Treatment of Macular Edema following Branch Retinal Vein Occlusion

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Abstract

Branch retinal vein occlusion (BRVO) is a relatively prevalent cause of reduced vision primarily due to macular edema. Vascular endothelial growth factor (VEGF) is the major stimulator of excessive vascular leakage and also contributes to retinal hemorrhages and progressive retinal nonperfusion (RNP). Progressive RNP results in worsening of retinal ischemia further increasing levels of VEGF, resulting in a positive feedback loop for disease worsening over time. Aggressive early treatment with a specific antagonist of VEGF causes rapid improvement in edema and visual acuity, speeds resolution of hemorrhages, and stabilizes or improves RNP. Therefore, first-line treatment of acute BRVOs is monthly injections of an anti-VEGF agent for at least 6 months. After that, a period of monthly follow up with anti-VEGF treatment, only if there is recurrent edema, can be used to gauge persistent disease activity and the need for grid laser photocoagulation to diffuse leakage in the macula outside the foveal avascular zone. Following grid laser, another period of monthly follow up with anti-VEGF treatment only if there is recurrent edema provides a measure of persistent disease activity, and if frequent injections are still needed to control edema, the benefits and risks for switching to dexamethasone implants should be discussed with the patient.

Keywords

Hypoxia, retinal ischemia, vascular leakage, vascular endothelial growth factor

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There are two types of retinal vein occlusion (RVO): central retinal vein occlusion (CRVO), in which there is obstruction of the main outflow vessel of the eye, and branch RVO (BRVO), in which a major branch of the central retinal vein is obstructed. RVO is the second most-common retinal vascular disease after diabetic retinopathy. There are approximately 180,000 new RVOs in the US each year: 150,000 BRVOs and 30,000 CRVOs.[1] Worldwide, it is estimated that 16.4 million people have had an RVO (5.2 per 1,000 persons), 13.9 million with BRVO (4.42 per 1,000 persons), and 2.5 million with CRVO (0.80 per 1,000 persons). There is a higher prevalence of BRVO in Asians and Hispanics than in other ethnic groups.[2] RVO typically occurs in the middle aged to elderly group (more than 50 years), with an equal gender distribution. While there are many similarities between BRVO and CRVO, there are also important differences. This review focuses on BRVO.

Risk Factors

Hypertension is a major risk factor for BRVO.[3] Chronic hypertension leads to the thickening of the walls of retinal arterioles and since retinal arterioles and veins share a common adventitia at crossings, this leads to venous constriction (particularly when the arteriole passes over rather than under the vein), turbulent blood flow, endothelial damage, and thrombosis.[4–6] Other associated risk factors include hypercholesterolemia/hyperlipidemia, smoking, increased body mass index, history of cardiovascular disease, and history of glaucoma.[7]

Pathogenesis and Clinical Presentation

Acutely there is dilation of veins draining into the occluded segment with transudation of blood resulting in retinal hemorrhages and edema, which are usually most severe posteriorly adjacent to the occlusion. The more proximal the occlusion, the greater the amount of retina that is affected. Occlusion of the first branch of the central retinal vein causes a hemiretinal vein occlusion that affects about half the retina, while more distal occlusions affect somewhat less than half. There is retinal ischemia that ranges from mild to severe and is manifested by cotton wool patches (nerve fiber layer infarcts) and areas of retinal nonperfusion (RNP) due to closure of capillaries and arterioles. The amount of RNP tends to be greater in older patients, particularly those that have evidence of atherosclerosis suggesting that the amount of RNP in the early stages

of BRVO is determined by the amount of pre-existent arterial disease. Measurements of the area of RNP on fluorescein angiograms are greater in patients with BRVO compared with CRVO, but it appears likely that this is an artifact of ascertainment, because measurements are made in the posterior pole of the retina within the temporal arcade vessels; there is clearly more posterior RNP on average in patients with BRVO, but wide-angle fluorescein angiography suggests that total RNP is greater on average in patients with CRVO.

Substantial progress has been made elucidating the pathogenesis of edema in RVO. Retinal ischemia causes high levels of vascular endothelial growth factor (VEGF), which is the major cause of excessive vascular permeability. Blockade of VEGF causes rapid reduction in edema and speeds resolution of intraretinal hemorrhages. Thus, VEGF contributes to both edema and intraretinal hemorrhages. In addition, high levels of VEGF contribute to worsening of RNP over time. Thus, the occlusion causes variable amounts of retinal ischemia that increases levels of VEGF and then it is the high VEGF levels that become the driver of the disease. This has important implications regarding treatment, which is discussed below.

Treatment

Laser Photocoagulation

The demonstration that focal/grid laser photocoagulation treatment provided benefit in diabetic macular edema (DME), suggested that it might also provide benefit in other retinal vascular diseases including BRVO. However, compared with DME, there is often more intraretinal hemorrhage in the macula of patients with acute BRVO, which can make laser photocoagulation more risky. Normally laser light is absorbed by the pigment of the retinal pigmented epithelium and converted to heat resulting in damage to photoreceptors with sparing of the overlying retina. If there is intraretinal blood where laser is delivered, hemoglobin absorbs the laser light and converts it to heat in the inner retina resulting in a superficial burn, which may damage ganglion cells and their axons, causing a permanent scotoma and reducing the damage in the photoreceptor layer thereby failing to reduce oxygen utilization by photoreceptors—the objective of the treatment. Also, compared with DME, the leakage in BRVO is more confluent, involving telangiectatic retinal vessels in the half of the macula on the side of the occlusion. In the late 1970s, the BRVO Study Group[8] designed a protocol to test the effect of grid laser photocoagulation throughout the area of diffuse fluorescein leakage in the macula, avoiding the foveal avascular zone, in BRVO patients. To allow reduction in hemorrhage and to exclude patients with spontaneous improvement, all patients were observed for 3 months after which patients who had macular edema (ME) causing reduction of best-corrected visual acuity (BCVA) to ≤20/40 were randomized to laser (n=69) or observation (n=70). The duration of disease at randomization ranged from 3 to 18 months. Patients randomized to laser, who had substantial intraretinal hemorrhage in the macula, had laser deferred until the hemorrhages had cleared sufficiently to allow laser to be performed safely. Patients were evaluated by fluorescein angiography 4 months after laser and additional grid laser photocoagulation was applied if untreated leaking areas were present with continued reduction in BCVA. Of the 69 patients in the laser group, 53, 10, two, and four received one, two, three, and five treatments, respectively. The mean follow up was 3.1 years, 115 patients had at least two years of follow up, and 78 had 3 years of follow up. Visual outcomes were reported only for the 78 patients who had a 3-year visit. Compared with the control group in which the mean improvement from baseline was 0.23 lines and 37 % gained ≥2 lines, in the laser group the mean improvement from baseline BCVA was 1.33 lines (about seven letters) and 65 % gained ≥2 lines. As a result of this study, grid laser photocoagulation according to the protocol of the study became standard care for patients with BRVO.

Anti-vascular Endothelial Growth Factor Therapy

A pilot study in which 20 BRVO patients were randomized to receive three injections once a month of 0.3 mg or 0.5 mg of ranibizumab (Lucentis™, Genentech, South San Francisco, CA) demonstrated that either dose of ranibizumab resulted in a marked reduction in edema and mean improvement BCVA of about 15 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol for measurement of visual acuity.[9] This provided the rationale for a large multicenter randomized control trial, the RanibizumaB for the Treatment of Macular Edema following BRAnch Retinal Vein Occlusion (BRAVO) Study.[10] Patients were randomized to receive monthly intraocular injections of 0.3 mg (n=134) or 0.5 mg (n=131) of ranibizumab or sham injections (n=132). The three groups were balanced in terms of baseline characteristics, with the following mean values among the three groups: age=66 years, BCVA Score=54.6 (approximate Snellen Equivalent 20/80), time from diagnosis of BRVO=3.5 months, and mean center point thickness (CPT)=520 µm. Starting at month 3, patients were eligible for grid laser treatment if hemorrhages had cleared sufficiently to allow safe application of laser, BCVA was ≤20/40, or mean central subfield thickness (CST) was ≥250 µm, and compared with the visit 3 months before the current visit, the patient had a gain of <5 letters in BCVA or a decrease of <50 µm in mean CST. If rescue laser was not given at month 3, the same criteria were applied at month 4, and if rescue laser was not given at month 4, the criteria were applied at month 5. At the 6-month primary endpoint, after having received monthly injections, mean change from baseline BCVA letter score was 16.6 and 18.3 in the 0.3 mg and 0.5 mg ranibizumab groups and 7.3 in the sham group ($p<0.0001$). The percentage of patients who gained ≥15 letters in BCVA was 55.2 % (0.3 mg) and 61.1 % (0.5 mg) in the ranibizumab groups and 28.8 % in the sham group ($p<0.0001$). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 67.9 % (0.3 mg) and 64.9 % (0.5 mg) compared with 41.7 % in the sham group ($p<0.0001$). The percentage of patients with a Snellen equivalent BCVA of 20/200 or worse was 1.5 % (0.3 mg) and 0.8 % (0.5 mg) compared with 9.1 % in the sham group ($p<0.01$). There was greater reduction of ME in the ranibizumab groups because CFT was reduced by 337.3 µm (0.3 mg) and 345.2 µm (0.5 mg) compared with 157.7 µm in the sham group. The percentage of patients with CFT ≤ 250 µm at 6 months was 91 % (0.3 mg), 84.7 % (0.5 mg), and 45.5 % (sham, $p<0.0001$). More patients in the sham group (54.5 %) received rescue grid laser therapy than in the 0.3 mg (18.7 %) or 0.5 mg (19.8 %) ranibizumab groups.[10] After the primary endpoint, patients were evaluated every month and if study eye BCVA was ≤20/40 or mean CST was ≥250 µm, they received an injection of ranibizumab; patients in the ranibizumab groups received their assigned dose and patients in the sham group received 0.5 mg. The mean number of ranibizumab injections between 6 and 12 months was 2.9, 2.8, and 3.8 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients that did not receive any injections was 17.2, 20.0, and 6.5, respectively. The improvement from baseline in ETDRS letter

score at month 12 was 16.4 (0.3 mg) and 18.3 (0.5 mg) in the BRAVO ranibizumab groups—similar to the month 6 results. Improvement from baseline BCVA was 12.1 letter score at month 12 in the sham/0.5 mg group compared with 7.3 at month 6. The percentage of patients who had an improvement from baseline BCVA letter score ≥15 at month 12 was 55.2 % (0.3 mg) and 61.1 % (0.5 mg) in the ranibizumab groups, almost identical to the month 6 results. In the sham/0.5 mg group, 43.9 % of patients improved from baseline ≥15 in letter score at month 12 compared with 16.9 % at month 6. At month 12, 67.9 % (0.3 mg) and 64.4 % (0.5 mg) of patients in the ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared with 56.8 % in the sham/0.5 mg group. Thus, patients in the sham groups showed a substantial improvement in vision during the second 6 months when they were able to receive ranibizumab as needed, but their vision at month 12 was not as good as that in patients in the ranibizumab groups. There were no safety concerns in patients treated for one year with ranbiziumab.[11]

Approximately 85 % of patients who completed BRAVO (n=304; sham/0.5 mg=97; 0.3 mg=103; 0.5 mg=104) participated in the follow-up study HORIZON (An Open-Label, Multicenter Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects With Choroidal Neovascularization Secondary to Age-Related Macular Degeneration or Macular Edema Secondary to Retinal Vein Occlusion Who Have Completed a Genentech-Sponsored Ranibizumab Study), in which patients were seen at least every 3 months and treated with 0.5 mg ranibizumab for recurrent ME.[12] In the midst of this two-year study, ranibizumab was approved by the US Food and Drug Administration (FDA) for treatment of RVO and, according to the protocol, all patients were discontinued from the study by 30 days after the approval date. As a result, duration of follow up varied considerably among patients enrolled in HORIZON, with a mean of ~14±4.7 months and a range of 1 to 24 months. Two hundred and five patients (63 %) had a 12-month study visit, (sham/0.5 mg=66; 0.3/0.5 mg=66; 0.5 mg=73). The mean number of ranibizumab injections (excluding the month 12 injection) was 2.4, 2.1, and 2.0 in the 0.3/0.5 mg, 0.5 mg, and sham/0.5 mg groups compared with 8.9, 8.8, and 3.8 during the 12 months of BRAVO. The reduction in frequency of ranibizumab injections during the second year of follow up had little effect on patients with BRVO. Mean BCVA gains achieved at month 12 of the BRAVO study were reduced by letter score values of 2.0 (0.3/0.5 mg) and 1.7 (0.5 mg) and increased by 2.4 in the sham/0.5 mg group, while mean CFT was increased by 16 µm, 30 µm, and 6 µm.[12] These data are consistent with a pilot study that demonstrated that after a period of monthly injections, patients with BRVO on average remained stable when seen every 2 months and given a ranibizumab injection for persistent or recurrent edema.[13] In the same pilot study, follow up every 2 months was not sufficient to maintain stability in patients with CRVO. Similarly, patients treated in the Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon (CRUISE) Study[14,15] lost some of the benefit they had obtained with monthly visits when followed up was reduced to every 3 months in HORIZON. A likely explanation for the difference is that patients with CRVO tend to have a greater amount of retinal ischemia and VEGF production. Also, the use of grid laser treatment in some patients with BRVO may have contributed to the greater stability in BRVO patients by decreasing production of VEGF. The percentage of BRVO patients enrolled in HORIZON who received grid laser treatment during BRAVO was 43 % (0.3/0.5 mg), 36 % (0.5 mg), and 67 % (sham/0.5 mg). The percentage was 13 % (0.3/0.5 mg), 11 % (0.5 mg), and 9 % (sham/0.5 mg) during HORIZON. Thus, a large proportion of patients with BRVO received grid laser treatment, with the majority of treatments occurring during BRAVO. Another strategy to reduce production of VEGF and reduce the need for prolonged injections of ranibizumab is scatter photocoagulation to peripheral areas of reduced perfusion. Currently, this strategy is being investigated for BRVO and CRVO in the Ranibizumab DosE Comparison and the Role of LAser in REtinal Vein Occlusions (RELATE) study (NCT01003106).

ME is not the only consequence of high intraocular levels of VEGF. The high levels of VEGF also promote retinal hemorrhages because, compared with sham-treated patients, those treated with monthly injections of ranibizumab have significantly more rapid clearing of intraretinal hemorrhages.[11] Also, sham-treated patients with BRVO or CRVO experience worsening in RNP over time, which is prevented by monthly injections of ranibizumab.[16] Thus, aggressive anti-VEGF treatment may prevent worsening of the disease and hence shorten the duration of treatment that is needed. There is considerable variability among patients with RVO treated with ranibizumab. Some stabilize after an injection of ranibizumab every month for 6 months and require few injections thereafter, while some require frequent follow up and continued injections to control edema. Thus far, using frequent injections for at least 2 years in patients who require them has not shown retinal toxicity or notable disadvantages.

Intraocular injections of bevacizumab (Avastin®) also provide benefit in patients with BRVO.[17] It is not clear how its effects compare with those of ranibizumab. Systemic suppression of VEGF is greater with bevacizumab than ranibizumab, and in patients with neovascular age-related macular degeneration (NVAMD) serious adverse events were greater in patients treated with bevacizumab than those treated with ranibizumab.[18] This has raised safety concerns in terms of the use of bevacizumab in patients with RVO. Balancing the possibility of a small increase in risk with bevacizumab with the substantial cost savings is something with which physicians and patients are wrestling. Aflibercept (Eylea®) is another anti-VEGF agent that has been approved for treatment of NVAMD. It provides benefit in patients with CRVO and is currently being investigated in patients with BRVO.[19–22]

Intraocular Steroids

Triamcinolone Acetonide

In the multicenter randomized control phase III Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) BRVO trial, the safety and efficacy of preservative-free intravitreal triamcinolone was compared against grid laser in BRVO patients.[23] Patients were randomized to receive 1 mg (n=136) or 4 mg (n=138) triamcinolone or grid laser (n=137). Baseline characteristics were well balanced with the following mean values among the three groups: age=67 years, BCVA Score=57 (approximate Snellen Equivalent 20/80), time from diagnosis of BRVO=4 months, and the mean CPT=523 µm. All patients were treated at 4-month intervals unless they met any of the following three criteria: a) treatment was successful (CST≤225 µm with BCVA≥20/25 or substantial improvement in edema that is expected to continue from prior treatment), b) treatment was contraindicated due to significant adverse events (e.g. intraocular pressure [IOP] rise requiring treatment) or maximum grid photocoagulation having been performed, or c) two

Table 1: Comparison of Major Inclusion/Exclusion Criteria of Clinical Trials Investigating Treatments for Macular Edema Due to Branch Retinal Vein Occlusion

	BRAVO	SCORE	GENEVA	BVOS
Key inclusion criteria				
Snellen BCVA	20/40–20/400	20/40–20/400	20/50–20/200	20–40 or worse
CST (µm)	≥250	≥250	≥300	–
Duration of disease (months)	≤12	≤12	1.5 to ≤12	3 to ≤18
Key exclusion criteria				
	General • DR or AMD • Prior episode of RVO • 10-letter improvement in BCVA between screening and day 0 • Brisk afferent pupillary defect Prior treatment: • Radial optic neurotomy or sheathotomy • Intraocular corticosteroid use in study eye within 3 months before day 0 • Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0 • Laser photocoagulation for ME within 4 months before day 0 Therapy specific: • CVA or MI within 3 months before day 0 • Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 • Systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0	General • ME due to a cause other than RVO • Ocular conditions such that visual acuity would not improve from resolution of the edema (e.g. foveal atrophy) • Substantial cataract estimated to have reduced VA by ≥3 lines Prior treatment: • Intravitreal corticosteroids at any time • Peribulbar steroid injection within 6 months before randomization • Focal/grid macular photocoagulation within 3.5 months • Panretinal photocoagulation within 4 months before randomization or anticipated need for panretinal photocoagulation within the 4 months after randomization • Pars plana vitrectomy • Major ocular surgery (including cataract extraction) within prior 6 months or anticipated within the next 6 months after randomization • Yttrium aluminum garnet capsulotomy performed within 2 months before randomization Therapy specific: • IOP ≥25 mmHg, open-angle glaucoma, steroid-induced IOP elevation that required IOP-lowering treatment • Pseudoexfoliation • Aphakia	General • DR, epiretinal membrane, active retinal or optic disc neovascularization, choroidal neovascularization, rubeosis iridis, active infection • Ocular condition that, in the opinion of the investigator, would prevent a 15-letter improvement in VA • Clinically significant media opacity • Any uncontrolled systemic disease Therapy specific: • Aphakia or anterior-chamber intraocular lens • Glaucoma or current ocular hypertension requiring more than one medication to control IOP in the study eye • History of steroid-induced IOP increase in either eye • Currently using or anticipating the use of systemic steroids or anticoagulants during the study	General • Presence of other ocular disease-threatening VA • Use of an anticoagulant (such as aspirin) for systemic conditions and could not discontinue medication

AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CST = central subfield thickness; CVA = cerebrovascular accident; DR = diabetic retinopathy; IOP = intraocular pressure; ME = macular edema; MI = myocardial infarction; RVO = retinal vein occlusion; VA = visual acuity.

treatments yielded no evidence of borderline improvement (defined as ≥five letter gain or decrease in ≥50 µm thickness, which is a reduction of more than a 20 %). The investigator had the option to treat even if these criteria were met. At the month 12 primary endpoint, mean change from baseline BCVA letter score was 5.7 (1 mg) and 4.0 (4 mg) in the triamcinolone groups compared with 4.2 in the grid laser group. The percentage of patients who gained ≥15 letters in BCVA was 26 % (1 mg) and 27 % (4 mg) in the triamcinolone groups compared with 29 % in the laser group. Thus, triamcinolone injections were not superior to grid laser after 1 year. There was no effect of triamcinolone on RNP. In patients who were followed up to a period of 3 years, the mean improvement in BCVA letters was 4.4 (n=44), 8.0 (n=38), and 12.9 (n=46), in the 1 mg, 4 mg and grid laser groups. Therefore, triamcinolone is not recommended for the treatment of BRVO.

Dexamethasone Implant

Two identical multicenter randomized controlled phase III trials comparing the effects of intraocular injection of 0.7 mg or 0.35 mg dexamethasone implants (Ozurdex®) to sham injections in patients with ME due to CRVO or BRVO were conducted by the Global Evaluation of implantable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) Study Group.[24,25] Pooled results from both trials for all RVO patients, along with a prospectively planned subanalysis on BRVO patients were reported. Out of the total of 1,267 RVO patients enrolled, 830 BRVO patients were

Table 2: Comparison of Clinical Trials Investigating Treatments for Macular Edema Due to Branch Retinal Vein Occlusion

	BRAVO*			SCORE			GENEVA			BVOS	
n	397			411			830			139	
Study drug	Ranibizumab			Triamcinolone			Dexamethasone				
Treatment group	0.3 mg	0.5 mg	Sham	1 mg	4 mg	Laser	0.7 mg	0.35 mg	Sham	Laser	Control
Baseline	n=134	n=131	n=132	n=136	n=138	n=137	All RVO patients			n=71	n=68
Mean ETDRS letter score	56.0	53.0	54.7	57.9	56.2	56.8	54.3	53.9	54.8	–	–
Median Snellen BCVA equivalent†/range††	20/80†	20/63–20/80††	20/80†	20/40–20/63††	20/40–20/63††	20/40–2 20/63††	20/80†	20/80†	20/80†	20/70–20/100††	20/70–20/100††
Mean CPT (µm)	522	552	488	495	483	497	562	555	539	–	–
Mean age/median age range (years)	66.6	67.5	65.2	67.2	68.1	66.9	64.7	64.9	63.9	60–69	60–69
Mean time from diagnosis/range of mean	3.6	3.3	3.7	4.1	4.6	4.5	5.6	5.5	5.6	56 %→0–12 34 %→13+	58 %→0–12 34 %→13+
Month 6/month 8	M6 n=128	M6 n=125	M6 n=123	M8 n=124	M8 n=122	M8 n=127	M6 n=291	M6 n=260	M6 n=279		
Mean ΔBCVA	16.6	18.3	7.3	5.0	4.3	1.6	7.5	7.5	5		
% who gained ≥15 letters	55.2	61.1	28.8	24	22	29	23	21	20		
Mean decrease in CPT (µm)	337	345	158								
% CPT ≤250	91	85	46								
Month 12	n=119	n=123	n=114	n=121	n=125	n=121					
Mean ΔBCVA	16.4	18.3	12.1	5.7	4	4.2					
% who gained ≥15 letters	56.0	60.3	43.9	26	27	29					
Mean decrease in CPT (µm)	314	347	274								
Median decrease in CPT (µm)				149	170	224					
Month 36				n=44	n=38	n=46			n=43	n=35	
Mean ΔBCVA ETDRS letters				4.0	8.0	12.9			6.65	1.15	
% who gained ≥15 letters				25	50	48					
% who lost ≥15 letters				14	21	7					
% who gained two or more lines									65	37	
% who lost two or more lines									12	17	

**All patients eligible to receive laser. BCVA = best corrected visual acuity; CPT = center point thickness; ETDRS = early treatment diabetic retinopathy scale; M = month; RVO = retinal vein occlusion.*

randomized to receive 0.7 mg (n=291) or 0.35 mg (n=260) of dexamethasone implant compared with sham (n=279). The baseline characteristics of all RVO patients were well balanced across the three groups with mean BCVA score=54 (approximate Snellen Equivalent 20/80), and mean CPT (CPT)=550 µm. At the 6-month primary endpoint, the mean change from baseline BCVA letter score was 7.5 in the two dexamethasone implant groups compared with 5.0 in the sham group (p=0.008). The percentage of patients who gained ≥15 letters in BCVA was 23 % (0.7 mg) and 21 % (0.35 mg) in the implant groups and 20 % in the sham group. At 6 months there was little evidence of benefit to patients with one injection; however, treatment response was seen at earlier time points. Peak response was noted at 2 months, the mean change from baseline BCVA letter score was 10 (0.7 mg) and 9 (0.35 mg) in the two implant groups, significantly better than sham (BCVA letter score=5; p<0.001), and 30 % and 26 % of patients gained ≥15 letters in BCVA compared with 13 % for sham. At 3 months, the mean change from baseline BCVA letter score was 9 (0.7 mg) and 8 (0.35 mg) in the two implant groups, significantly better than sham (BCVA letter score=5; p<0.001), and 24 % and 23 % of patients gained ≥15 letters in BCVA compared with 15 % for sham.

After the primary endpoint, patients were enrolled in an open-label extension with all groups being eligible for a 0.7 mg implant at month 6 if BCVA was <84 letters (20/20) or retinal thickness was >250 µm, if in the investigator's opinion the procedure would not put the patient at significant risk. The same response was seen with peak effect at month 2 after dexamethasone implant. In the 0.7/0.7 mg group, the 227 patients who received two treatments had an improvement of 10 letters at month 2, which came down to about seven at month 6. After the second implant, the BCVA letter score improvement from baseline returned to approximately 10 at month 8 gradually falling to around 7.5 letters by month 12. In the sham/0.7 group, the 210 patients who received treatment in the open-label phase had peak improvement at month 2 of five letters and a mean improvement of approximately three letters when they were treated at month 6. The peak gain was around 8.5 letters at month 8 and declined to around seven letters at month 12.

There was also a corresponding increase in IOP parallel to drug activity and observed letter gain, with the percentage of patients with IOP of ≥35 mmHg or ≥25 mmHg, or an IOP increase of >10 mmHg increasing at month 2 in the implant treatment groups and at month 8 for those patients receiving treatment at month 6. There was a higher rate of cataract progression with the increased use, and the higher dose, of dexamethasone implant. There was no effect of the dexamethasone implant on progression of RNP as observed at month 6. There was no effect of the dexamethasone implant on progression of RNP as observed at month 6.[26]

A summary of BVOS, BRAVO, SCORE-BRVO and GENEVA trials is presented in *Tables 1* and *2*.

Prognostic Factors

Older age, history of coronary disease, and longer duration of edema are associated with reduced visual acuity outcomes in BRVO.[8,27] BRVO patients with a shorter duration of disease are more likely to have a higher visual acuity gain and better final visual acuity when treated with ranibizumab or a dexamethasone implant.[10,13,28]

Poor visual outcome correlates with increased foveal avascular zone (FAZ)[29] or disruption of perifoveal capillaries seen in fluorescein angiograms.[30–32] Similarly in BRVO patients treated with grid laser, those with intact perifoveal capillaries have a better visual prognosis than those with perifoveal capillary disruption.[31]

Nonperfusion is a significant baseline factor for development of disc or retinal neovascularization in patients with BRVO with the highest risk at ≥5.5 disc areas.[33]

The use of optical coherence tomography (OCT), particularly spectral domain OCT (SD-OCT), has brought attention to a correlation between visual acuity and the visualization of inner segment/outer segment (IS/OS) and/or external limiting membrane (ELM) at the fovea.[34–36] It is clear that absence of the IS/OS and/or ELM on OCT is strongly correlated with poorer BCVA at baseline in the presence of edema, and after resolution of edema following treatment.[34–36] However, absence of IS/OS visualization in a patient with edema may be due to damage/loss of photoreceptor cells or may be due to disarrangement of the photoreceptors due to fluid.

Patients with intact IS/OS and ELM at baseline have been reported to fare better in one retrospective analysis, which used a multiple regression model with CPT at baseline as a predictor variable to suggest that baseline IS/OS and ELM status are predictors of final BCVA independent of thickness,[35] but further studies are required to validate this. It has also been shown that the IS/OS status can improve and this change is accompanied with BCVA gain compared with no change in IS/OS status.[36]

Recommendations

When a patient presents with ME due to a recent BRVO, intraocular injections of ranibizumab or bevacizumab are the treatment of choice. Because systemic exposure is greater with bevacizumab, which is a potential safety risk, we prefer ranibizumab. After six injections a month apart, it is reasonable to see patients monthly and treat only if there is recurrent intraretinal or subretinal fluid demonstrated by OCT. If frequent injections are required and there is diffuse leakage in the macula, grid laser photocoagulation should be considered. If 6 months or more after grid laser photocoagulation frequent injections of ranibizumab are still required, it is reasonable to consider switching to dexamethasone implant if the patient does not have glaucoma and has no documented episodes of steroid-induced ocular hypertension. This has the advantage of reducing the frequency of visits and injections, but has the disadvantage of increased risk for increase intraocular pressure and cataract. The benefits and risks for scatter photocoagulation to ischemic peripheral retina are not known, but this technique is being tested. ■

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