Intravitreal Bevacizumab for Neovascular Glaucoma

Deepta Vasudev, Michael P. Blair, John Galasso, Rashmi Kapur, and Thasarat Vajaranant

Abstract

Purpose: To report 6-month and 1 year outcomes of eyes treated for neovascular glaucoma (NVG) with intravitreal bevacizumab injection and panretinal laser (PRP) compared to those receiving PRP alone.

Design: retrospective, consecutive case series.

Methods: Charts of patients with NVG from retinal ischemia and at least 6 months of follow-up were reviewed. Patients were treated with one injection of 1.25 mg intravitreal bevacizumab followed by PRP or with PRP alone. The primary outcome was the long-term angle anatomy. Secondary measures included intraocular pressure (IOP), visual acuity, patient compliance, and control of systemic diseases.

Results: Fourteen eyes of 12 patients treated with bevacizumab and PRP and 15 eyes of 11 patients treated with PRP alone were included in the study. Mean sectors of open angle at baseline was 1.31 in the bevacizumab group and 1.47 in the retinal ablation group ($P = 0.73$). Mean sectors of open angle was 2.14 and 1.18 in the bevacizumab and retinal ablation groups, respectively ($P < 0.05$) at 6-month follow-up, and 2.27 and 1.18, respectively ($P < 0.05$) at 1-year follow-up. Mean baseline IOP was 32.3 mmHg (± 14.8) in the bevacizumab group and 31.8 mmHg (± 13) in the PRP group ($P = 0.75$). At 6-month follow-up, the mean IOP was 18.28 mmHg (± 10) in the bevacizumab group and 23.33 mmHg (± 14.6) in the PRP group ($P = 0.05$), and 19.12 mmHg (± 6.8) and 26.2 mmHg (± 18) ($P = 0.1$), respectively at 1-year follow-up. Nineteen patients were judged to be noncompliant, 10 had uncontrolled diabetes and 7 had uncontrolled hypertension.

Conclusions: This study documents better long-term preservation of open angle and IOP control in eyes receiving bevacizumab along with PRP. We stress that NVG is still associated with poor visual acuity outcomes.

Introduction

NEOVASCULAR GLAUCOMA (NVG) is a potentially devastating consequence of fibrovascular proliferation of the anterior chamber angle with subsequent obstruction of the trabecular meshwork. The production of peripheral anterior synechiae (PAS) along the trabecular meshwork leads to progressive angle closure. The subsequent elevation in intraocular pressure (IOP) is difficult to manage, often leading to rapid progression of glaucoma and significant loss of vision. NVG has many etiologic causes, the vast majority resulting from retinal ischemia secondary to relatively common diseases such as central retinal vein occlusion, proliferative diabetic retinopathy, and ocular ischemic syndrome.¹ Ischemia initiates the release of multiple factors that promote new vessel growth such as Vascular Endothelial Growth Factor (VEGF).² VEGF levels are increased in the aqueous humor and vitreous of patients with NVG, as compared to patients without NVG.³⁻⁵ It is now well known that inhibition and regression of new blood vessel growth occurs by blocking this molecule.⁵⁻⁸

Although panretinal photocoagulation and/or cryoablation are mainstays of conventional treatment for NVG,⁹⁻¹¹ the delayed therapeutic effect of these interventions can often result in the formation of PAS and permanent angle closure. Successful treatment also depends on a clear media and early recognition before formation of PAS. With significant angle closure secondary to PAS, IOP may not decrease after adequate retinal ablation. In this situation, diode laser cyclodestruction and surgical treatment options such as tube shunts or trabeculectomies have been employed. While these methods are successful in lowering IOP, long-term visual acuity outcomes have been variable.¹²⁻²⁰

Inhibition of VEGF-A by bevacizumab has been shown to be successful in causing short-term regression of retinal neovascularization. Recently, intravitreal injection of this agent has demonstrated rapid regression of neovascularization of the iris (NVI). Small case series have shown regression of NVI for 4–10 weeks after a single intravitreal injection of bevacizumab.²¹⁻²⁵ While these studies have shown promise for the use of bevacizumab in NVG in the short-term period,

the long-term treatment outcomes are less clear. Two recent studies^{26,27} report longer-term continued IOP reduction as well, but long-term angle anatomy was not consistently reported.

The present study is a retrospective review reporting 6-month and 1-year outcomes of patients receiving intravitreal bevacizumab and conventional treatment for the management of NVG compared to patients receiving conventional treatment alone. The primary outcome measure is long term angle anatomy. Secondary outcome measures include IOP, visual acuity, patient compliance, and control of systemic diseases.

Methods

This study was an Institutional Review Board approved retrospective consecutive case series of patients with NVG. Patients with NVG were identified using ICD-9 code 365.63. Charts of patients with NVG were retrospectively reviewed from the Retina and Glaucoma services at the University of Illinois Eye & Ear Infirmary from January 2004 to December 2007. Inclusion criteria for the study consisted of: (1) NVG secondary to chronic retinal ischemia from proliferative diabetic retinopathy, central retinal vein occlusion, central retinal artery occlusion, ocular ischemic syndrome, or other vascular occlusions; and (2) patient follow-up for a minimum of 6 months. Patients with a history of retinal detachment were excluded from the study. Patients were treated with one injection of 1.25 mg (0.05 mL) intravitreal bevacizumab followed by retinal ablation therapy within 1 week or retinal ablation alone. Bevacizumab was administered in a sterile fashion through the pars plana. Full retinal ablation therapy was performed on all patients in either single or multiple procedures depending on severity of disease, view to the retina, and patient tolerance.

The medical records of the patients were reviewed for prior retinal ischemic diagnosis, known systemic diseases, and ophthalmic findings: visual acuity, IOP, angle and iris neovascularization, number of glaucoma medications used, extent (number of shots) and timing of retinal ablation therapy, and additional procedures required to lower pressure or clear media. In patients receiving bevacizumab, time points were defined as baseline (day of injection), 1 week, 1 month, 3 months, 6 months, and 1 year postinjection. Decision to use bevacizumab depended on physician and patient preference after obtaining informed consent. The treating physicians at our institution tended to offer bevacizumab from 2006 onward for initial therapy to all patients with NVG except in those with severe comorbid conditions such as uncontrolled severe diabetes, hypertension, and history of stroke. In patients receiving retinal ablation only (mainly patients seen initially from 2004 to 2006), baseline was defined as first visit when diagnosis of NVG was made (defined as elevated IOP from angle obstruction associated with neovascularization of the angle (NVA) and/or NVI requiring pressure lowering strategies).

Medical records for all patients were reviewed for control of chronic systemic diseases, compliance with recommended ophthalmic follow-up, and compliance with ophthalmic medical regimen. A patient was placed under the category of poor follow-up if he or she missed more than one follow-up appointment. A designation of uncontrolled Diabetes Mellitus (DM) was given if at any time the records showed

an HbA1C of over 7.5%, if the blood sugar was recorded as over 200 units, or if the patient reported widely fluctuating blood sugars. A designation of uncontrolled hypertension was given if the blood pressure was recorded as over 170 mmHg systolic or over 100 mmHg diastolic on any given chart, or if the patient reported poor control. Charts were also reviewed for any history of stroke.

Given the inability to standardize the treatment and data collection in this retrospective review, gonioscopy data were divided into three categories in each quadrant: open, NVA, or PAS. NVI was quantified as: severe (>2 quadrants of NVI present, given a score of 3), moderate (2 quadrants of NVI present, given a score of 2), mild (<2 quadrants of NVI present, given a score of 1), or not present (given a score of 0). Visual Acuity was measured using the Snellen Visual Acuity chart. Given the relatively poor level of vision of many patients with NVG, attainment of visual acuity of 20/200 or better was defined *a priori* to be a favorable outcome.

Statistical analysis was performed using Microsoft Excel and qualitatively comparing the median values for all data between the two groups. The means for all outcome measures were also calculated and compared between both groups using an online standard student *t*-test (www.quantitativeskills.com/sisa/statistics/t-test.htm). Categorical values were compared using the chi-square test.

Results

A total of 100 charts were identified by billing code for NVG and retrospectively reviewed from the Retina and Glaucoma services at the University of Illinois Eye & Ear Infirmary from 2004 to 2007. Twenty-nine eyes (23 patients) met the inclusion criteria. Of these, 14 (12 patients) were treated with one injection of 1.25 mg (0.05 mL) intravitreal bevacizumab followed by retinal ablation within 1 week while 15 (11 patients) were treated with retinal ablation therapy alone. All patients were given the diagnosis of NVG at our institution and seen promptly by both the Glaucoma and Retina services. Six-month follow-up data was available for all patients included in the study and 1-year follow-up data was available for 15 pts (seven in bevacizumab group, eight in retinal ablation group).

Baseline characteristics

See Table 1. In the Bevacizumab group, 8/14 eyes had a minimum of 1,200 shots of PRP to the peripheral retina in one setting within 1 week of Bevacizumab injection, while 6/14 eyes received a minimum of 1,200 shots over 2 settings (within 1 week apart) after bevacizumab injection. In the PRP group, 7/15 eyes had at least 1,200 shots in 1 setting, while 8/15 eyes received a minimum of 1,200 shots over 2 settings (also 1 week apart). There was no statistical difference between number of PRP sittings (1 or 2) in both groups ($P = 0.57$).

Iris neovascularization

See Table 2.

Angle anatomy

See Table 2.

TABLE 1. PATIENT BASELINE CHARACTERISTICS

Parameter	Bevacizumab group	Retinal ablation group	P value
Number of eyes/pts	14/12	15/11	
Mean age ($\pm$ SD)	59.4 $\pm$ 7.5	57.8 $\pm$ 7.6	0.57
Ischemic retinal disease, no. eyes			
PDR	8	10	
CRVO	5	4	
OIS	1	0	
CRAO	0	1	

Abbreviations: pts, patients; SD, standard deviation; PDR, proliferative diabetic retinopathy; CRVO, central retinal vein occlusion; OIS, ocular ischemic syndrome; CRAO, central retinal artery occlusion.

IOP control

See Table 2. Mean number of pressure lowering topical medications required was not statistically significant between groups at all time points (Table 2). The number of eyes requiring further pressure lowering strategies was not significantly different between groups: acetazolamide required chronically, described as more than one time point (one eye in the bevacizumab, three eyes in the retinal ablation), diode laser cyclodestruction (nine eyes in both groups), trabeculectomy (one eye in the bevacizumab group, two eyes in the retinal ablation group), or tube shunts (one eye in the bevacizumab group vs. four eyes in the retinal ablation group); $P = 0.3$.

Visual acuity outcome

Visual acuity was 20/200 or better in 3/15 eyes in the retinal ablation group compared to 2/14 eyes in the bevacizumab group at baseline ($P = 0.68$). At 6 months, there was no change in the visual acuity outcomes in either group. In the retinal ablation group, 3/15 eyes and 5/14 eyes in the

bevacizumab group gained more than one line of vision after 6 months, while 6/15 eyes in the retinal ablation group and 7/14 eyes in the bevacizumab group lost more than one line of visual acuity (Figure 1).

Patient compliance and systemic disease

The number of patients that missed more than one follow-up appointment was 10 and 9 in the bevacizumab and retinal ablation groups, respectively. Three patients in the bevacizumab group were found to have uncontrolled DM, as compared to seven in the retinal ablation group ($P = 0.06$). Uncontrolled hypertension was seen in two bevacizumab patients and five retinal ablation patients ($P = 0.14$), and two patients in both groups had a history of stroke.

Discussion

This retrospective qualitative study reports the 6-month and 1-year outcomes of patients with NVG treated with intravitreal bevacizumab therapy and panretinal laser, compared to panretinal laser alone.

FIG. 1. Scatter plot demonstrating initial and 6-month visual acuity (Snellen) in the bevacizumab and retinal ablation groups. Points below the line demonstrate improved visual acuity whereas points above the line demonstrate declining visual acuity. *2 represents 2 eyes in the same group with same initial and 6-month VA outcomes; Bv + PRP represents bevacizumab eye and retinal ablation eye with same initial and 6-month VA outcome. Axes labels: CF, counting fingers at 3 feet; HM, hand motions; LP, light perception; NLP, no light perception.

TABLE 2. TABLE OF OUTCOME MEASURES FOR BOTH GROUPS AT ALL TIME POINTS

Outcome	Bevacizumab group N = 14 (N = 8 at 1 yr)	Retinal ablation group N = 15 (N = 11 at 1 yr)	P value
Presence of NVA, no. eyes			
Baseline	11	10	0.47
1 week	6	10	0.20
1 month	2	7	0.05*
3 months	2	3	0.68
6 months	0	2	0.15
1 year	0	2	0.15
Median/mean ($\pm$ SD) sectors of open angle			
Baseline	1/1.31 ($\pm$ 1.1)	1/1.47 ($\pm$ 1.3)	0.73
1 week	1.5/1.71 ($\pm$ 1.4)	1/1.47 ($\pm$ 1.3)	0.64
1 month	2/1.79 ($\pm$ 1.4)	1/1.40 ($\pm$ 1.3)	0.45
3 months	3/2.00 ($\pm$ 1.4)	1/1.40 ($\pm$ 1.2)	0.23
6 months	3/2.14 ($\pm$ 1.3)	1/1.18 ($\pm$ 1.1)	0.04*
1 year	3/2.27 ($\pm$ 1.3)	1/1.18 ($\pm$ 0.7)	0.01*
Median/mean ($\pm$ SD) sectors of PAS			
Baseline	1/1.43 ($\pm$ 1.1)	2/1.53 ($\pm$ 1.3)	0.82
1 week	1/1.43 ($\pm$ 1.1)	2/1.60 ($\pm$ 1.4)	0.72
1 month	1/1.5 ($\pm$ 1.2)	2/1.8 ($\pm$ 1.3)	0.52
3 months	2/1.64 ($\pm$ 1.4)	2/2 ($\pm$ 1.3)	0.48
6 months	2.5/1.64 ($\pm$ 1.2)	2/2.07 ($\pm$ 1.2)	0.34
1 year	2/1.75 ($\pm$ 1.2)	3/2.36 ($\pm$ 1.1)	0.17
Median/mean ($\pm$ SD) no. IOP lowering drops			
Baseline	1/1.64 ($\pm$ 1.6)	3/2.73 ($\pm$ 1.6)	0.07
1 week	3/2.86 ($\pm$ 1.3)	4/2.93 ($\pm$ 1.4)	0.89
1 month	2.5/1.92 ($\pm$ 1.6)	4/2.87 ($\pm$ 1.5)	0.11
3 months	1.5/1.57 ($\pm$ 1.4)	3/2.47 ($\pm$ 1.4)	0.09
6 months	1/1.57 ($\pm$ 1.3)	3/2.47 ($\pm$ 1.6)	0.11
1 year	0.5/1.41 ($\pm$ 1.3)	3/2.5 ($\pm$ 1.7)	0.06
Median/mean ($\pm$ SD) IOP			
Baseline	34.5/32.4 ($\pm$ 14.8)	30/31.8 ($\pm$ 13.0)	0.75
1 week	16/20.0 ($\pm$ 12.8)	24/24.2 ($\pm$ 11.7)	0.4
1 month	18/20.7 ($\pm$ 14.3)	22/26.1 ($\pm$ 12.6)	0.3
3 months	16.5/18.4 ($\pm$ 12.0)	20/23.6 ($\pm$ 14.4)	0.3
6 months	15.5/18.3 ($\pm$ 10.0)	25/23.3 ($\pm$ 14.6)	0.05*
1 year	18.5/19.1 ($\pm$ 6.8)	19/26.2 ($\pm$ 18.0)	0.1
Median/mean ($\pm$ SD) NVI			
Baseline	2/2.43 ($\pm$ 0.5)	2/2.06 ($\pm$ 0.7)	0.65
1 week	1/0.64 ($\pm$ 0.63)	2/1.78 ($\pm$ 0.8)	0.001*
1 month	0/0.46 ($\pm$ 0.87)	1/1.40 ($\pm$ 0.8)	0.005*
3 months	1/1.2 ($\pm$ 0.90)	1/1.13 ($\pm$ 0.9)	0.83
6 months	1/1.28 ($\pm$ 1.1)	0/0.8 ($\pm$ 1)	0.2
1 year	1/1.30 ($\pm$ 1.1)	0.5/0.9 ($\pm$ 1)	0.6

*Denotes statistical significance.

Abbreviations: NVA, neovascularization of the angle; SD, standard deviation; PAS, peripheral anterior synechiae; IOP, intraocular pressure; NVI, neovascularization of the iris.

Iris neovascularization

Our study confirmed prior reports of more rapid regression of NVI following bevacizumab injection.^{26,27} After the 1-month time point following bevacizumab injection, there was an increase in the average NVI score. Regression of NVI occurred less rapidly in the retinal ablation group initially; however, unlike the bevacizumab group the amount of NVI did not increase substantially at later time points in the retinal ablation group. Recurrence of retinal neovascularization following regression due to anti-VEGF therapy is well

known in diabetic retinopathy.^{6,22,23,28} The reason for reappearance following more permanent panretinal ablation in some eyes is less clear. Perhaps there are some areas of the retina that are injured initially by laser treatment but later recover sufficient function to produce lower levels of VEGF.

Angle anatomy

There was no difference in mean amount of NVA, sectors of open angle, or sectors of PAS at baseline between both groups. Despite this similar angle anatomy at baseline, there

was significantly more average open angle in the bevacizumab eyes by 6-months follow-up, which persisted at 1-year follow-up. This result is understandable given the ability of bevacizumab to cause quick regression of neovascularization. With the timely regression of NVA (followed by full panretinal ablation therapy), PAS formation can be prevented and the resulting preservation of open angle can be achieved. This long-term gonioscopically documented preservation of open angle is a major advantage of bevacizumab combined with retinal ablation over standard laser alone.

IOP control

Although we did not find an early significant difference in mean IOP after bevacizumab injection as compared to retinal ablation alone as did other studies,^{26,27} the median IOP was lower in the bevacizumab group at every time point after treatment and appeared to decline more rapidly. However, we found that eyes receiving bevacizumab had significantly lower mean IOP at the 6-month time point than eyes receiving laser alone, and this trended toward significance at 1 year. Both groups did not show any statistically significant difference in number of IOP lowering drops required at any time point.

One important difference in our study from others is the larger number of eyes (nine in each group) that received ciliary body destructive procedures. The reason for the frequent cyclodestructive procedures as compared to other studies is not clear, but may be a treatment preference for uncontrolled pressures in NVG by the glaucoma service at our institution. The majority of patients in both groups were not compliant with follow-up, with 19 of 23 patients missing more than one follow-up appointment during the study period. Given this poor compliance, invasive glaucoma interventions such as trabeculectomies and tube shunts, which require close post-operative follow-up care, may not be preferred treatment strategies.

VA outcome

There was no statistical significance between visual acuities at baseline in both groups, and the long-term visual acuity was similarly poor in both groups, with few eyes having visual acuity of 20/200 or better at any time point. Less than half of the eyes in either group improved by more than one line of vision at the 6-month time point. Similarly, poor visual outcomes were found by Ehlers and colleagues²⁶ In their study, only 3/11 eyes treated with bevacizumab for NVG had final acuity better than 20/100.

As stated earlier, cycloablative procedures were employed more frequently in our study, which could also be contributing to the poor visual outcomes.

Compliance and control of systemic medical conditions

While a large retrospective study by Wu and colleagues²⁸ reported a low risk of stroke following intravitreal bevacizumab injection for retinal and choroidal neovascularization, we believe that patients with NVG have poorer general medical health. In fact, our study confirms that a large proportion of patients with NVG have poor control of general medical conditions, with 10/23 having poorly controlled

diabetes and 7/23 having poorly controlled hypertension. Although no patient in our small series suffered a stroke after treatment, two patients in each group had a prior history of stroke. Despite the small sample size, a history of stroke in 17% of our patients further confirms our impression that patients with NVG are at a higher risk for stroke than the general population. We feel that caution should be used when offering bevacizumab to patients with poor systemic health, since they are at a higher risk for stroke and other thromboembolic events, in general, and since anti-VEGF medications may increase the risk of these events even when given intraocularly.

We also documented poor compliance with prescribed medications and poor follow-up in 19/23 patients with NVG. We believe this is also an important consideration when treating NVG with bevacizumab, especially given the finding of NVI recurrence seen after the 1-month time point. A patient who initially does well after bevacizumab injection and is subsequently lost to follow-up without adequate panretinal ablation or glaucoma management could be at high risk for visual loss.

Limitations of the current study are the retrospective nature, small sample size, and lack of best-corrected visual acuity protocol. Despite these limitations, it is the largest longer-term study to date comparing outcomes for NVG after bevacizumab injection and panretinal ablation with panretinal ablation alone. It is also one of the first studies, to our knowledge, to document better long-term preservation of open angle in eyes receiving bevacizumab. We stress that NVG is still associated with poor visual acuity outcomes and many patients require pressure lowering interventions. We believe that general medical health and patient compliance are important considerations in directing treatment for patients with NVG.

Author Disclosure Statement

Dr. Blair receives the following grants:

- An Unrestricted Grant from Research to Prevent Blindness, New York.
- NEI Core Grant P30EY001792.

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Received: April 11, 2009

Accepted: July 16, 2009

Address correspondence to:

Dr. Michael P. Blair
University of Illinois
Eye and Ear Infirmary
1855 W Taylor Street
Chicago, IL 60612

E-mail: Mblair2@uic.edu