the mean improvement in visual acuity from baseline was 16.6 and 18.3 letters in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, and 7.3 letters in the sham group ($P < 0.0001$ for both ranibizumab groups vs. the sham group), and the mean central macular thickness was reduced by 337 μ and 345 μ in the 0.3 mg and 0.5 mg ranibizumab

groups, respectively, and 158 μ in the sham group ($P<0.0001$ for both ranibizumab groups vs. sham group). In conclusion, the researchers suggested that intravitreal injection of 0.3 mg or 0.5 mg of ranibizumab is an effective and safe treatment modality for macular edema secondary to BRVO. At the 12-month follow-up and with an as-needed treatment regimen, the mean change rates from baseline were 16.4, 18.3, and 12.1 letters in the 0.3 mg and 0.5 mg intravitreal ranibizumab and sham groups, respectively ($P<0.01$ for both ranibizumab groups vs. the sham group).[31]

Karagiannis et al evaluated 22 cases with macular edema secondary to BRVO.[32] Each patient was treated with 2 monthly intravitreal 0.5 mg ranibizumab injections and followed for at least 12 months. The results indicated that macular edema recurred in 59% of cases (13 of 22 eyes).

Hladíková et al reported the 2-year follow-up results of 16 patients with macular edema secondary to BRVO who were treated with intravitreal ranibizumab.[33] The mean interval from diagnosis to first injection was 6 months. The mean improvement in BCVA was 18.7 letters in the first year and 19.7 letters in the second year; the mean number of injections was 7 in the first year and 3.2 in the second year. Their results showed that intravitreal ranibizumab is a safe and effective treatment option for the treatment of macular edema due to BRVO.

In a retrospective study, Son et al compared the efficacy of 0.5 mg ranibizumab (24 eyes) with 1.25 mg bevacizumab (56 eyes) for the treatment of macular edema secondary to BRVO.[34] Initially, 3 monthly injections were given in each group, followed by as-needed injections. The BCVA improvement, central subfield thickness reduction, and number of injections were not significantly different between the 2 treatment groups.

Sugiura et al evaluated the effects of intravitreal ranibizumab injections on metamorphopsia in patients with BRVO (39 eyes).[35] They found that the BCVA and central retinal thickness improved significantly ($P<0.0001$ and $P<0.0001$, respectively), but the metamorphopsia did not improve. The higher pre-treatment metamorphopsia score, longer duration of symptoms, and disruption of external limiting membrane in OCT were correlated with worse post-treatment metamorphopsia results in this study.

3. Pegaptanib

Pegaptanib sodium (Macugan) is a selective anti-VEGF. Few studies have evaluated the efficacy of pegaptanib in ocular diseases associated with VEGF up-regulation, including diabetic macular edema, proliferative diabetic retinopathy, central retinal vein occlusion (CRVO), and neovascular age related macular degeneration.[36-40] The efficacy of pegaptanib has not been studied in patients with BRVO-associated macular edema. Udaondo et al enrolled 5 eyes with BRVO and refractory macular edema which had been previously treated with bevacizumab or triamcinolone into the prospective study.[41] They used 0.3 mg intravitreal pegaptanib for the treatment of these eyes; after 3 months, both visual acuity and central macular thickness had improved. Wroblewski et al compared the efficacy of 0.3 mg and 1 mg pegaptanib in the treatment of macular edema due to BRVO.[42] Twenty eyes were randomized 3:1 into groups receiving 0.3 mg (15 eyes) or 1 mg (5 eyes) intravitreal pegaptanib injections. The best corrected visual acuity (BCVA) was 20/40 to 20/320, and duration of presentation was more than 1 month and fewer than 6 months in all cases. At the 54-week follow-up, visual acuity, central subfield thickness, central point thickness, and macular volume had improved. The results were similar in both groups.

4. Aflibercept

Aflibercept (Eylea; Regeneron, Tarrytown, NY, USA) is a recombinant fusion protein consisting of VEGF-binding receptors 1 and 2 fused to Fc protein of human immunoglobulin G. Kaldirim and Yazgan compared the efficacy of 0.5 mg ranibizumab (22eyes, group1) 0.7 mg dexamethasone implant (20 eyes, group 2), and 2 mg aflibercept (20 eyes, group 3) for the treatment of BRVO-associated macular edema.[43] Intravitreal ranibizumab and aflibercept were injected 3 times at 1-month intervals and based on clinical evaluation in groups 1 and 3. Only one dexamethasone implant was injected in patients in group 2. After 6 months of follow-up, the mean numbers of injections were 3.64 ± 0.49 in group 1 and 3.35 ± 0.49 in group 3. In the first 3 months, the visual acuity was better in group 2; however, at the 6-month follow-up, it became the worst among the 3 groups. In the first 3 months, central macular thickness did not differ between the 3 groups, but at the 6-month follow-up, it was greater in the eyes in group 2. Intraocular pressure was significantly higher at the 3- and 6-month follow-up periods in eyes in group 2. The authors concluded that intravitreal dexamethasone implant may be more effective for maintaining visual acuity for the first 3 months, but at the end of 6 months, ranibizumab and aflibercept were more effective.

In a multicenter, randomized clinical trial (VIBRANT), Compochiaro et al compared the efficacy of aflibercept with grid laser photocoagulation.[44] Treatment-naïve patients with macular edema secondary to BRVO and BCVA between 20/40 and 20/320 were randomized into either the intravitreal aflibercept group (91 eyes) or the grid laser photocoagulation group (92 eyes). Eyes in the aflibercept group received 2 mg intravitreal aflibercept every 4 weeks for 20 weeks, and eyes in the laser photocoagulation group underwent grid laser at baseline and then one grid laser rescue treatment if needed. At the 24-week follow-up, 52.7% of eyes in the aflibercept group and 26.7% of eyes in the grid laser group gained ≥15 ETDRS letters ($P=0.0003$). At the 24-month follow-up, the mean central macular thickness reduction from baseline was 280.5 μ in the aflibercept group and 128 μ in the laser group ($P<0.0001$). This study found that intravitreal aflibercept injection leads to better visual and anatomical outcomes than grid laser photocoagulation. Sakanishi et al evaluated intravitreal aflibercept injections for the treatment of BRVO-associated macular edema.[45] Patients were divided into 2 groups: those with no history of previous treatment (27 eyes), and those who had initially been treated with ranibizumab injection and then switched to aflibercept injection due to the recurrence of macular edema (27 eyes). Patients in the

switching group had a history of an average 2.9 intravitreal ranibizumab injections. BCVA was significantly improved from 20/62 to 20/37 in the treatment-naïve group and from 20/60 to 20/49 in the switching group 1-month post-injection. The mean central macular thickness decreased from 559 μ at baseline to 204.2 μ at 1-month post-injection in the treatment-naïve group and from 511.7 μ to 238.2 μ in the switching group. This study showed that in the short-term, aflibercept is an effective modality in both patients with treatment-naïve BRVO-associated macular edema and patients with refractory macular edema due to BRVO.

In their retrospective study, Tagami et al evaluated the results of switching from ranibizumab to aflibercept in the treatment of BRVO-associated macular edema (15 eyes).[46] The mean time of treatment with ranibizumab was 11.8 ± 4.2 months. In the ranibizumab treatment period or after switching to aflibercept, patients were examined every month and re-treated with ranibizumab or aflibercept if any reduction in visual acuity from a previous examination had occurred or if the central retinal thickness was more than 300 μ. The mean interval between intravitreal injections was significantly prolonged from 68.2 ± 26.4 days to 91.8 ± 33.2 days in the ranibizumab period and aflibercept period, respectively ($P = 0.0011$). The authors concluded that switching from ranibizumab to aflibercept can prolong the intravitreal injections interval without any functional or anatomical outcome degradation.

Intravitreal Steroid Injection

1. Triamcinolone

The SCORE-BRVO trial was a multicenter, prospective, randomized clinical trial that compared the efficacy of 1 mg and 4 mg intravitreal triamcinolone acetonide and grid laser photocoagulation in the treatment of BRVO-associated macular edema.[47] Totally, 411 patients with BRVO were included in the SCORE-BRVO study. The mean duration of macular edema was 4 months, and the mean baseline visual acuity was 57 letters (20/80). At the 12-month follow-up, the percentages of patients with ≥15 score visual acuity improvement were 28.9%, 25.6%, and 27.2% in the laser photocoagulation group, 1 mg and 4 mg triamcinolone groups, respectively; thus, all 3 study groups had a similar visual gain. Another finding in this study was that patients with BRVO for a duration of more than 3 months benefitted more from laser photocoagulation, and patients with a disease duration of 1-3 months benefitted more from treatment with triamcinolone. The occurrence of side effects such as intraocular pressure elevation and cataract was higher in the 4 mg triamcinolone group than either the 1 mg triamcinolone group or the laser photocoagulation group.

Ozkiris et al evaluated the efficacy of intravitreal triamcinolone in the treatment of persistent BRVO-associated macular edema with a history of unsuccessful laser photocoagulation.[48] During an average of 6.2 months of follow-up, the mean BCVA was significantly improved from 1.01 logMAR at baseline to 0.55, 0.56, and 0.62 logMAR at one month, 3 months, and at the end of the follow-up period, respectively. The researchers concluded that intravitreal triamcinolone can be effective in patients with a history of failed laser photocoagulation.

In their randomized clinical trial, Ramezani et al compared the efficacy of 4 mg triamcinolone (16 eyes) with sham injections (14 eyes).[49] The duration of BRVO was less than 10 weeks in both groups. The authors concluded at the 4-month follow-up that a single intravitreal injection of 4 mg triamcinolone resulted in a non-significant improvement in visual acuity and central macular thickness in patients with acute BRVO compared with the control group.

Previous studies have shown that the duration of intraocular availability of triamcinolone is short, and repeated injections are required. Moreover, the efficacy of triamcinolone is better following the first intravitreal injection than repeated injections.[50,51]

The peri-ocular injection of triamcinolone acetonide was also evaluated for BRVO-associated macular edema. Hayashi and Hayashi compared the efficacy of retrobulbar triamcinolone injections and intravitreal injections for the treatment of macular edema secondary to BRVO.[52] They showed that the intravitreal triamcinolone injection group achieved a greater improvement in visual acuity, and more re-injections were required in the retrobulbar group. Ehrlich et al evaluated the efficacy of combined intravitreal injections of 1.25 mg bevacizumab and 2 mg triamcinolone in the treatment of 8 patients with macular edema secondary to BRVO.[53] The authors concluded that at the 6-month follow-up, the combination of intravitreal bevacizumab and triamcinolone improved structural results; however, no more improvement in visual acuity were detected.

Moon et al compared the efficacy and safety of 1.25 mg intravitreal bevacizumab injections with a single injection of 40 mg sub-tenon triamcinolone combined with intravitreal bevacizumab.[54] Intravitreal bevacizumab was re-injected based on the recurrence of macular edema in optical coherence tomography (OCT) associated with a reduction in visual acuity. At the 6-month follow-up, significant improvement had occurred in the BCVA and central macular thickness of both groups, but the difference between the 2 groups was not statistically significant. Moreover, the number of intravitreal bevacizumab re-injections was significantly lower in the combination therapy group.

2. Dexamethasone

Dexamethasone is another corticosteroid agent that may decrease the inflammatory mediators implicated in macular edema.[55] Intravitreal injections of dexamethasone have a short half-life; therefore, the intravitreal sustained release implant (Ozurdex; Allergan, Inc, Irvine, VA, USA) was developed. Ozurdex delivers 700 μ of dexamethasone to the retina and vitreous. A study known as the Dexamethasone Intravitreal Implant in patients with Macular Edema due to Retinal Vein Occlusion (GENEVA) study was a multicenter, randomized sham controlled clinical trial that evaluated dexamethasone implants for the treatment of patients with macular edema secondary to BRVO or CRVO, visual acuity between 20/50 and 20/200, and central subfoveal thickness ≥300 μ.[56] A total of 1267 patients were evaluated in the GENEVA study; 65%

of them had macular edema due to BRVO. Patients were randomized into 3 groups: the dexamethasone implant 0.35 mg, the dexamethasone implant 0.7 mg, and the sham injection groups. At the 6-month follow-up, the percentage of patients gaining 15 letters was not significantly different between the 3 groups. However, at 2 months, the visual acuity was significantly better in both the 0.35 mg and the 0.7 mg dexamethasone implant groups compared with the sham injection group. A small subgroup of cases who received Ozurdex in the GENEVA study (17 patients) were examined at 50 months after treatment.[57] The prognosis of patients with BRVO was better than that of patients with CRVO, and the mean visual acuity was improved significantly among patients with BRVO; however, it was not improved significantly in patients with CRVO. Elevated intraocular pressure occurred in only one patient, and cataract progression occurred in 10 patients. The authors suggested that in the long-term Ozurdex is safe and effective for the treatment of BRVO-associated macular edema. In the GENEVA study, 2 dexamethasone implants were injected at a 6-month interval. During the intervening period, no injection was done regardless of any reduction in visual acuity or elevation in macular thickness.

In a retrospective multicenter study, 289 treatment-naïve cases with macular edema secondary to BRVO (18 eyes) or CRVO (21 eyes) were treated with 2 or more intravitreal dexamethasone implants.[58] Before the first implant, the mean duration of macular edema was 4.9 months. The patients received a mean of 2.9 (2-9) dexamethasone implants. Both BRVO and CRVO patients experienced improved visual acuity. Overall, 83.8% and 70.3% of patients gained ≥2 lines or ≥3 lines in BCVA, respectively, and a central macular thickness ≤250 μ was achieved in 56.4% of them. An intraocular pressure ≥25 mm Hg occurred in 15 eyes, and none of them required surgical management. This study showed that 2 or more intravitreal dexamethasone injections institute a safe and effective modality for the treatment of patients with treatment-naïve macular edema secondary to BRVO or CRVO.

Previous studies have shown that intravitreally injected dexamethasone implants can be effective for about 4 months (3-7 months); therefore, re-treatment intervals in most cases should be less than 6 months.[59-61]

Querques et al evaluated 33 eyes with macular edema related to BRVO and CRVO who were treated with 0.7 mg intravitreal dexamethasone implants.[62] Re-treatment was needed 4.7 ± 1.1 months after the first injection and 5.1 ± 1.5 months after the second injection. The BCVA was significantly improved from 0.65 ± 0.43 logMAR at baseline to 0.50 ± 0.42 logMAR at 1.4 ± 0.7 months after the first injection and to 0.48 ± 0.44 logMAR at 1.8 ± 0.80 months after the second injection. Transient intraocular pressure elevation occurred in 12 eyes, and cataract surgery was performed in 2 eyes. The authors concluded that Ozurdex on an as-needed basis with re-treatment intervals of less than 6 months may be effective in the treatment of macular edema associated with BRVO and CRVO.

In their prospective study, Singer et al compared the efficacy of combination therapy with bevacizumab and Ozurdex with Ozurdex alone in the treatment of retinal vein occlusion (RVO)-related macular edema.[63] Of all cases, 65% were diagnosed with BRVO. This study showed that combination therapy with bevacizumab and Ozurdex implant can improve visual acuity and decrease macular edema more than Ozurdex monotherapy. Yuksel et al evaluated 44 patients with BRVO-associated macular edema.[64] The patients were divided into 3 treatment arms: grid laser photocoagulation (15 eyes), intravitreal ranibizumab (14 eyes), and dexamethasone implant (15 eyes). At the last follow-up visit, the mean letter gain was 13.5 letters, 7.1 letters, and 4.5 letters in the dexamethasone implant, ranibizumab, and laser photocoagulation arms, respectively. The researchers concluded that both dexamethasone implant and ranibizumab treatments lead to significant improvement in macular edema, and grid laser photocoagulation is not a suitable first-line treatment modality in the era of intravitreal pharmacotherapies.

Conclusion

Macular edema is the most frequent cause of visual impairment in patients with BRVO. A large number of treatment modalities have been advocated for the management of BRVO-associated macular edema. For many years, grid laser photocoagulation was the standard treatment for macular edema secondary to BRVO that was used for patients affected for longer than 3 months and with a visual acuity of ≤20/40. Today, different anti-VEGF agents have revolutionized the management of macular edema due to BRVO. Bevacizumab, an off-label drug, was shown in a recent study to possibly be effective and safe in the treatment of BRVO-associated macular edema. Furthermore, other anti-VEGFs such as ranibizumab, pegaptanib, and aflibercept are also effective agents. Switching to intravitreal aflibercept injections in eyes with refractory macular edema and a history of treatment with intravitreal bevacizumab or ranibizumab may be an effective alternative modality. The combination of intravitreal anti-VEGFs with grid laser photocoagulation may improve outcomes or prolong the intervals between intravitreal injections. Intravitreal dexamethasone implant is another therapeutic option for treatment-naive or refractory cases; however, its effect usually diminishes during the first few months after implantation, and intraocular pressure may become elevated.

The follow-up period in most available studies was short (usually between 6 to 24 months); thus, at this time, the question of which is the best treatment modality in general or for each distinct patient cannot be answered.

Conflict of Interest Disclosures

The authors declare they have no conflicts of interest.

Ethical Approval

Not applicable.

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