INTRAVITREOUS BEVACIZUMAB IN THE TREATMENT OF MACUAR EDEMA FROM BRANCH RETINAL VEIN OCCLUSION AND HEMISPHERE RETINAL VEIN OCCLUSION (AN AOS THESIS)

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ABSTRACT

Purpose: To compare intravitreous bevacizumab to other current treatments of branch retinal vein occlusion (BRVO) and hemisphere retinal vein occlusion (HRVO) with consideration to visual outcome, cost, convenience, and risk of treatment.

Methods: This is a retrospective chart review from a large referral retina practice. The data comprise 56 patients with BRVO and HRVO treated by intravitreous bevacizumab, with and without intravitreous triamcinolone acetonide. Initial visual acuities at the time of first bevacizumab injection, best acuities through the follow-up time, final acuity at last visit before review, initial macular thickness, and final macular thickness were measured. Changes in vision and thickness were calculated, as were the percentage of eyes improving, stabilizing, and worsening.

Results: The data were compared to composite data derived from several current treatments of BRVO. The subgroup of 39 eyes that received only bevacizumab without triamcinolone acetonide had the most improvement in vision. The median change in visual acuity was 1.5 lines (P = .012) over a mean follow-up of 8.8 months. Twenty-three eyes (59%) improved visually, with 20 eyes (51%) improving 2 or more lines. These results are similar to those for eyes that received argon grid laser and chorioretinal anastomosis, but are worse than in eyes that received arteriovenous adventitial sheathotomy, macular decompression surgery, and intravitreous triamcinolone acetonide.

Conclusions: Visual benefit from intravitreous bevacizumab compares well against laser treatments for BRVO and HRVO but not as well opposed to surgical techniques and intravitreous triamcinolone acetonide. Intravitreous bevacizumab injection has a risk, cost, and convenience profile that is favorable.

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INTRODUCTION

OVERVIEW

The circulation to the inner retina derives from the central retinal artery and central retinal vein. The central retinal vein forms at the nerve head by the confluence of tributaries of retinal veins and accompanies the central retinal artery, which emerges out of the nerve. Usually there are 2 main contributors, a superior and an inferior branch. Sometimes the 2 retinal veins remain separate until uniting within the substance of the nerve.[1] The central vein then goes on through the central nerve to leave the optic nerve posterior to the globe in the orbit. Within the nerve head, as they cross the sclera foramen, the artery and vein traverse the lamina cribrosa, a rather rigid mesh of fibrous tissue. Within the retina, the retinal arteries and veins follow roughly the same paths and cross extensively. At crossings, the 2 vessels share a common wall and adventitial sheath.[2]

There are 2 general categories of retinal vein occlusion: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). These categories have both common and unique features and vary substantially as to etiology and prognosis. The common characteristics are due to occlusion of the vein and include venous congestion, ischemia, retinal hemorrhages, and retinal edema. Although retinal vein occlusions are infrequent in the population, they are a major cause of visual disability.[3,4] The Blue Mountains Eye Study was a population-based study in suburban Australia with data collection at 5 and 10 years. The 10-year incidence of BRVO was 1.2% and of CRVO was 0.4%.[5] Many treatments addressing congestion, ischemia, and edema have been considered, as well as efforts to treat the occlusion directly and to treat the underlying systemic associations thought to predispose to progression. Generally, these treatments have been disappointing as to long-term visual outcomes. With the exception of focal argon laser photocoagulation, few treatment methods have been subjected to prospective randomized clinical trials. This thesis reviews the etiology, prognosis, and current treatment possibilities of BRVO and hemisphere retinal vein occlusion (HRVO) and compares results in the literature with a series of BRVOs treated with bevacizumab, collected retrospectively from a large retinal practice.

In both CRVO and BRVO, the occlusion occurs in a location where the vein and accompanying artery run along in proximity and share an adventitial sheath. The artery wall is thicker and less flexible and impinges on the vein.[6] Turbulence occurs, and the combination of a narrowing of the lumen and turbulence allows endothelial cell damage and a thrombus to form. The sequelae of a venous occlusion depend on the extent of tissue involvement, ischemia, and edema created by the insufficient flow. Accordingly, CRVO affects a larger area, since the occluded vessel controls flow from the whole retina. Because the fovea is at a watershed and is usually influenced by at least 2 vessels, obstruction of a branch vessel would be likely to have less macular injury.

For the central vein this narrowing occurs as the artery and vein traverse the lamina cribrosa in the optic nerve head.[7] There is sharing of a common wall, and the lumen is impinged on and narrowed by the stiffness of the lamina. The stagnation of free flow associated with narrowing of the vessel lumen at the lamina causes turbulence, then thrombus formation, and ultimately occlusion of the vein. The thrombus forms at the lamina or somewhere posterior to the lamina cribrosa. Prognosis with central vein occlusions varies and is based primarily on the degree of ischemia associated with the occlusion. According to Gass,[8] the degree of occlusion and the concomitant ischemia produced may depend on the degree of collateralization that is possible. The potential for collateral development is less when occlusion occurs at the lamina than when occlusion is located more posteriorly within the nerve. Those vein

occlusions associated with little ischemia have been termed venous stasis, perfused, or nonischemic and generally have a good prognosis. Those with greater ischemia have a substantial reduction in vision and smaller chance of recovery. Additionally, severe ischemia produces a neovascular process both on the retinal surface and on the iris that creates the additional issues of vitreous hemorrhage and fibrosis and neovascular glaucoma. Thus, the visual loss in CRVO is frequently severe and due to a combination of factors, only one of which is edema.

With BRVO, the site where the artery and vein are proximate and the lumen of the vein is impinged by the more robust arterial wall is at an arteriovenous (AV) crossing.[6] This occurs more frequently when the artery overlies the vein, more often in the superior temporal quadrant.[9] Branch retinal vein occlusions have perhaps less opportunity for collateralization.[8] Visual outcome depends on the degree of ischemia, hemorrhage, and edema associated with the process.

Hemisphere vein occlusions are a subcategory with characteristics of both CRVO and BRVO. Hayreh and associates[10,11] have shown that many HRVOs are etiologically more closely associated with central vein occlusion than branch vein occlusion. The occlusion may occur at the lamina or posteriorly in eyes where the branching to superior and inferior veins occurs behind the lamina.[8] An association of HRVO with chronic open-angle glaucoma reinforces the correlation with central vein occlusion.[12] Alternatively, analysis of the point of obstruction suggests an association with branch veins in many cases. In a series of 104 eyes, Sanborn and Margargal[13] found that only 90% of hemispheric vein occlusions occurred at a branch distal to the optic nerve head. These findings suggest that the etiologic relationship of hemispheric vein occlusion may be associated with both categories. As to prognosis and perhaps response to treatment, the extent of the occlusion and the degree of macular ischemia would likely be the more important considerations, and thus prognosis and good response might be more likely associated with BRVO.

Bevacizumab

Vascular endothelial growth factor (VEGF) is a vasoactive protein made by many tissues both physiologically for tissue maintenance and pathologically in response to various drivers, such as ischemia and resulting hypoxia. VEGF is required for normal development, and reduction of VEGF during embryogenesis causes defects in the development of the cardiovascular system in mice.[14] VEGF has 5 isoforms. VEGF 165 has been shown to be associated with human pathologic responses while having less effect on physiologic responses.[15] However, when selectively blocked, VEGF 165 had less effect on choroidal neovascularization than when VEGF 121 was also blocked.[16,17]

Bevacizumab (Avastin, Genentech) is a monoclonal antibody that blocks all VEGF isomers in the human. Although there are few data from controlled trials, there is a large clinical experience with the use of bevacizumab administered intravitreally. This experience encompasses myriad retinal diagnoses, including retinal vein occlusions.

Ischemia

To limit the degree of ischemic injury to the tissue would require either reopening the occluded vessel, producing collateral flow, or influencing the involved tissue to be more tolerant of the ischemia. Unlike possible surgical alternatives, which might reopen the affected vessel or influence collateralization, it is difficult to explain how bevacizumab would reduce the ischemia of the affected tissue. Perhaps a reduction of tissue swelling might reduce compression on either large or small vessels, or reduction of edema could improve the metabolism of the neural or structural retinal cells, allowing them to better withstand the ischemic insult.

A secondary effect of ischemia is to signal the up-regulation of VEGF, which, if present in adequate quantity, produces neovascularization of the retina or iris and increased retinal capillary permeability, causing retinal edema.

Edema

Edema, acute and chronic, affects the function of the retina. Ischemia causes intracellular edema with obstruction of axoplasmic flow and constipation of organelles. This causes a whitening of the retina either as a cotton-wool spot or in broader areas. Extracellular accumulation of fluid commonly occurs in the macula in the Henle layer. With more chronic swelling, lipid deposition is prominent as serous fluid resorbs more rapidly.

In venous occlusive disease, there is an increase in hydrostatic pressure in the vascular tree, causing hemorrhages and driving fluid out of the vessels according to the dictates of the Starling law.[18] Additionally, there is ischemia and production of vasoactive proteins and cytokines, which increase vascular permeability.[19] Bevacizumab should be helpful for those portions of the edema mediated by VEGF.

Neovascularization

If VEGF is produced in adequate quantity, neovascularization of the retina or iris, or both, may occur. These complications are driven by substantial VEGF production and are more common with vein occlusions with larger areas of involvement; thus they are more common with CRVO than with BRVO. Since ischemia drives the VEGF production, these complications are often present in the most severely affected eyes, and visual prognosis is poor. Treatment with bevacizumab would not be expected to improve visual acuity markedly. If rubeosis and neovascular glaucoma occur, preservation of the globe may be considered an adequate result.

CURRENT TREATMENTS OF BRANCH RETINAL VEIN OCCLUSION

Antiplatelet Agents

Klein and associates[4] reported in the Beaver Dam Eye Study that aspirin intake was not associated with the incidence or prevalence of retinal vein occlusion. Yamamoto and associates[20] have shown that the number of small platelet aggregates is higher in patients with CRVO than in controls, but there was no difference with BRVO. Ticlopidine prevented small platelet aggregates, and beraprost, an

experimental platelet inhibitor, inhibited all sizes of platelet aggregates. Houtsmuller and associates[21] showed improved visual outcomes compared to placebo with ticlopidine therapy when used in 54 patients with BRVO.

Hemodilution

Hemodilution is the process that lowers the hematocrit of blood by increasing the plasma. Acute isovolemic hemodilution has been used primarily as a presurgical technique to reduce the likelihood of needing an allogeneic transfusion postoperatively. This is accomplished by removal of blood immediately prior to surgery and replacement with an equal quantity of a plasma expander to replace the volume of blood taken. After surgery the patient can be transfused with his or her own blood.

Hemodilution also serves to reduce the viscosity of the blood, which may have an advantageous effect on the circulation after retinal vein occlusion. Wiek and associates[22] have shown that patients with retinal vein occlusions who are treated by hemodilution have a reduction in the hematocrit and the whole blood viscosity, but no change in plasma viscosity, red cell aggregation, or red cell filterability. Several studies, mostly European, have shown that isovolemic hemodilution may result in improved visual outcomes with CRVO. Glacet-Bernard and associates[23] collected 142 patients with significant visual loss and without widespread nonperfusion and treated them by hemodilution. The hematocrit was decreased to less than 35 for 6 weeks. These patients were compared with a group of similar patients with CRVO who did not have hemodilution. Although the control group had better visual acuity initially, with 48% better than 20/40 compared to 30% in the treated group, they were equal at 41% after treatment. The percentage of eyes with visual acuity worse than 20/200 was 24% in the treated group and 42% in the untreated group. Additionally, fewer of the eyes in the treated group converted to ischemic CRVO, 34% vs 54%. Vision improved immediately in 43% of the treated eyes. Plasma viscosity substantially decreased, as did plasma fibrinogen. Other studies have found an advantage for hemodilution for CRVO.

One study has looked at the use of hemodilution in BRVO. Chen and associates[24] studied 34 patients with a major BRVO in the temporal quadrant and neovascularization. All but 3 patients had more than a macular BRVO (a nonmajor temporal BRVO), and patients with macular BRVO were excluded because they were thought to have a better natural prognosis. Hemodilution was performed on 18 patients by removing up to 500 mL of blood and replacement by an equal volume of a 6% solution of hydroxyethylstarch as a plasma expander. The hematocrit was maintained just below 35% for 6 weeks. This level was thought to reduce viscosity but maintain oxygen-carrying capacity. Sixteen patients provided a control group. At 6 weeks the treated patients showed a 2-line Snellen advantage visually, and this increased to 4 lines over the period of a year. The control patients improved by a little more than 1 line, and the treated patients improved by 4 lines. Initial visual acuity for both groups was 20/120, and the final acuity of the treated group was 20/40. Macular grid laser photocoagulation was applied to 28% of the treated group and 44% of the controls. Hemodilution did not influence the final degree of capillary nonperfusion. Hematocrit was lowered in these treated patients, but other parameters of viscosity and rheology were not measured. The investigators concluded that hemodilution improved visual outcomes for BRVO.

Intravitreous Injections

Injecting a therapeutic substance directly into the vitreous offers the advantage of achieving high levels of medications locally in the retina and vitreous while minimizing the systemic risks and bypassing the barrier effects of the retinal circulation. Early attempts included the injection of urokinase to clear vitreous hemorrhage and antibiotics for retinitis and endophthalmitis.[25-28] The idea of intravitreous injection of substances that might influence macular edema followed, with the development of pegaptanib and ranibizumab to block VEGF. Intravitreous triamcinolone acetonide (IVT) with vascular stabilizing properties has also become popular. Other products have been tried, including bevacizumab and tissue plasminogen activator (tPA).

Intravitreous Triamcinolone Acetonide.

Intravitreous corticosteroid injections have been used for a variety of retinovascular conditions that produce edema, including exudative diabetic retinopathy, CRVO, BRVO, and cystoid macular edema (CME).[29,30] The mechanism of action is multifold and not well understood. Theories include suppression of VEGF and providing a stabilizing influence on the retinal vasculature by increasing the tight junctions of the retinal capillary endothelium and by suppressing leukocyte adhesion to vessel walls.[31] Intravitreous triamcinolone acetonide gained popularity after the turn of the century and has been applied widely. Several large series have been reported using IVT for exudative diabetic retinopathy and age-related macular degeneration. Retinal vein occlusion has been treated as well, with series reported for CRVO and BRVO.[32] CRVO is a particularly appealing target because little has been found effective for the treatment of the nonischemic variety of the disease, where diffuse exudation in the macular area predominates and reduces acuity. Specifically, focal grid laser photocoagulation has not proven effective in such cases. Branch retinal vein occlusion also has a rather diffuse pattern of leakage and may or may not respond to laser photocoagulation.

The first single case reports of the use of IVT in BRVO were published in 2003 and 2004. Degenring and coworkers[33] reported a case of BRVO with CME and visual acuity reduced to 20/80 and with macular thickness of 400 μm. Five weeks after injection of 25 mg of triamcinolone acetonide, visual acuity improved to 20/40 and macular thickness improved to 210 μm. Chen and associates[34] reported on a patient with BRVO with macular edema and visual acuity of 20/200 and macular thickness of 337 μm. After IVT (4 mg), visual acuity improved to 20/80 and macular thickness to 160 μm. The investigators in both cases were cautious but optimistic about this form of treatment.

Yepremyan and coworkers[35] treated 12 eyes with BRVO and macular edema with 4 mg of IVT. Eyes thought to be at risk of progression because of substantial macular edema were treated early. Vision improved almost immediately with mean visual acuity of 20/70 in 1 week and improvement to 20/60 after an average 15-month follow-up. Macular thickness also improved from an initial

mean thickness of 589 µm to 235 µm at the final visit. Five eyes required a second injection.

Hayashi and Hayashi[36] compared the effectiveness of IVT with retrobulbar injections of triamcinolone acetonide. Four milligrams was injected intravitreously in 27 eyes, and 40 mg was given by retrobulbar injection in 25 eyes. The mean logMAR acuity improvement in the IVT groups, from 0.598 logMAR (about 20/80) to 0.312 logMAR (about 20/40), was statistically significant, whereas the improvement effected by the retrobulbar injections was not significant (0.433 logMAR to 0.341 logMAR). Foveal thickness improved significantly, from 398 µm to 211 µm, in the IVT group of patients. Intraocular pressure increase was more frequent in the IVT group, 25% vs 12%, but fewer of the IVT group required reinjection, 22% vs 76%. The reinjections for the retrobulbar group were usually IVT, and all reinjections were IVT after the 3-month data were collected. The conclusion was that IVT was more effective than retrobulbar triamcinolone acetonide.

Jonas and associates[37] treated 10 patients with macular edema secondary to BRVO using 25 mg IVT and followed up for approximately 9 months. To attempt to demonstrate efficacy, they compared preinjection vision with the best postinjection vision rather than the final vision. Such a comparison showed a significant improvement, from 0.57 logMAR to 0.35 logMAR, a 2-line improvement. Sixty percent had a best vision improvement of greater than 2 lines. Unfortunately, the final vision was not significantly improved. Although no macular thickness measurements are reported, the investigators state that macular edema showed a marked decrease. Ocular hypertension occurred in 70% of patients.

Cekic and associates[39] reported a straightforward series of 13 eyes with macular edema from BRVO treated with 4 mg IVT and followed up for a mean of 13 months.[38] Vision improved from a baseline acuity of 20/96 (0.68 logMAR) to a final acuity of 20/54 (0.43 logMAR), for a mean gain of 2.5 lines. The best vision recorded at any time point after injection averaged 20/45 (0.35 logMAR). These mean visual acuities were calculated by me from data in the Table 1 of the report, because the investigators did not present this information. The mean macular thickness decreased from 563 µm to 291 µm after IVT. Ocular hypertension occurred in 62% of patients. The development of cataract was a confounding factor affecting final vision. Essentially the same group presented a report including CRVO and HRVO. Three cases of HRVO were included, and on average no improvement in vision was found, with one patient 3 lines better, one 3 lines worse, and one patient 1 line better.

Jonas and Schlichtenbrede[40] reviewed 359 eyes with diffuse macular edema from multiple causes. Twelve cases of BRVO were included and were given one injection of about 20 mg of triamcinolone acetonide. The average initial logMAR prior to injection was −0.79, and at the end of follow-up it had improved to only −0.75, a 2-letter ETDRS improvement. The time of last follow-up was not stated. The average maximal acuity, the best acuity at any measurement after injection, was −0.56 logMAR, a significant improvement over baseline (P = .032), which did not continue. Second injections were not given. The investigators believe that this represents a less impressive response than the response of pseudophakic CME, because a BRVO is partially ischemic and has more retinal damage.

Another series having a single triamcinolone acetonide injection in BRVO was reported by Ozkiris and coworkers.[41] Nineteen eyes with BRVO were first treated by focal laser, then when found unresponsive, were given an IVT injection of 8 mg. Second injections were not given. Mean follow-up after injection was about 6 months. The mean baseline visual acuity was −1.01 logMAR, with 13 of 19 eyes having −1.0 logMAR. The maximal mean acuity after injection was −0.55 logMAR, a significant improvement over preinjection acuity (P < .001). In this series the mean acuity at 1 month and 3 months was virtually identical, −0.61 logMAR. Even at the final visit (mean 6.2 months), mean logMAR was −0.66, statistically better that the preinjection mean of −1.01 (P < .001). The investigators also mapped edema using the HRT II macula edema module and found a statistically significant reduction of edema at all points in time compared with preinjection values.

Karacorlu and associates[42] have shown the effect of IVT on eyes that have serous macular detachment from BRVO. In all 8 eyes attempted, the macular detachment regressed after 4 mg of IVT. Detachment recurred in 2 patients, and they were reinjected. Visual acuity improved from a baseline mean of 0.19 logMAR (20/100) to 0.36 logMAR (20/55), an average of 2.8 lines improvement. The best mean acuity after injection was 0.44 logMAR (20/45) for a 3.7-line improvement. These are my calculations from Table 1 of the article.

Several other series have been reported using IVT to treat macular edema in BRVO, and they are summarized along with the above cases in Table 1.[43-46]

Intravitreous tPA. Tissue plasminogen activator is a thrombolytic agent used extensively in vascular occlusive disease to reestablish circulation after thrombotic occlusion. Retinal vein occlusion is considered a thrombotic process and might be helped by tPA. Administration of tPA has been attempted intravenously systemically, intravenously locally, and intravitreously.

Elman and associates (discussion by Andrew Vine)[47] have presented a series and summarized the literature of the use of tPA for CRVO. They treated 9 eyes with CRVO with 100 µg intravitreous tPA within 1 month after onset or after worsening of visual acuity. Over a 4-month follow-up period, 44% gained 3 lines of vision, and these findings were in context to the 2 other published series. There were no complications.

Murakami and associates[48] have used intravitreous tPA on a group of patients with BRVO. Seventeen patients received 40,000 IU tPA at a mean time of 3.6 weeks after the onset of symptoms. Visual acuity and foveal thickness were measured. Acuity improved from 0.603 logMAR to 0.359, and foveal thickness improved from 738 µm to 253 µm by 6-month follow-up. No toxicity was noted. The investigators attempted to determine if flow was reestablished by measuring the retinal circulation time before and after injection in 5 eyes, and the difference was not significant. One patient developed a retinal hole that was successfully treated by photocoagulation and gas tamponade. The investigators followed this report with another report showing that the optical coherence tomography (OCT) finding of the absence of a third high reflectance band in the foveal area gave a statistically significant correlation with a lack visual acuity recovery.[49] Presumably, the disruption of this third high reflectance band demonstrates disorganization of the

photoreceptors.

TABLE 1. SUMMARY OF STUDIES USING INTRAVITREOUS TRIAMCINOLONE FOR BRANCH RETINAL VEIN OCCLUSION INCLUDING VISION AND MACULAR THICKNESS

SERIES	CASES	DOSE	PRE VISION (logMAR)	BEST POST VISION (logMAR)	FINAL VISION (logMAR)	VISION Δ BEST (LINES)	VISION Δ FINAL (LINES)	% VISION IMPROVED	PRE THICKNESS (μm)	POST THICKNESS (μm)	Δ THICKNESS	F/U (mo)
Degenring[33]	1	25	0.60	0.30	0.30	3.00	3.00	100	400	210	-190	1.25
Chen[34]	1	4	1.00	0.60	0.60	4.00	4.00	100	337	160	-177	3
Yepremyan[35]	12	4	0.88	0.46	0.49	4.20	3.90	83	589	235	-354	15
Hayashi[36]	27	4	0.60	0.31	0.31	2.86	2.86		389	211	-178	3
Jonas[37]	10	25	0.57	0.35	0.51	2.22	0.60	60			0	9
Cekic[39]*	13	4	0.68	0.35	0.43	3.31	2.51	54	563	291	-272	13
Karacorlu[42]*	8	4	0.72	0.35	0.44	3.65	2.81	88	556	292	-264	6
Lee[43]	6	4	0.92		0.84		0.83	83			0	5
Krepler[45]†	9	4	1.30	0.60	0.90	7.00	4.00		479	329	-150	6
Ozkiris[41]	19	8	1.01	0.55	0.62	4.60	3.90	89	2.1 HRT	1.6 HRT	0	6
Patel[44]	8	4	0.92	0.44	0.99	4.75	-0.70				0	12
Prasad[46]	1	4	1.82		1.00		8.20	100			0	2
Jonas(2)‡[40]	12	25	0.79	0.56	0.75	2.30	0.40				0	
Totals	**127**		**0.82**	**0.41**	**0.57**	**3.71**	**2.48**	**77**	**484**	**253**	**-231**	

HRT, Heidelberg retinal thickness analyzer.
Key: Pre Vision is the vision prior to intravitreal triamcinolone acetonide (IVT). Best Post Vision is the best vision recorded at any of the postinjection visits. Final Vision is the last vision recorded. Vision Δ Best is number of lines as an ETDRS equivalent between the preinjection vision and the best vision at any postinjection visit. Vision Δ Final is the number of lines as an ETDRS equivalent between the preinjection vision and the final vision. % Vision Improved is the percentage of eyes that had a visual acuity improvement after injection, often a 2-line improvement. Pre and Post Thickness (μm) are foveal thickness measured by optical coherence tomography, in μm. F/U is follow-up time in months.
*My vision calculations from data in article.
†Final retinal thickness was at 1 year following a single injection. At 1 week the thickness was 329.
‡This study was a broad review including multiple diagnoses and may include patients from the previous series.

Laser Photocoagulation for BRVO

Argon Laser Photocoagulation. Argon laser photocoagulation began in the 1960s, and several early series suggested that photocoagulation for macular edema associated with BRVO might increase the chance for visual acuity improvement.[50,51] The natural course of BRVO is variable, and these early studies, although intriguing, were not definitive. In 1976, the Branch Vein Occlusion Study Group undertook what has become the reference for comparing various treatment methods for BRVO.[52] Group III was designed to evaluate the role of argon laser photocoagulation for the benefit of macular edema. A grid of laser photocoagulation, guided by fluorescein angiography, was applied over the area of vein occlusion within the arcades on a group of eyes with 20/40 visual acuity or worse. Seventy-eight eyes, 43 treated and 35 controls, reached 3 years follow-up. The treated eyes had a statistically significant better chance for gain of 2 or more lines of vision and for having better than 20/40 acuity. The percentage gaining 2 or more lines was 65% in the treated group vs 37% in the control group. Sixty percent of the treated eyes had a 3-year visual acuity of 20/40 or better, whereas this was true for only 34% of the control eyes. There was no difference between treated and control groups as to the percentage of eyes losing 2 or more lines, 12% and 17%, respectively. The average initial visual acuity was not stated, but at 3 years treated eyes had an average visual acuity of 20/40 to 20/50, whereas untreated eyes had acuity of 20/70. (Implied from Table 4 in the article, using the 3-year average vision and the average vision gained, initial visual acuity was slightly better, about 20/60, in the treatment group compared with 20/70− in the control group.) There was no statistical difference in the improvement outcomes whether the interval from the onset of the occlusion was less than or greater than 1 year. The differential in treatment outcome between treated and control eyes was greater after 1 year because very few eyes improved in the control group after a 1-year interval, whereas treatment was still beneficial after 1 year. It is of note that the vision improved in the control group in 60% of eyes if the duration of the BRVO was less than 1 year at the time of entrance into the study. There were virtually no complications from treatment.

Two studies have shown little effect from argon laser for macular edema from BRVO. Shilling and Jones[53] looked at 90 patients, but several were lost to follow-up, and at 1 year and 2 years the number with better vision was almost identical in both groups. Accordingly, Parodi and coworkers[54] performed a grid of argon laser photocoagulation on a group of 99 patients with macular branch vein occlusions. After 1 and 2 years, both the mean visual acuity values and the percentage of eyes that had improvement in macular edema were the same in the treated and control groups. There was little explanation for the difference in these results and the Branch Vein Occlusion Study Group's data. The investigators noted that most of the patients in these studies had a broken perifoveal capillary network, and there may be a correlation between ischemia of the fovea and visual acuity outcomes.

Parodi and associates[55] have shown that the use of an infrared micropulse diode laser and subthreshold burns produces results equivalent to a grid of threshold level burns administered with a krypton laser. Both visual acuity and foveal thickness are improved with both treatments. The threshold laser produces reduction of thickness and improvement in acuity by 6 months, whereas the eyes treated with subthreshold treatment lag. By 1 year both are better, and this result holds at the 24-month evaluation. Average vision improved by 2 lines in the subthreshold group and 1.5 lines in the threshold group. Foveal thickness improved from about 460 μm to 221 μm on average. These results are similar to those of the Branch Vein Occlusion Study Group.

Laser-Induced Chorioretinal Anastomosis. In retinal vein occlusion, whether central or branch, the main outflow channel is blocked, reducing flow through the affected circuit and causing increased hydrostatic pressure within the vessels distal to the obstruction. If collateral channels of flow could be established, flow could recommence and hydrostatic pressure normalize. Given time, collaterals develop spontaneously after venous occlusion, giving an alternative outflow path. In central vein occlusion these collaterals occur on the optic nerve head as optociliary anastomoses, shunting flow through to the choroidal outflow, bypassing the retinal vein occlusive site, which is often just behind the lamina cribrosa.[56] In BRVOs and HRVOs, the anastomoses form between retinal veins by enlargement of local capillaries. Spontaneous anastomosis formation is a slow process and, depending on the severity of the occlusion, may be neither rapid nor thorough enough to preserve tissue viability. The purposeful creation of a retinochoroidal anastomosis could prove useful in rerouting outflow after a retinal vein occlusion. Successful application of this treatment should apply to all types of retinal vein occlusions if retinal tissue remains viable.

In 1992, McAllister and coworkers,[57] using high-intensity laser burns, created chorioretinal anastomoses in dogs. Immediately after having induced a BRVO, a tributary vein in the drainage area of the occlusion was treated with argon laser to disrupt the vessel and the underlying retinal pigment epithelium and Bruch membrane. A functional chorioretinal anastomosis developed at 3 to 6 weeks after the laser procedure, and both the proximal and distal veins drained into the choroid. The unused vein proximal to the occlusion narrowed and occluded. No substantial complications secondary to the laser were seen, although possible complications related to rupture of the Bruch membrane were discussed.

Following the animal work, McAllister and Constable[58] reported on the production of laser-induced chorioretinal anastomosis in central vein occlusions. High-intensity laser was used to attempt to create a chorioretinal anastomosis in 24 eyes with nonischemic CRVO. An anastomosis was created in 33% of cases. High-intensity argon laser was applied over a vein in the inferior half of the retina, attempting to disrupt the vein wall and Bruch membrane. Patients were followed up, and if the original attempt was unsuccessful, the laser was repeated. Success was determined by fluorescein angiography and by the presence of a large retinal vein flowing into the laser scar. Success required, on average, 2.2 attempts at 2.6 sites. The anastomosis remained open over the 1- to 3-year follow-up. In the successful cases, vision improved an average of about 5 lines (0.48 logMAR) as derived from the Figure 1 in the article. Unsuccessful cases had about an equal number with improvement and loss, and 31% became ischemic. Complications included vein closure distal to the site in 11%, preretinal fibrosis at 13% of sites, and subretinal fibrosis at 5% of sites. None of these complications affected outcomes. This report proved the feasibility of creating a laser-induced anastomosis with subsequent

improvement of vision if an anastomosis could be created.

Subsequently, several papers have discussed results and complications associated with laser-induced anastomoses. Browning and Antoszyk[59] were frustrated in attempting to duplicate the technique. Only 2 successful anastomoses were produced in 20 attempts, and the vision did not improve in these 2 eyes. Complications were numerous, including rubeosis, retinal neovascularization at the laser site, significant vitreous hemorrhage, traction retinal detachment, preretinal and subretinal fibrosis, and a need for later surgery. McAllister and coworkers,60 in a larger series, were able to produce an anastomosis in 54% of 91 eyes with CRVO, with an average improvement of 4.3 lines in the 84% of eyes that improved. Significant complications included closure of the distal vein in 29% of eyes, neovascularization at the laser site in 20% of eyes, and fibrous tissue proliferation in 9% of eyes. One eye with fibrosis and macular traction required vitrectomy.

Fekrat and coworkers61 attempted laser-induced anastomosis in 6 eyes with nonischemic BRVO. All patients had visual acuity of 20/100 or worse for an average duration of 13 to 15 months. Four of these patients had a previous macular grid laser. An anastomosis was achieved in 3 patients (50%), and 2 had some improvement of vision (1 to 3 lines). No substantial complications occurred, but there were one vitreous hemorrhage of short duration and two patients with mild localized preretinal fibrosis.

A second series of 5 eyes with BRVO treated by laser-induced anastomosis was reported by Bevbek and associates.[62] An anastomosis occurred in 2 eyes (40%), and acuity improved 2 lines in each. Complications included closure of a distal segment of vein accompanied by choriovitreal neovascularization and a choroidal neovascular membrane.

Several other reports discuss other methods and complications of laser-induced anastomosis in CRVO.[63-67] Leonard and associates68 have described a technique, confirmed by others,69 by which 10% of 19 eyes had an anastomosis established in CRVO. Treatment was applied adjacent to the vein wall, avoiding direct treatment to the vein, with enough power to rupture Bruch's membrane. This success rate was much higher than others.

In summary, laser-induced chorioretinal anastomosis is possible to achieve. Overall, about 50% or less of the attempts are successful. Complications are frequent and sometimes substantial. Most cases have been in eyes with CRVO. There are 11 cases of laser-induced chorioretinal anastomosis for BRVO in the English literature, and 5 eyes achieved an anastomosis. Four-fifths (80%) of the eyes that successfully achieved an anastomosis had about a 2-line increase in visual acuity; thus 4 in 11 (36%) of the attempted eyes had a 2-line improvement in acuity. Complications included vein closure, choriovitreal neovascularization, choroidal neovascular membrane, vitreous hemorrhage, and slight preretinal fibrosis.

Surgical Alternatives

Arteriovenous Adventitial Sheathotomy. Virtually all BRVOs occur at the site of crossing of a branch artery over a branch vein, presumably because the lumen is constricted in such areas and endothelial damage and thrombus formation eventuate. The structure of the AV crossings has been studied histologically. In about 80% of cases the artery courses over the vein.[9] When proximate, the vessels share a common adventitial sheath and the course of the vein deviates around the artery. Decompression of the AV crossing might allow an improvement in the diameter of the vein and allow reperfusion of the retina distal to the occlusion, improving ischemia and reducing edema.

Osterloh and Charles,[70] in 1988, developed a procedure for AV sheathotomy using porcine eyes, then performed a sheathotomy at the site of an AV crossing in one patient with BRVO. The adventitial sheath was severed using a bent microvitreoretinal blade, and the overlying arteriole was freed. This patient experienced a reduction in CME and improvement in visual acuity (20/200 to 20/25). No complications occurred. Inexplicably, no further procedures were done by the investigators.

The next cases were reported in 1999 by Opremcak and Bruce.[71] In 15 cases, vitrectomy and sheathotomy were successful in separating the artery from the vein. Postoperatively, 10 of 15 (67%) had an improvement of vision (average improvement of 4 lines), an additional 2 of 15 remained the same, and only 3 of 15 (20%) worsened. Immediately after this series, Shah and coworkers[72,73] reported 5 similar cases, all with initial visual acuity worse than 20/200. Over 24 months the average improvement was about 8 lines in the 4 of 5 eyes (80%) that improved. One eye did not improve. Complications included a retinal detachment and cataract formation in 3 eyes.

All reports were not as favorable. Le Rouic and associates[74] reported 3 eyes with surgically successful AV sheathotomy that had no improvement in vision over an average 10-month follow-up. Two eyes were unchanged, and one worsened. In 2 cases the vein was completely occluded at the end of the follow-up period. Complications were minimal.

Mester and Dillinger[75] reported 43 eyes with BRVO undergoing AV sheathotomy. These were matched by a similar group of 25 eyes of patients who refused surgery. All eyes had 20/50 or less visual acuity initially with macular edema on fluorescein angiography. All patients had isovolemic hemodilution therapy. Vitreous scissors were used to separate the adventitial sheath between the artery and vein. All cases had a successful dissection. Sixteen eyes also had removal of the internal limiting membrane (ILM) in the macular area. The mean vision improvement was from 20/125 to about 20/60, an improvement of about 3.5 lines. Sixty percent gained 2 lines, and 28% gained 4 lines. The control eyes did not gain vision on average. Of the 16 patients who also had the ILM removed, 38% had a 4-line gain. Macular edema resolved in all eyes. No complications were reported.

Cahill and associates[76] looked at outcomes after sheathotomy in a different way. They segregated visual outcomes as to the presence of persistent CME after sheathotomy in a retrospective review of 27 eyes. Complete resolution of CME occurred in 8 of 27 cases (29.6%), and mean visual acuity improved from 20/200 to 20/80 (4 lines). In eyes with a partial reduction in CME, 14 of 27 eyes (52%), vision did not improve on average, and in the 5 eyes with persistent CME (18.6), mean vision worsened. The combined mean visual acuity of all 27 eyes showed no statistical improvement after sheathotomy, 20/200 to 20/160 (1 line). The investigators reasoned that their results may have differed from other, more optimistic results because this group included large BRVOs and more

long-standing disease (7 months). They did demonstrate retinal reperfusion in many eyes, with 87% reperfusion in the group with CME resolution, 21% with CME reduction, and 40% with CME persistence. The investigators concluded that most eyes had neither vision improvement nor CME resolution. A new complication was reported—a macular detachment originating from the sheathotomy site in 2 cases.

Another surgical variation was shown by Han and coworkers,[77] who found it impossible to achieve a separation of the artery and vein in 19 of 20 cases. In each case they used a microvitreoretinal blade to dissect the artery free from the surface of the retina both proximal and distal to the AV crossing. An attempt was then made using the microvitreoretinal blade to separate the artery and vein, but this effort was abandoned in most cases because of fear of damage to the retina or vessels. Four surgeons were involved, and all had the same experience. All eyes had a vitrectomy, and all 20 eyes had a separation of the posterior hyaloid at the end of surgery. Despite the inability to separate the artery and vein, visual acuity improved in most cases, with a mean improvement of 4.4 lines (20/260 to 20/90) over a follow-up of 10.5 months. Vision improved at least 2 lines in 80% of cases. The investigators concluded that separation of the vessels at an AV crossing may be unnecessary for visual improvement. A similar surgical technique was reported by Lakhanpal and associates,[78] who describe a procedure they called a limited AV-crossing manipulation. No vitrectomy was done, no vitreous cutter was used, and the posterior hyaloid was not surgically separated. A blunt, flexible pick was used to separate the artery from the retinal surface proximal and distal to the AV crossing, and the crossing artery was then gently elevated, stretching the adhesion between the artery and vein, without separating the vessels at the crossing. Eleven of 12 eyes (92%) had visual improvement of ≥2 lines. No patients lost vision. Mean preoperative visual acuity was 20/200, and mean final acuity was 20/60 (4.4-line gain). Macular thickness improved from 401 μm to 179 μm. Mean follow-up was 50 weeks. Cataract progressed in 33% but did not require removal.

Several other series have been reported, and some are summarized in Table 2.[79-85] Hemodynamics after sheathotomy have been measured.[86-88]

TABLE 2. SUMMARY OF VISUAL CHANGE AND COMPLICATIONS FROM SURGICAL RESULTS FOR ARTERIOVENOUS ADVENTITIAL SHEATHOTOMY FOR BRANCH RETINAL VEIN OCCLUSION

SERIES	CASES	MEAN VISUAL CHANGE (LINES)*	% IMPROVED VISUAL ACUITY	COMPLICATIONS
Osterloh[70]	1	9	100	None
Shah[72,73]	5	6.3	80	
Le Rouic[74]	3	-1	0	None
Mester[75]	43	¾	60	None
Cahill[76]	27	1	48	Tears, localized retinal
Han[77]	20	2.8	80	Slight cataract progression
Lakhanpal[78]	12	4.4	92	Slight cataract progression
Fujii[79]	1	11	100	
Mason[80]	20	6	75	Slight cataract progression
Garcia-Arumi[81]	40	4	70	Vitreous hemorrhage—cleared
Charbonnel[82]	13	2	69	None
Sohn[83]	22	2.2	45	
Feltgen[84]	35	2.7	69	Cataracts
Crafoord[85]	12	3	67	Macular hole, slight cataract
Total	**254**	**3.2**	**68**	

*In ETDRS equivalents.

Macular Decompression. It has been suspected that the vitreous may play a role in diabetic macular edema. Careful examination has shown that the vitreous is attached in the macula more commonly in eyes that have diabetic macular edema than in eyes that do not.[89] Producing a vitreous detachment surgically might then improve macular edema in diabetes and other conditions with similar leakage. Such an approach has been entitled macular decompression.

Tachi and associates[90] performed a vitrectomy in 29 eyes of patients with BRVO and macular edema. The posterior hyaloid was separated, the lens was removed, and an intraocular lens was implanted. Macular edema improved and visual acuity changed from a preoperative mean of 20/100 to 20/40 (4 lines) over an average 16-month follow-up period. The time to edema resorption was shorter in eyes operated on early after the onset of the BRVO. Complications included retinal tears and a macular hole. Since the series included eyes with CRVO as well as BRVO, it was not possible to determine which diagnostic group had the complications. The investigators speculated that the effect of surgery may be due to the removal of tangential traction on the macular surface.

Adding a variation to the surgical procedure, Saika and colleagues[91] surgically created a posterior vitreous detachment (PVD) combined with gas tamponade. Nineteen patients were studied. The mean time interval between the onset of the BRVO and the surgery was 11.3 months, and the mean follow-up was about 9 months. Visual acuity and central foveal thickness were measured before and after vitrectomy and lensectomy. Central thickness was significantly different after surgery—a mean of 383 preoperatively and 208 postoperatively. Normal foveal contour was achieved in 10 of 19 patients (53%). For the whole group, the final visual acuity did not vary significantly from the preoperative vision (0.66 logMAR, about 20/90, before surgery, and 0.53 logMAR, about 20/70, finally). However, the investigators noted 2 factors that correlated with a significant visual change: the interval between onset of the BRVO and surgery and the return of normal foveal contour. In the 10 patients that were operated on within 11 months of onset, visual acuity improved from 0.59 logMAR (about 20/80) to 0.45 logMAR (about 20/55). In the 10 patients that had a return of normal foveal contour, acuity improved from 0.4 logMAR (20/50) if contour was normal but 0.67 logMAR (20/95) if normal contour was not regained. The investigators thus concluded that if surgery is done early and if normal contour is achieved, vitrectomy and creation of a PVD may help macular edema caused by BRVO.

One series compared visual outcomes if surgery is limited to vitrectomy alone or vitrectomy was combined with sheathotomy in eyes with BRVO. Yamamoto and colleagues[92] performed a sheathotomy in 20 eyes and vitrectomy with PVD in 16 eyes. Vision and foveal thickness were measured. The groups were reasonably well matched. Vision improved 0.29 logMAR (2.9 lines) in the sheathotomy group and 0.30 logMAR (3 lines) in the PVD group. Foveal thickness was reduced 255 μm in the sheathotomy group and 194 μm in the PVD group. Neither of these outcome measurements reached statistical significance. The investigators noted that reperfusion of the occluded vein occurred much more often in the sheathotomy group, but that collateral channels developed in the remaining eyes, providing the functional and anatomic improvement seen in the PVD group. The conclusion was made that in this series, vitrectomy with the production of a PVD was as effective as sheathotomy in improving macular edema. This series was challenged by Chalam and colleagues,[93] who questioned the timing of early surgery during a period when recovery might be expected, the confounding factor of lens extraction, and the somewhat different criteria used to select the type of surgical intervention.

Kumagai and associates,[94] in a study similar to that of Yamamoto, compared sheathotomy with vitrectomy in 36 eyes (18 vitrectomy and 18 sheathotomy). They found no statistical difference in visual or anatomic outcomes between the 2 groups. They suggested that sheathotomy might be the better procedure if done in the first 4 weeks. In this series, among those eyes having early surgery, the group having sheathotomy had a trend toward a better visual outcome (0.62 logMAR change after sheathotomy compared to 0.48 logMAR change after vitrectomy).

Two other series have looked at macular decompression for BRVO. Mandelcorn and coworkers[95] performed vitrectomy with ILM removal in 19 eyes with BRVO. Vision improved in 13 eyes (68%). The degree of improvement could not be determined because the BRVO cases were combined with 31 cases of CRVO. The investigators suggest that removing the ILM might allow retinal edema to move from the retina into the vitreous cavity, decompressing the retina. A larger series of 120 eyes was done by Kumagai and associates.[96] They performed vitrectomy for macular edema and macular hemorrhage associated with BRVO and included cataract extraction on all eyes that were not already pseudophakic. Vision improved from a preoperative 0.63 logMAR to a 1-year postoperative 0.24 logMAR and a final (mean, 48 months) 0.18 logMAR. Improvement was thus 0.39 logMAR (about 4 lines) at 1 year and 0.45 logMAR (about 4.5 lines) at an average of 48 months. All postoperative improvements were statistically significant. The investigators speculated that the improvement might relate to the removal of vitreous traction and possibly the removal of cytokines that may increase retinal vessel permeability.

Table 3 summarizes the cases of macular decompression surgery.

Since these 2 surgeries, AV sheathotomy and vitrectomy for macular decompression, are similar and often done together, a total of 475 procedures have been done with a mean visual change of 3.6 lines of improvement. Overall, 72% of the eyes had improvement of vision.

Hypothesis: Intravitreous injection of bevacizumab will compare favorably with other current treatments of BRVO and HRVO with consideration to visual outcome, cost, convenience, and risk of treatment.

METHODS AND MATERIALS

This study is a retrospective chart review including 56 patients who received intravitreous bevacizumab (IVB) for macular edema associated with BRVO or HRVO. The study was approved by the Institutional Review Board of Presbyterian Hospital of Dallas. The patients were derived from a large retinal practice (Texas Retina Associates), which includes a collective of 11 different physicians with patients seen in 6 different offices. All patients in this study were treated at the discretion of the treating physician and the patient in the course of routine care.

An original group consisted of all patients with a diagnosis of retinal vein occlusion that had received IVB. The list of patients was derived from a computer-generated listing matching the diagnosis of retinal vein occlusion with bevacizumab injection. Charts, fundus photographs, and fluorescein angiograms, when available, were reviewed, and only eyes with a clear diagnosis were included. Those

patients with CRVO included a variety of situations, such as macular edema, proliferative retinopathy, vitreous hemorrhage, and rubeosis. It was deemed that analysis of such a group would be impossible because of the complexity of the clinical spectrum, and they were excluded. One patient with hemisphere vein occlusion had diabetes, vitreous hemorrhage, and rubeosis and was excluded.

TABLE 3. SUMMARY VISUAL ACUITY AND MACULAR THICKNESS CHANGES FROM REPORTS OF VITRECTOMY WITH POSTERIOR HYALOID SEPARATION FOR BRANCH RETINAL VEIN OCCLUSION

SERIES	CASES	MEAN VISUAL CHANGE (LINES)*	% IMPROVED VISUAL ACUITY	OCT CHANGE (μm)†	COMPLICATIONS
Tachi[90]	29	4			None
Saika[91]	19	1.3	53	175	
Yamamoto[92]	16	3	75	260	Cataract progression
Mandelcorn[95]	19		68		Optic atrophy, cataract
Kumagai[94]	18	4.4	78	229	
Kumagai(2)[96]	120	4.5	85		
Total	**221**	**4.0**	**71.8**	**221**	

OCT, ocular coherence tomography.

*In ETDRS equivalents.

†Change in the foveal thickness in μm.

The study group consisted of 56 patients with a primary diagnosis of BRVO or HRVO treated with bevacizumab and with follow-up. All patients had reduced vision secondary to the vein occlusion, and macular edema was a consistent finding. Cataract, diabetes, hypertension, and dry age-related macular degeneration were not exclusion criteria. The number of follow-up visits varied from 1 to 14 after the initial bevacizumab injection. Many patients had other treatments, most commonly argon laser photocoagulation and/or an injection of IVT. The data generated for this study include only that subsequent to the first bevacizumab injection. Since injection of IVT has been a common approach and similar in its indications to IVB, some patients have had both. In this analysis, the patients who received both are evaluated and compared to a subgroup that did not receive triamcinolone acetonide (bevacizumab alone). No calculation of sample size was done prior to the study. One patient had a BRVO in both eyes and both were included.

This is a retrospective chart review. There was no study contemplated at the time of the bevacizumab injections. The patients received the injections based on the judgment of the physicians, the knowledge that anti-VEGF agents might theoretically help in diseases where VEGF is known to play a role, scattered reports of efficacy, and anecdotal information gathered by the physician in daily practice. These issues were discussed with the patients, and the patients signed informed consent acknowledging the ambiguity and lack of information. Informed consent specified that there is a lack of clear information about either the risks or the benefits of the treatment. Specific known risks were discussed. The patients understood that unknown and potentially serious side effects could occur.

Visual acuity and central macular thickness were measured in all patients. Color photographs were available for all but one patient. Fluorescein angiography was available on many patients. Distance vision was assessed on either a standard projected Snellen chart or an ETDRS chart, interchangeably. Visions were taken using the current optical correction, and a pinhole overcorrection was used. The vision recorded was the better of these 2 values. If the patient was unable to see the 20/400 letter, vision was recorded as counting fingers or hand motions, or the patient was moved closer to the chart and the numerator adjusted according to the necessary distance. To convert nonnumerical values to numerical, a value of 20/1490 or decimal 0.014 was used for counting fingers, and 20/3846 or decimal 0.0052 was used for hand motions. These equivalents were taken from the study of Schulze-Bonsel and coworkers,[97] who derived them from a group of 100 eyes. Alternatively, Elman and associates[47] suggested 20/800 for counting fingers and 20/1600 for hand motions, simply doubling the minimal angle of resolution for each designation. I elected to use the numbers from Schulze-Bonsel, since they were derived by measurement. Vision was converted to the log of the minimal angle of resolution (logMAR) because of the convenience of correlating the acuity scores over time with lines of improvement. On the logMAR scale, a change of 0.1 corresponds very closely to a 1-line change on the ETDRS chart, and a change of 0.3 corresponds to a 3-line change, the accepted level of change to circumvent the effects of visual fluctuation.

In those cases when a fluorescein angiogram was done, an attempt was made to determine if the macula was ischemic. Since many eyes were hemorrhagic at the time of the angiogram and some eyes did not have an angiogram, this information was of limited value.

Optical coherence tomography was done using the Zeiss Stratus OCT scanners (Carl Zeiss Meditech, Inc, Dublin, California). Scans were recorded over 6 mm of the central retina at each clock hour, and the computer-generated central field thickness was used when accurate. All OCT data in this study are based on average retinal thickness of the foveal subfield on the retinal thickness tabular

output report produced by the scanner. The central thickness map was compared with the cross-sectional scan to determine if it appeared to be accurate. On some scans, the computer-generated central field thickness reading was noted to be inaccurate, and on these scans a manual measurement was made from the cross-sectional representation. The thickness of the central retina was measured from the inner surface of the retinal pigment epithelium to the inner surface of the retina in the foveal region using a factor of 27 µm/mm. These cases with manual measurement were all associated with severe edema. Slight variance in accuracy associated with a manual technique would make little percentage difference in these severe cases.

The technique for intravitreous injection has been documented, and since there were several physicians involved with these patients, the technique varied somewhat. Preinjection consent was given by the patient after a thorough discussion of risks and benefits with the patient. Generally, 0.12 mg (a volume of 0.05 mL) of bevacizumab was injected 3.5 to 4.0 mm from the limbus (through the pars plana) in the inferotemporal quadrant of the affected eye using a 30- to 32-gauge half-inch needle after anesthesia and application of povidone iodine to the injection site. After injection, pressure was applied to the injection site using a sterile cotton-tipped applicator for a short time to limit subconjunctival hemorrhage and perhaps seal the injection opening. The volume of 0.05 mL was well tolerated; no method of reduction of intraocular volume prior to injection was necessary. The presence of the central retinal artery flow was verified after injection either by direct observation or by the presence of hand motions vision postinjection. However, if the central retinal arterial flow was diminished and did not quickly recover, a tap of volume reestablished flow. Either topical or subconjunctival anesthesia was used. With topical anesthesia, 2% or 4% lidocaine was applied locally by holding a soaked cotton-tipped applicator at the site of injection for a short period. With subconjunctival anesthesia, 2% lidocaine was given over the site of injection. The povidone iodine was applied directly to the globe, either as a flush of the entire surface with 5% solution or, at times, by application of 10% solution directly to the site with a sponge-tipped applicator. One physician gave some injections through the inferonasal pars plana. Most physicians asked that the patients use postinjection antibiotics for several days.

The bevacizumab was supplied in sterile single-use syringes prepared under sterile conditions by a local pharmacy. The concentration of the bevacizumab is that of the commercially available preparation without dilution, 1.2 mg in 0.05 mL volume. Those patients that received IVT received various dosages, depending on the physician's choice. Dosage varied from about 4 mg to an undetermined dosage of 0.05 mL of crystals only. In some cases the supernatant was removed and replaced by sterile water or sterile saline solution, whereas in other cases the supernatant was not removed. Some cases used preservative-free triamcinolone acetonide prepared sterilely by a local pharmacy for single use at a concentration of 80 mg/mL. A volume of 0.05 mL gives a dose of 4 mg. The technique for IVT injections was the same as that described above, except that a 28-gauge needle is usually used.

The visual and OCT outcomes were analyzed in several ways, attempting to derive useful data that might be compared with information from various other studies involving the natural history of the disease or other treatment techniques. Visual outcomes were measured at the last visit (final vision) and at the best time during the follow-up period. The percentages of eyes that improve, stabilize, and deteriorate were found. The percentages of eyes with 2 and 3 lines of visual acuity gain or 3 lines of visual loss were calculated. The data are evaluated in all eyes that received bevacizumab at any time during the treatment period and in all eyes that received only bevacizumab without triamcinolone acetonide. When the distribution was not normal, medians were also calculated and used to determine the significance of the data. Means are also presented to help in comparisons with other data.

With normal distribution, statistical analyses were performed using the paired Student *t* test using Microsoft Excel and the calculator found on the web at http://www.physics.csbsju.edu/stats/t-test.html.[98] Normality tests were done using the Kolmogorov-Smirnov test. For data that were not normally distributed, median scores were compared with the Wilcoxon matched pairs test. The software used was Statistica 7.1 by StatSoft, Inc (Tulsa, Oklahoma), and Analyse-it, a Microsoft Excel add-in by Analyse-it Software, Ltd (Leeds, United Kingdom).

RESULTS

This retrospective study shares problems common to the genre. Not all information is available for all patients, the timing of visits is variable, data collection is less rigorous than in prospective trials that have specialized personnel, and procedures were not standardized. Therefore, the objective of this study is to derive as much information as possible concerning the usefulness of IVB for the control of macular edema in eyes with BRVO and HRVO. Hemisphere vein occlusion is by etiology more similar to CRVO and shares common attributes with both BRVO and CRVO. The area affected is larger and, presumably, the intensity of ischemia could be more problematic than with BRVO. Because the treatment by bevacizumab does not depend on the etiologic issues, HRVO was included here, since the primary effect being countered by treatment was macular edema. Although HRVO affects a larger area of retina than BRVO, macular ischemia is related to the completeness and the degree of macular involvement of occlusion, as well as the total area, and BRVO may produce as much ischemia and edema as HRVO.

The data have been grouped and analyzed in an attempt to be comparable with various other studies for other treatment methods.

The collection of patients consists of a general group and a subgroup. The general group consisted of 56 patients with BRVO and HRVO who received IVB for macular edema associated with the vein occlusion. Some of these patients also received IVT interspersed into the treatment scheme, either as the initial choice with IVB added at a later time or, secondarily, when the treating physician deemed it necessary. The number of bevacizumab injections per patient varied from 1 to 7 injections. The indication for reinjection varied with the treating physician, with most injections being given for recurrence of edema.

From this general group, a subgroup of 39 patients was separately analyzed because they received IVB but had no IVT. These patients may have had laser, nonsteroidal anti-inflammatory topical medications, or aspirin or other oral medications.

VISION DATA

Visual acuity is analyzed in several ways. The final visual outcome was represented by the change of vision from the date of the first bevacizumab injection to the final visual acuity available for the patient at the time of review. Both the overall quantity of change and the percentage of eyes with improvement, stability, and worsening over the time of the follow-up were calculated. The best visual improvement within the follow-up period was determined, and lastly, visual change was determined at certain time points along the follow-up period in temporal relation to the injection. Additionally, the percentage of patients with vision improving, stabilizing, and deteriorating was assessed.

   All Eyes

The amount of change in vision from the initial injection of bevacizumab to the vision on the final recording for the 56 patients was a mean of 0.10 logMAR, or about 1 line ETDRS. These data are included in Table 4. The mean acuity at the onset of bevacizumab treatment was 0.78 logMAR or about 20/120 (range, 20/30 to counting fingers [CF]), and the mean acuity at the final visit was 0.68 logMAR or 20/95 (range, 20/20 to CF). The visual acuity data were not normally distributed (Kolmogorov-Smirnov $d_{initial}$ = 0.23, *P* <.01, d_{final} = 0.18, *P* <.05); therefore median scores for initial visual acuity and final visual acuity were compared using the Wilcoxon matched pairs test. The median initial logMAR acuity was 0.7 or 20/100, and the final logMAR acuity was 0.477 or about 20/60. This was statistically significant, *z* = 2.09, *P* = .04. The median visions with interquartile intervals for all eyes that received IVB and for all visits are shown in Figure 1. The average follow-up time was 10 months. Four patients deemed to be ischemic by either fluorescein angiography or clinical appearance and having an initial acuity of 20/200 or worse (200, 400, 2×CF) showed no improvement on any visit and after multiple injections.

TABLE 4. A SUMMARY OF GROUPINGS BASED ON INITIAL VISION AND TREATMENT METHOD FOR EYES WITH BRANCH RETINAL VEIN OCCLUSION GIVEN INTRAVITREOUS BEVACIZUMAB

INITIAL VISION	ALL INITIAL VISIONS	ALL INITIAL VISIONS	≥20/40 INITIAL VISION
Treatment method	Bevacizumab and triamcinolone	Bevacizumab only	Bevacizumab only
Number of patients	56	39	36
Mean initial acuity logMAR (Snellen)	0.78 (20/120)	0.75 (20/110)	0.80 (20/220)
Mean final acuity logMAR (Snellen)	0.68 (20/95)	0.59 (20/80)	0.63 (20/130)
Mean change acuity (lines ETDRS equivalent)	1.0	1.6	1.7
Mean best acuity logMAR (Snellen)	0.46 (20/60)	0.40 (20/50)	0.43 (20/70)
Mean change best acuity (lines ETDRS equivalent)	3	3.5	3.7
Median initial acuity logMAR (Snellen)	0.70 (20/100)	0.70 (20/100)	0.70 (20/100)
Median final acuity logMAR (Snellen)	0.48 (20/60)	0.40 (20/50)	0.48 (20/60)
Median change acuity (lines ETDRS equivalent) with (*P* value)	1.1 (*P* = .037)	1.5 (*P* = .012)	1.8 (*P* = .012)
Median best acuity logMAR (Snellen)	0.35 (20/45)	0.30 (20/40)	0.35 (20/45)

TABLE 4 (CONTINUED). A SUMMARY OF GROUPINGS BASED ON INITIAL VISION AND TREATMENT METHOD FOR EYES WITH BRANCH RETINAL VEIN OCCLUSION GIVEN INTRAVITREOUS BEVACIZUMAB

INITIAL VISION	ALL INITIAL VISIONS	ALL INITIAL VISIONS	≥20/40 INITIAL VISION
Median change best acuity (lines ETDRS equivalent) with (*P* value)	3 (*P* <.001)	3 (*P* <.001)	3.3 (*P* <.001)
Mean follow-up time (months)	10.2	8.8	8.5
Number better (%)	29 (52%)	23 (59%)	21 (58%)
Number same (%)	12 (21%)	6 (15%)	6 (17%)
Number worse (%)	15 (27%)	10 (26%)	9 (25%)
Number ≥2-line improvement (%)	26 (46%)	20 (51%)	20 (56%)
Number ≥3-line improvement (%)	17 (30%)	13 (33%)	13 (36%)
Number ≥6-line improvement (%)	7 (13%)	6 (15%)	6 (17%)
Number ≥3-line loss (%)	10 (18%)	4 (10%)	6 (11%)
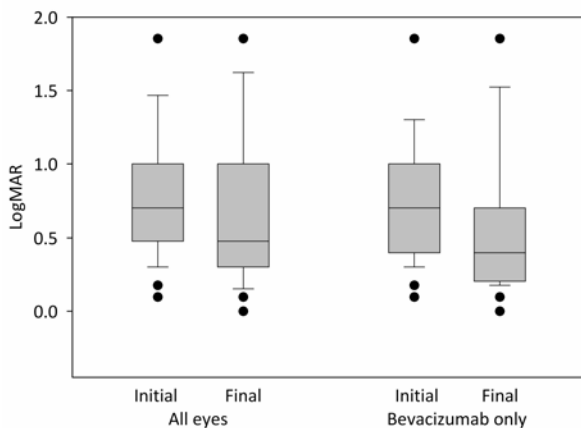
FIGURE 1

Combines the data from 2 groups. The columns labeled *Initial* are the visions, measured in logMAR, at the time of the first bevacizumab injection. The columns labeled *Final* are the visions at the last visit available at the time of the chart review. The data for the first group, all eyes, come from the whole group of 56 eyes that received bevacizumab for branch retinal vein occlusion. Some of these eyes also received intravitreous triamcinolone acetonide during the course of treatment. The data for the second group, bevacizumab only, come from the subgroup of 39 eyes that received only bevacizumab and no triamcinolone acetonide. The box plots show the 25th to the 75th percentiles surrounding the median, represented by the included line. The error bars indicate the 10th and 90th percentiles. Outlying points are shown. The differences were statistically significant in both groups, *P* <.01 and *P* = .011, respectively.

The percentage of eyes with some improvement in vision, initial to final, was 51% (average follow-up, 8.9 months). The percentage of eyes with the same vision, initial to final, was 21% (average follow-up, 11 months), and 27% of the eyes had a worsening of vision (average follow-up, 12.1 months). Thus, overall, vision improved or remained stable in 72% of the eyes and worsened in 27% of the eyes over the course of the follow-up time. Improvement of 3 lines (0.3 logMAR) occurred in 30%, whereas improvement of 2 lines occurred in 46% and of 6 lines in 13%. A decrease of 3 lines occurred in 18% of eyes. The initial visions in the 3 groups was somewhat different, 0.74 logMAR (20/108) in the group that improved, 1.09 logMAR (20/245) in the group that stayed the same, and 0.63 (20/84) in the group that worsened. The group of 24 eyes that had at least a 1-year follow-up had less

improvement, with 9 (38%) better, 7 (29%) the same, 8 (33%) worse, and 16 (67%) the same or better.

The change of vision was also analyzed from the initial vision to the best vision within the follow-up time. Eight-two percent of eyes had improvement at some time during the follow-up course, with an average of 0.30 logMAR (3 lines) gained (*P* < .001).

The change of vision was determined at several time points after the initial injection, 1 month (28-45 days), 3 months (45-135 days), 6 months (135-225 days), and 1 year (225-400 days). All visual changes measured during each time interval were averaged and were 0.18, 0.15, 0.1, and 0.1 (all logMAR) corresponding to 1.8 lines, 1.5 lines, 1 line, and 1 line, respectively.

Additionally, the effect of each bevacizumab injection was determined on the vision measured at the next patient visit. There were 138 injections, and 57 patients returned within 30 days with an average visual gain of 1.6 lines. An additional 51 patients returned between 30 and 45 days, and these patients maintained a 1.6-line gain. For those patients seen from 45 to 60 days, the average gain dropped to 0.4 lines, and for those returning after 60 days, there was slight loss of vision. Since these data represented more than one injection in the same patient, a more accurate method of calculation looked at only the first injection for each patient. The acuity data for each injection were not normally distributed (Kolmogorov-Smirnov $d_{initial}$ = 0.23, *P* <.01, $d_{after\ injection}$ = 0.18, *P* <.05); therefore the interclass correlation approach to correct for multiple observations from the same patients could not be used. Median scores for initial visual acuity on the first injection and the visual acuity at the first postinjection visit were compared using the Wilcoxon matched pairs test. The overall visual acuity change of each bevacizumab injection was a mean improvement of 1.55 lines, and the median time to return was 28 days. This improvement was highly significant (z = 3.90, *P* < .0001). The median visions with interquartile intervals for changes in vision after each injection are shown in Figure 2. Figure 3 is a bar graph showing the mean acuities at the different follow-up times.
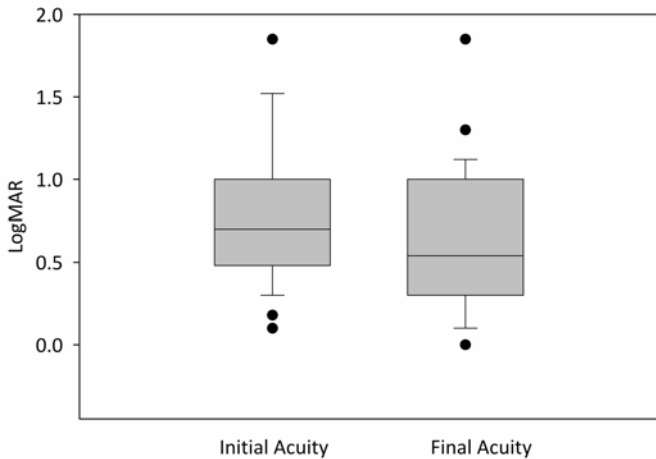

FIGURE 2

Vision data from the first injection of each of the 56 patients, one injection per patient. The initial acuity is the acuity, measured in logMAR, at the time of the bevacizumab injection. The final acuity is the acuity, measured in logMAR, at the time of the next available visit after the injection. This represents the effect of a single injection. The box plots show the 25th to the 75th percentiles surrounding the median, represented by the included line. The error bars indicate the 10th and 90th percentiles. Outlying points are shown. The differences were statistically significant, *P* <.0001.

Bevacizumab-Only Subgroup

Since triamcinolone acetonide is used in much the same way and has been shown to have some effect on macular edema from various causes, a group without the confounding influence of triamcinolone acetonide was separately considered. It is likely that those patients receiving both bevacizumab and triamcinolone acetonide were not responding to the initial choice as well as expected, or that a complication or the risk of complication motivated the change in selection. All patients in this study were treated at the discretion of the treating physician and patient after informed consent considering known and unknown risks and benefits as well as alternative therapies.

Data from the subgroup of 39 patients who received IVB but did not receive triamcinolone acetonide at any time were analyzed. These data are included in Table 4. The mean change in vision from the initial bevacizumab injection until the final recorded vision was 0.16 logMAR or 1.6 lines ETDRS. The mean acuity at the onset of bevacizumab treatment was 0.75 logMAR or 20/112 (range, 20/25 to counting fingers), and the mean acuity at the final visit was 0.59 logMAR or about 20/80 (range, 20/20 to counting fingers). The visual acuity data were not normally distributed (Kolmogorov-Smirnov $d_{initial}$ = 0.26, *P* <.05, d_{final} = 0.22, *P* <.10); therefore, median scores for initial visual acuity and final visual acuity were compared using the Wilcoxon matched pairs test. The median initial logMAR acuity was 0.7 or 20/100, and the final logMAR acuity was 0.477 or about 20/60. This was statistically significant, z = 2.53, *P* = .011. The median results with interquartile intervals of the overall change for all eyes having bevacizumab only and for all visits is shown in Figure 1, and a scatter graph of all visions is shown in Figure 4.

The change of vision was also analyzed from the initial vision to the best vision within the follow-up time. Eight-seven percent of eyes had improvement at some time during the follow-up course with a median of 0.30 logMAR (3 lines) gained (*P* < .001).

The percentage of eyes with vision change from the initial injection to the last follow-up visit was 59% having improvement, 15% having the same vision, and 26% with worsen of vision. Thus overall, 74% improved or remained the same visually over the course of follow-up, and 26% worsened. Improvement of 3 lines (0.3 logMAR) occurred in 13 eyes (33%), while improvement of a lesser 2 lines occurred in 20 eyes (51%) and a greater 6 lines improvement in 6 eyes (15%). A decrease of 3 lines occurred in 4 eyes (18%).

A subgroup of this category was composed of the 36 eyes that had 20/40 or worse visual acuity at the initial treatment. This was

calculated to allow direct comparison with the benchmark study by the Branch Vein Occlusion Study Group. These data are shown in Table 4.
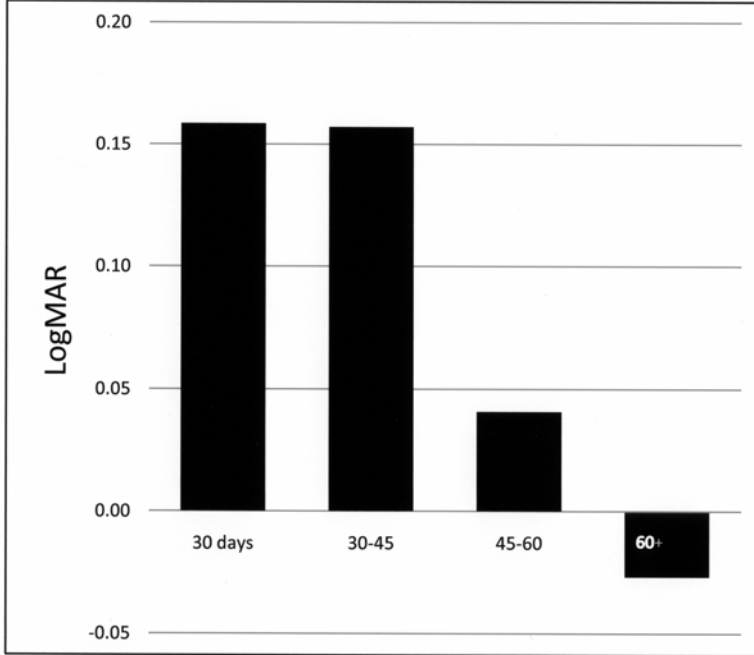

FIGURE 3

Mean change in vision, in logMAR, measured at various visitation times after injections for all 56 patients. After 45 days the vision drops off substantially, and by 60 days there is a worsening.
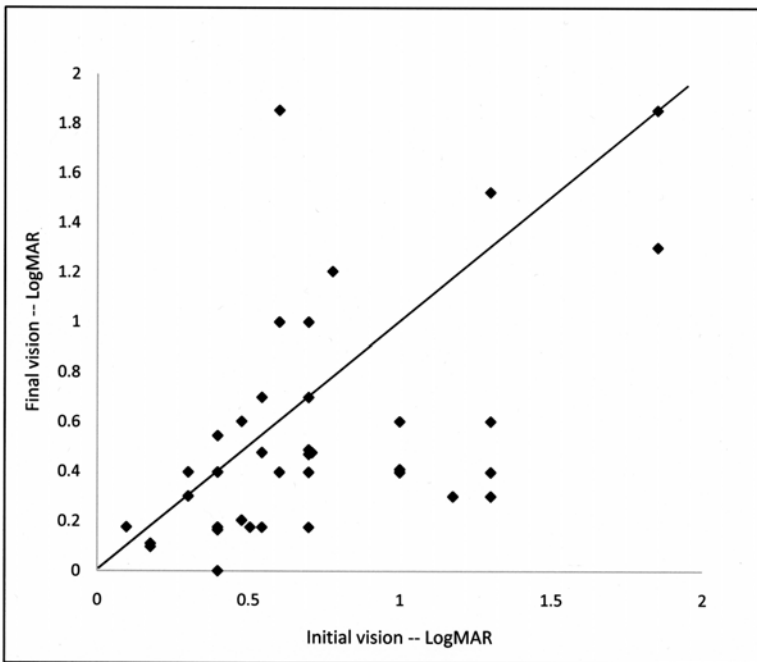

FIGURE 4

Data for the 39 eyes that received only bevacizumab and no triamcinolone acetonide. Horizontal axis reflects the initial logMAR vision at the time of the first bevacizumab injection and the vertical axis the final logMAR vision at the last visit available at the time of the chart review. Points on the diagonal line had no change in vision. Points below the line had an improvement in vision, and those above a reduction. Overall, the vision improved in most eyes that received bevacizumab.

OCT DATA

All OCT data are based on average retinal thickness of the foveal subfield on the retinal thickness tabular output report calculated by the Zeiss Stratus unit.

Of the 56 patients in the general group, 41 had an OCT at the initiation of treatment and one or more OCT measurements on subsequent visits. Over the maximal time course for each patient, there was a mean 97-μm change in the foveal thickness measurement. The average of the initial measurement was 422 μm, and the final measurement was 315 μm ($P = .00009$. The means with 95% confidence intervals are shown in Figure 5. Thirty-two eyes (78%) improved, and 8 eyes (22%) worsened. The average time between the initial and final measurement was 9.6 months, and the average vision change associated with these visits was 0.02 logMAR or 1 letter.
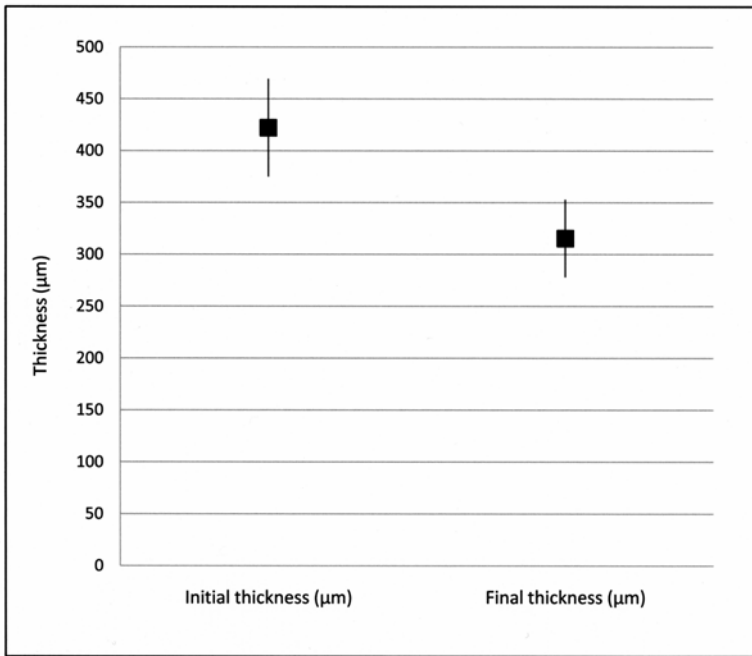
FIGURE 5

Mean foveal thickness measurements (by ocular coherence tomography) from the initial injection visit to the final visit, the last visit available with a measurement at the time of the chart review. The dots are the mean thickness, the lines the 95% confidence intervals. These results were statistically significant (P <.0001).

We analyzed the effect of each bevacizumab injection for the 103 injections where OCT information was available. At an average time interval of 39 days, there was a mean reduction of 128 μm in foveal thickness per injection. Initial thickness was 407, and at next follow-up thickness was 279. The average visual change associated with this reduction in thickness was 0.1 logMAR or 1 line ETDRS, from an average of 20/100 to 20/80. However, since multiple tests on some patients were correlated, the *t* test was done on a group consisting of one measurement per patient, using the first injection with a follow-up measurement within 65 days (2 months). The mean initial thickness was 427, and the follow-up thickness was 273, which was statistically significant (*P* < .001). These mean measurements with 95% confidence interval are shown in Figure 6.
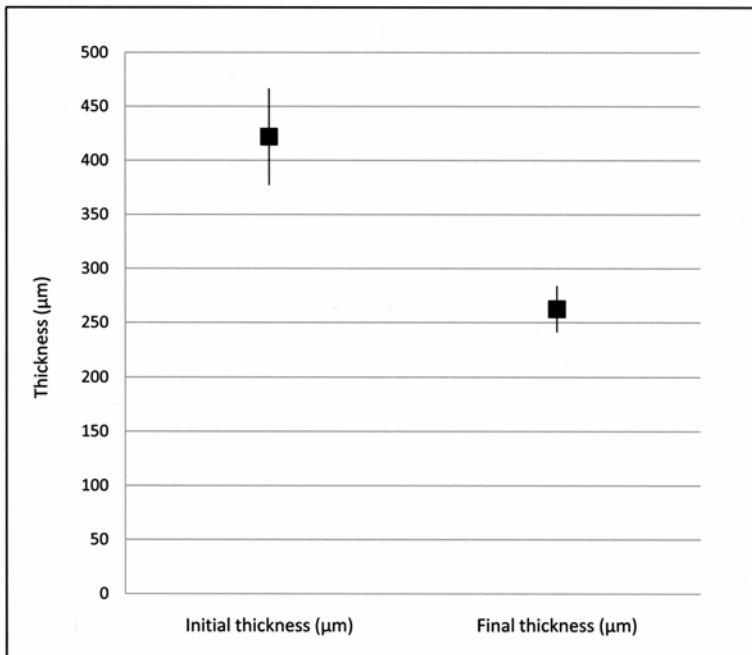
FIGURE 6

Mean foveal thickness measurements (by ocular coherence tomography) from the first injection with follow-up within 65 days of each of 41 patients in whom data was available, one injection per patient. The initial thickness was measured at the time of the bevacizumab injection. The final thickness was measured at the time of the next available visit after the injection. This represents the mean effect of a single injection. The difference was statistically significant (*P* <.001).

Data concerning foveal thickness changes are shown in Table 5.

There was a difference in the degree of reduction of foveal thickness, depending on when the follow-up measurement was taken. Figure 7 shows the effect of bevacizumab on foveal thickness over time. Those patients who were seen at 1 month had an average reduction of 161 μm and a vision gain of 1.4 lines. At 6 to 8 weeks the average effect on foveal thickness dropped to a reduction of 88 μm without visual gain, and those seen after 2 months had little remaining effect on either thickness or vision.

TABLE 5. SUMMARY OF MACULAR THICKNESS MEASUREMENTS (OCT) AFTER INTRAVITREOUS BEVACIZUMAB

CATEGORY	CHANGE OVER THE DURATION OF FOLLOW-UP	CHANGE OVER ONE FOLLOW-UP VISIT
Number of patients	48 μm	103 μm
Initial measurement	421 μm	407 μm
After measurement	319 μm	279 μm
Change in thickness	102 ($P = .00013$)	128 ($P < .0001$)
Mean time	9.7 months	39 days
Number better (%)	38 (78%)	90 (87%)
Number worse (%)	11 (22%)	13 (13%)
Mean vision gained (ETDRS equivalent)	1 line	1 line

OCT, ocular coherence tomography.

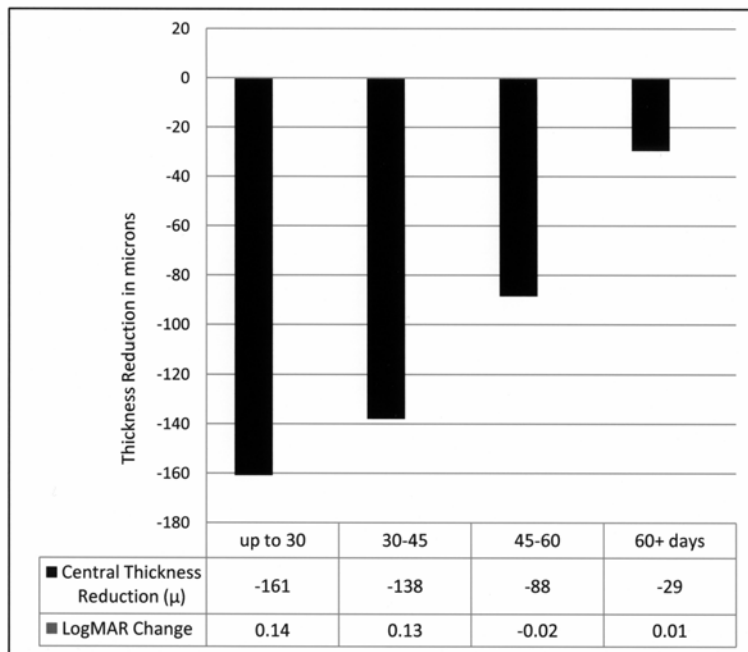|	up to 30	30-45	45-60	60+ days
Central Thickness Reduction (μ)	-161	-138	-88	-29
LogMAR Change	0.14	0.13	-0.02	0.01

FIGURE 7

Effect bevacizumab injection on foveal thickness at various time intervals after injection. Bars represent the mean foveal thickness after several time intervals after intravitreous bevacizumab. The effect is reduced substantially after 45 days, and the visions in this subgroup of patients who had ocular coherence tomography measurements reflect the same loss of effect after 45 days.

OTHER

Photographs and fluorescein angiography were not always adequate to determine ischemia. A best effort estimated that 17 of 56 patients (30%) were possibly ischemic and 10 of 56 (18%) were probably ischemic.

No episodes of vitreous hemorrhage, retinal detachment, or endophthalmitis associated with injection were seen in these patients. A subconjunctival hemorrhage was common after injection and self-limited without permanent sequelae.

DISCUSSION

The hypothesis of this study was that the injection of IVB, a low-risk office procedure, would be as good for improving the visual loss associated with BRVOs and HRVOs as are other currently used modes of therapy. The challenge was to extract useful data from a

retrospective chart review consisting of a group of patients treated by many physicians without protocol over several years. Since there is no prospective, randomized trial assessing this point thus far, it is appropriate to do this. The physicians involved were acting in the best interest of their patient at each visit, attempting to apply their best current knowledge to the situation.

Intravitreous injections have recently become commonplace in retinal practice. Pegaptanib and ranibizumab have been proven effective for the treatment of age-related macular degeneration, a very common retinal disease.[16,17] The risk of endophthalmitis has varied from study to study but seems to be 0.2% or less.[99] No systemic complications directly related to bevacizumab have been reported. The technique of injection has not been completely standardized but fits general guidelines that govern most procedures.[100] We carried out the injections in the office examination room and usually injected on the same day the need for injection was determined. In some cases, patients received preinjection antibiotics on the initial visit and then returned for a scheduled injection.

Treatment results for BRVO have been disappointing overall. Laser photocoagulation has been the most widely applied treatment and the only one with good data produced by a multicenter prospective randomized trial.

COMPARISON WITH PHOTOCOAGULATION

Laser shares the advantage of convenience with intravitreous injections. It is an office procedure that takes only a short time and can be done on routine visits on an as-needed basis. Laser requires equipment, but most retinal practices and many general ophthalmologic practices have lasers in the office, and many hospitals have available a communal unit. Laser is also of low risk. The Branch Vein Occlusion Study Group proved that a grid of photocoagulation across the macular area, avoiding the fovea, was helpful for improving the vision of patients with macular edema that reduces vision to less than 20/40.[52] Our data is comparable to that of this group and derives from a subgroup of 36 patients with initial visual acuity better than 20/40 who received IVB without triamcinolone acetonide. Our group had a mean visual gain of 1.7 lines (ETDRS equivalent) and a median visual gain of 1.8 lines, with an average follow-up time of 8.5 months. The Branch Vein Occlusion Study Group data was from 3-year follow-up, a time currently impossible for accumulation of bevacizumab data. Based on Figure 2 from the Branch Vein Occlusion Study Group report, at about 8 months, 20% of treated eyes had improved 2 lines. At 8 months average follow-up, 20 of 36 eyes (56%) had improved 2 lines. These follow-up times are not the same, however, because the Branch Vein Occlusion Study Group had an absolute follow-up of 8 months for all patients, whereas our data has an average follow-up. Still, bevacizumab appears no less effective than argon laser for visual improvement. Also, some of our patients had argon laser with less than optimal resolution of the macular edema, prompting the bevacizumab injections.

COMPARISON WITH LASER-INDUCED CHORIORETINAL VENOUS ANASTOMOSIS

Laser-induced chorioretinal venous anastomosis shares the convenience of being a procedure of short duration and office-based. Most cases of laser-induced chorioretinal venous anastomosis have been in eyes with CRVO. Complications are fairly frequent but may not affect the visual outcome. Eleven cases by 2 groups of investigators have succeeded in achieving an anastomosis in 5 eyes.[61,62] If an anastomosis is created, visual improvement is likely. However, overall, only 4 of 11 eyes (36%) improved 2 lines over a follow-up period of about a year. In comparison, 46% of our patients who had a combination of bevacizumab and triamcinolone acetonide, and 51% of the patients who had bevacizumab alone, improved by at least 2 lines. The mean follow-up time in this cohort was less (7 to 8.8 months). Still, bevacizumab appears no less effective than laser-induced chorioretinal venous anastomosis for visual improvement.

COMPARISON WITH ARTERIOVENOUS ADVENTITIAL SHEATHOTOMY AND VITRECTOMY WITH MACULAR DECOMPRESSION

Arteriovenous adventitial sheathotomy presumes to improve BRVO not only by lowering the hydrostatic pressure but by reestablishing flow more quickly and completely than collateralization. Sheathotomy has been performed for BRVO in at least 254 published cases, with 68% of patients having improvement in vision. Mean visual acuity improvement was 3.2 lines. The visual improvement with surgery was quite consistent across studies (see Table 2). The most frequent complications were progression of cataracts and retinal tears. The patients in our combined bevacizumab and triamcinolone acetonide group had a 52% improvement rate but only a 1-line change in vision. The patients in our bevacizumab-only group had a 59% improvement rate with a median 1.5-line change. Thus, it appears that sheathotomy produces a somewhat better visual outcome than IVB. This somewhat better outcome must be balanced against the complications, cost, and inconvenience of a surgically based procedure when compared to an office-based procedure.

Macular decompression is a similar surgical technique but less technically difficult than sheathotomy. Decompression does not reestablish flow but attempts to provide another route for fluid movement out of the macula. The main objective is to separate the posterior hyaloid from the macular area. At least 221 cases have been published for BRVO, with 72% of patients having improvement in vision and a mean improvement of 4 lines (see Table 3). Cataract progression is the main complication. IVB does not appear to be as effective as macular decompression. Again, the risks, cost, and convenience must be factored into the comparison. It is possible that the best, least invasive approach might be to try IVB initially and reserve sheathotomy for those cases that were not substantially and immediately improved.

INTRAVITREOUS TRIAMCINOLONE ACETONIDE

Intravitreous triamcinolone acetonide has been a popular treatment in retinal practices the past 5 years for the treatment of macular edema. At least 127 cases using IVT for BRVO have been published, with 77% of patients having improvement of vision (see Table 1). The mean change in vision over a follow-up of generally less than 1 year was 2.5 lines. Since the suppression of leakage often

dissipates over time, most studies measure the best vision after injection at any time during the follow-up period in addition to the final vision. The mean best vision was an improvement of 3.7 lines. Many studies also measured macular thickness using OCT, and the mean change in thickness was a reduction of 231 μm. Since our IVB had a 59% improvement rate with a median line change of 1.5 and a 97-μm change in foveal thickness, IVB does not appear to be as effective as IVT. It is hard to explain this deficiency, because our group combining bevacizumab with triamcinolone acetonide had less improvement in visual outcomes than the bevacizumab-only group. These differences may have to do with patient inclusion differences. The amount of change to the best vision after injection, however, is similar between our bevacizumab-only group and the IVT group, having a mean 3.5-line change and a median 3-line change from initial to best vision. Bevacizumab does not cause either cataract or glaucoma, as does triamcinolone acetonide, giving a factor to balance against a poorer visual outcome.

HEMODILUTION

One study using hemodilution in patients with BRVO had an average of 2 to 4 lines of visual improvement over time. This is better than visual improvement with IVB. This series included only 18 patients treated by hemodilution and therefore is difficult to compare because of the small number. Additionally, visual acuity at 1 year with the control group was 20/80, the same as our final vision in our treatment group. This suggests that the group considered had less severe disease. It is difficult to derive a comparison between hemodilution and IVB.

INTRAVITREOUS TPA

One study of 17 patients receiving intravitreous tPA showed a 2.5-line improvement in vision and a 485-μm reduction in foveal thickness over 6 months follow-up. These numbers are better than IVB. Comparison is difficult, however, because of the small number of patients studied and the early onset of treatment, at an average of 30 days after onset of symptoms. The initial vision in this group was 1.5 lines better than the initial vision in our group and about the same as our final visual acuity. It is therefore impossible to compare these 2 studies.

INTRAVITREOUS BEVACIZUMAB FOR BRVO, OTHER STUDIES

Two papers in the English literature present series of cases of eyes with macular edema due to BRVO that were treated with IVB. Pai and associates[101] treated 12 eyes with BRVO and mean improvement was from 1.19 logMAR (20/300) to 0.8 logMAR (20/126), an average improvement of 4 lines. This change was statistically significant (P = .02). Foveal thickness was reduced from an initial mean thickness of 672 μm to 300 μm at 6 months. Rabena and coworkers[102] treated 27 patients with BRVO with IVB. Initial mean acuity was 20/200, and this improved to 20/100+ at last follow-up (mean, 5.3 months). Foveal thickness improved from an initial 478 μm to 146 μm at last follow-up. Both vision change and foveal thickness improvement were significant (P < .001). These 2 studies show results that are similar to ours, reinforcing the usefulness of IVB.

ADVANTAGES OF IVB

The use of IVB has the advantages of being a simple, inexpensive, convenient, relatively low-risk treatment that can be done in the office setting without requiring a second scheduled visit. It can be given early in the course of BRVO and HRVO because there is no requirement to wait for retinal hemorrhages to clear. It can even be given in the presence of vitreous hemorrhage if there is knowledge that the way is clear. This can reduce posterior neovascularization and reduce the possibility of further hemorrhage pending clearing.[103] In our group, the reduction of macular edema was quick and significant. If visual recovery should depend on minimizing the duration and severity of macular structural abnormality, then early treatment might increase the rate and quantity of recovery. This idea is logical, if not proven, and has analogies in other macular diseases, such as long-standing macular holes and chronic CME. However, whether several months of macular edema lead to permanent and irreversible changes is not known.[52] Additionally, our data suggest that even if there were no final, long-term improvement, the visual acuity is improved significantly by a median of 1.5 lines at a median of 28 days after each injection (P < .0001). This visual improvement lasted up to 60 days before quickly worsening again. This temporary improvement would likely justify an injection.

One eye with vitreous hemorrhage and neovascularization before bevacizumab was initially excluded. No patient included developed neovascular complications among the study group. Whether this was due to this group being less ischemic than other patients with larger BRVO and HRVO or to the use of IVB is unknown. The risk of neovascular changes has been reported to be from 12% to 22% by the Branch Vein Occlusion Study Group.[104] The risk depended on treatment and time. Perhaps our patients have not been followed long enough. It is likely this group of 56 patients would have had some cases if left to the natural history. Additionally, some patients in this group had laser photocoagulation as well as IVB, and this could have reduced the incidence of neovascular complications; however, most lasers treatments were focally applied to reduce macular edema.

REASONS FOR LACK OF IMPROVEMENT AND WHAT WE MIGHT DO BETTER.

Our patients did not fare as well overall as the published IVT data or the surgical interventions. The reasons for a lack of response include ischemia and chronic edema as well as the possible need to improve the treatment protocol. Ischemia was important in this study. Of the 11 eyes that had an entry visual acuity of <20/200, 8 were ischemic. Four of the 5 patients with an original vision of counting fingers were ischemic, and 4 of 5 remained at counting fingers at the conclusion. These eyes would not be likely to respond to a simple reduction in the edema, but none had neovascularization and perhaps thus benefited. Case selection might improve the

percentages of improvement. Still, other eyes with 20/200 to 20/400acuity at the onset benefited several lines, and good criteria to predict which eyes will improve have not been developed.

This group of patients was treated following multiple protocols. We found that the vision falls quickly about 45 days postinjection. Rabena and colleagues[102] had a similar experience, with the effect lasting 2.1 months in their group. By reinjecting more regularly, it might be possible to produce a steady-state without the rapid recurrence of edema that is sometimes seen. The requirements for constant suppression of VEGF for bevacizumab are not known. There is little coordination among the physicians involved in the care of these patients. The most likely approach is one of injections as needed to suppress the recurrence of edema. With vein occlusions the return of leakage after a therapeutic reduction may be quite sudden and severe. It is noteworthy that a high percentage of the eyes (82% overall) improved from the initial acuity at some point in the course of treatment. Consistent injections at a more frequent interval might prove more successful. The obvious disadvantages of this approach are that more injections subject the patient to more risk, and without monitoring for recurrence, it is difficult to know where one is in the course of treatment.

Although improved long-term vision is the benchmark, shorter-term improvement is still a reasonable goal as long as the risks and inconvenience of the treatment are low.

SHORTCOMINGS OF THE STUDY

This study was a retrospective analysis, a chart review. There was no predetermined protocol for measurements of either vision or macular thickness, or frequency or schedule of either testing or treatment. This produced data with variability between patients and physicians. Visual acuity was determined with the patient's current spectacle correction and additional pinhole correction. Visions were measured on a variety of charts—Snellen charts in different locations under differing conditions and ETDRS charts on occasion. Manifest refraction using a standardized ETDRS test chart would have produced a more reliable and reproducible visual result. Fluorescein angiography was not routinely done, and no information was obtained regarding the effect that blocking VEGF might have on the retinal blood flow. All patients, except one with HRVO, receiving bevacizumab for BRVO and HRVO who had follow-up were included. Including early cases might have biased the visual outcome positively if patients were included subject to spontaneous resolution. Including eyes with more severely reduced vision and perhaps more ischemic eyes might have biased the visual outcome negatively if the patients had tissue function loss unassociated with edema.

Another shortcoming was the lack of a consistent time interval for measurement of the "final vision." The vision at the last patient visit at the time of the chart review was used. Since the vision and the macular thickness may vary with the timing of the visit relative to the last injection, it is likely that variability was induced by the lack of a consistent protocol. The treatment of these patients was ongoing at the time of the chart review. Repeat analysis at a future time after treatments have been discontinued because of maximal benefit would give a clearer idea of the long-term efficacy of this mode of therapy.

RETROSPECTIVE ANALYSIS—A COMMENT

Most of the day-to-day patient care decisions made in a retinal practice, both medical and surgical, have not been based on information from a quality, prospective, randomized trial. Many of the myriad reports reviewed for this thesis noted their deficiencies and the need for a larger well-controlled trial. Currently the speed of evolution of medical knowledge is escalating. The breakthroughs in basic science data, the introductions of many new medicines, and the rapid progress in engineering in measurement and surgery are quickly changing the practice of ophthalmology. Such speed makes it difficult to design, initiate, recruit, analyze, and report information from a major trial in a time-relevant manner. Retrospective trials could be more useful if certain information were gathered routinely, at certain time points after interventions, and in standardized fashions. This would make it possible to better correlate information among studies, although differences in inclusion criteria would still make analysis difficult.

CONCLUSION

The treatment of BRVO and HRVO by the intravitreous injection of bevacizumab is an effective way to reduce edema in the short term. A substantial visual acuity increase and macular thickness decrease occurred frequently after injection. Studies using surgical methods of reestablishing flow and reducing macular edema showed better visual improvements than our group given IVB. Also, IVT produced somewhat better results. Most of the studies reviewed were small, and none were randomized, although some were controlled. Intravitreous bevacizumab has the advantages of simplicity, relative safety, and cost when compared to the other treatments. Results using IVB might be improved by more careful case selection, avoiding eyes with visual acuity <20/400. It is likely that injections regularly at 6-week intervals would continuously suppress the macular edema and might improve long-term visual outcomes.

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