

SCOPING: A Multidisciplinary Treatment Protocol for Neovascular Glaucoma with Completely Open or Partially Open Angles

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Introduction: A standardized multidisciplinary treatment protocol for NVG was developed in 2020 at the University of Chicago and has been termed Salvaging the Conventional Outflow Pathway in Neovascular Glaucoma (SCOPING). We describe 9 eyes with anterior segment neovascularization and at least partially open angles that underwent the SCOPING protocol to suppress the underlying neovascular drive, control intraocular pressure, and medically or surgically salvage the angle whenever possible.

Methods: Nine eyes from 8 patients with first-time anterior segment neovascularization, at least partially open angles, and normal or elevated IOP were treated with 6 serial monthly intravitreal bevacizumab injections interspersed with pan-retinal photocoagulation.

Results: Five eyes with completely open angles without any peripheral anterior synechiae and each achieved and/or maintained physiologic IOP without requiring surgery. The other 4 eyes presented with partially open angles. Three out of these 4 eyes required subsequent IOP-lowering surgery. None of the 9 eyes developed recurrence of anterior segment neovascularization during the treatment protocol.

Discussion: This protocol may be utilized to salvage the conventional outflow pathway for patients with partially or completely open angles. The etiology and diagnosis of neovascular glaucoma have been established. Current treatment strategies include reduction of neovascular drive including panretinal photocoagulation, intravitreal injections, intraocular pressure lowering medications, and filtration surgery. However, a protocol has not been developed to treat neovascular glaucoma (NVG). Our SCOPING protocol may be helpful for glaucoma specialists in treating patients with neovascular glaucoma.

Keywords: neovascular glaucoma, micro invasive glaucoma surgeries, anti-vascular endothelial growth factor, pan-retinal photocoagulation

Introduction

Neovascular glaucoma (NVG) is a secondary glaucoma that occurs when retinal ischemia leads to the proliferation of fibrovascular tissue anteriorly, leading to neovascularization of the iris (NVI) and/or angle (NVA) with a subsequent increase in intraocular pressure (IOP).¹ The management of NVG centers around reducing the vascular endothelial growth factor (VEGF) load and controlling IOP. The two approaches to reduce the VEGF load are intravitreal anti-VEGF therapy such as bevacizumab (IVB) and panretinal photocoagulation (PRP). IVB leads to rapid regression of NVA and NVI which can also contribute to IOP-lowering if the angle is at least partially open and functional.² While anti-VEGF works immediately, PRP is the gold standard long term solution as it decreases the underlying neovascular drive by inducing tissue coagulation thereby decreasing the production of angiogenic factors by peripheral ischemic retina.³

If the patient presents with NVI or NVA without synechial closure, regression of the anterior neovascularization through anti-VEGF and PRP may be sufficient to achieve physiologic IOP without the need for any glaucoma intervention.⁴ However, eyes with NVG that have already developed partial or total synechial angle closure often require interventions such as tube

shunt implantation or cyclophotocoagulation (CPC) to achieve long-term IOP control.^{5,6} As a whole, long-term NVG outcomes leave much to be desired,⁷ and there are many barriers to achieving optimal outcomes in NVG.⁸ For this reason, a standardized multidisciplinary treatment protocol for NVG was developed in 2020 in collaboration between a glaucoma (MQ) and retina (DS) specialist at the University of Chicago and has been termed Salvaging the Conventional Outflow Pathway in Neovascular Glaucoma (SCOPING). For eyes with anterior segment neovascularization (NVI or NVA) and at least partially open angles, regardless of presenting IOP or presumed visual potential (as long as not already NLP at presentation), we offer an aggressive anti-neovascular treatment protocol in an attempt to medically salvage the conventional outflow pathway and reduce the need for subsequent IOP-lowering surgeries. If IOP becomes uncontrolled on maximum medical therapy, angle-based surgeries may be offered to qualifying patients with the goal of salvaging the conventional outflow pathway whenever possible and delaying or potentially avoiding a tube shunt or CPC.

Materials and Methods

Approval was obtained from the University of Chicago Institutional Review Board (IRB) to perform a retrospective chart review to describe treatment outcomes. Patient consent to review medical records was not required per the University of Chicago IRB given the deidentified nature of the data collected. This work adhered to the 1964 Helsinki declaration and its later amendments. Patients with first-time anterior segment neovascularization (NVI or NVA) and at least partially open angles (defined as no more than 270° of synechial closure) and normal or elevated IOP⁹ were treated with 6 planned serial monthly IVB injections interspersed with sessions of PRP at the discretion of the retina service with the goal of providing anti-neovascular coverage with the planned monthly injections while sufficient PRP is administered. Given the practice patterns of the retina service, we collaboratively decided to standardize the treatment protocol to 6 scheduled monthly injections, to provide up to 6 months of time for the PRP to be completed. However, depending on the retina specialists' practice pattern, patients may require greater or fewer than 6 monthly injections to provide an adequate umbrella of anti-neovascular protection while sufficient PRP is completed. Qualifying patients were stratified into 3 stages of disease: patients with NVI or NVA, normal IOP, and absence of PAS; patients with NVI or NVA, elevated IOP, and absence of PAS; and patients with NVI or NVA, elevated IOP, and presence of PAS with partial synechial closure (<75% closure). IVB injections were encouraged to be spaced by 28 days to maintain continuous anti-neovascular protection while the eye undergoes multiple sessions of PRP which has a slower onset of action.^{3,10,11} If the IOP became elevated despite maximum medical IOP-lowering therapy, and there was no active anterior segment neovascularization, then angle surgery such as gonioscopy assisted transluminal trabeculotomy (GATT) was offered in an attempt to surgically salvage the conventional outflow pathway. Contraindications for GATT included monocular status and inability to hold antiplatelet/anticoagulation. Patients who were considered candidates for GATT first could alternatively elect primary aqueous shunt or CPC instead, depending on the clinical circumstances. Herein, we report pilot results from 9 consecutive NVG eyes that completed the SCOPING protocol, defined as completing 6 scheduled monthly anti-VEGF injections, with as many interspersed PRP sessions as was deemed necessary by the retina service.

Results

In total, 9 eyes from 8 patients qualified for and completed the SCOPING protocol. Presenting clinical characteristics and outcomes are shown in [Table 1](#). Humphrey visual field and OCT testing can be confounded in the setting of NVG due to corneal and retinal findings leading to misinterpretation, thus they were not necessarily performed at baseline in these NVG patients.^{12,13} The 2 eyes with anterior segment neovascularization and normal IOP were diagnosed despite being asymptomatic because their fellow eye presented symptomatically with NVG and total synechial angle closure.

There were 5 male patients, and 5 patients were African American. The median age was 60.5 years (range 25–68). The median presenting VA was 20/40 and the mean presenting IOP was 31 mmHg on 0 medications. IVB was given within 1 day of diagnosis for all but 1 patient who received an injection at a referring doctor's office 7 days prior to urgent follow up with University of Chicago. Median duration between subsequent IVBs was 35 days (range 23 to 77), median time from IVB #1 to IVB #6 was 203 days (range 152 to 224), and median number of PRP sessions during the protocol period was 2 (range 1–3). One month after IVB #6, median IOP was 15 mmHg (range 9–20) on a median of 2 medications (range 0–2).

Table 1 Demographic Characteristics and Clinical Features of Eyes Presenting with NVI/NVA and Completely or Partially Open Angles Undergoing SCOPING Protocol

Eye	Age at Presentation	Gender (M/F)	Race	Etiology	PRP Prior to Presentation of NVG	Aspirin/AC Use	Initial VA	Initial IOP (mmHg)	Iris/Angle Exam	Duration Between 6 IVBs (Days)	# PRP Session (# of Spots) Within Protocol Period	VA 1 Month After IVB #6	IOP 1 Month After IVB #6	Recurrent NV During Study Period?	Recurrent NV After Study Period?	IOP-Lowering Surgery at Any Point	Subsequent Anti-VEGF Therapy After Protocol Period	# Days Since Protocol Completion to Last Visit	VA at Last Visit	IOP at Last Visit
Anterior Segment Neovascularization with Normal IOP																				
Eye #1	60s	F	Black	PDR	Yes	AC	20/25	14 on 0 meds	NVI, no NVA, no PAS	33, 37, 48, 43, 42	3 (1677)	20/20	9 on 0 meds	No	No	None	Subsequent IVB & PRP† and aflibercept	980	20/40	14 on 0 meds
Eye #2*	60s	M	Black	PDR	Yes	AC	20/50	15 on 0 meds	NVI, no NVA, no PAS	28, 30, 77, 33, 28	1 (642)	20/30	19 on 0 meds	No	No	None	Subsequent IVB	539	20/30	18 on 0 meds
Anterior Segment Neovascularization with Elevated IOP and an Open Angle without PAS																				
Eye #3*	60s	M	Hispanic	PDR	Yes	ASA	20/30	38 on 0 meds	NVI, faint NVA, no PAS	28, 69, 42, 42, 28	3 (1878)	20/25	12 on 2 meds	No	No	None	None at 56 days	44	20/25	12 on 2 meds
Eye #4*	60s	M	Hispanic	PDR	Yes	ASA	20/40	41 on 0 meds	NVI, faint NVA, no PAS	28, 63, 42, 42, 28	2 (1303)	20/30	10 on 2 meds	No	No	None	Subsequent PRP	51	20/30	10 on 2 meds
Eye #5	60s	M	Caucasian	OIS	No	None	20/50	47 on 0 meds	NVI, faint NVA, no PAS	28, 35, 28, 28, 33	3 (1907)	20/20	19 on 0 meds	No	Yes‡	None	Subsequent IVB & PRP	920	20/20	19 on 0 meds
Anterior Segment Neovascularization with Elevated IOP and Partial Synechial Closure (<75% closure)																				
Eye #6	20s	M	Black	PDR	No	None	20/40	22 on 0 meds	NVI, frank NVA, 30% PAS	29, 28, 28, 28, 28	3 (3268)	20/40	20 on 0 meds	No	Yes**	No	Subsequent IVB & PRP	459	20/40	17 on 2 meds
Eye #7	40s	M	Hispanic	PDR	No	None	20/100	31 on 4 meds	Regressed NVI, no NVA, 50% PAS	28, 38, 29, 23, 40	1 (§§)	20/50	13 on 3 meds	No	Yes	GATT & IVTA†† between IVB #1 and #2; subsequent BGI 350	241	20/400	18 on 1 med	
Eye #8*	50s	F	Black	CRVO	No	None	HM	45 on 0 meds	NVI, frank NVA, 50% PAS	35, 61, 51, 33, 44	2 (2386)	20/200	15 on 2 meds	No	Yes***	GATT between IVB #2 and #3; subsequent CPC & BGI 350	439	20/125	8 on 0 meds	

(Continued)

Table 1 (Continued).

Eye	Age at Presentation	Gender (M/F)	Race	Etiology	PRP Prior to Presentation of NVG	Aspirin/AC Use	Initial VA	Initial IOP (mmHg)	Iris/Angle Exam	Duration Between 6 IVBs (Days)	# PRP Session (# of Spots) Within Protocol Period	VA 1 Month After IVB #6	IOP 1 Month After IVB #6	Recurrent NV During Study Period?	Recurrent NV After Study Period?	IOP-Lowering Surgery at Any Point	Subsequent Anti-VEGF Therapy After Protocol Period	# Days Since Protocol Completion to Last Visit	VA at Last Visit	IOP at Last Visit
Eye #9	50s	F	Black	PDR	No	ASA	20/40	31 on 0 meds	NVI, frank NVA, 50% PAS	34, 23, 40, 72, 35	2 (1933)	20/30	18 on 0 meds	No	No	BGI 350 between IVB #1 and #2	Subsequent IVB & PRP§	776	20/30	11 on 4 meds

Notes: *Four eyes from 3 patients who died after completion of the protocol; †Starting 152 days after IVB #6 for vitreous hemorrhage; §§ # of PRP spots not documented in electronic medical record. ††80 days after IVB #6 for recurrent NVA; **158 days after IVB #6; ††intravitreal triamcinolone acetonide; ***119 days after IVB #6 for recurrent NVA; §Further IVB in order to dry out CME prior to performing fill-in PRP.

Abbreviations: AC, anticoagulation; BGI350, Baerveldt 350; CPC, Cyclophotocoagulation; CRVO, Central retinal vein occlusion; F, female; GATT, Gonioscopy-assisted transluminal trabeculotomy; HM, Hand motion; IOP, Intraocular pressure; IVB, Intravitreal bevacizumab; M, male; NVA, Neovascularization of the angle; NV, Neovascularization; NVG, Neovascular Glaucoma; NVI, Neovascularization of the iris; OIS, Ocular ischemic syndrome; PAS, Peripheral anterior synechiae; PDR, Proliferative diabetic retinopathy; PRP, Panretinal photocoagulation; VA, Visual acuity; VEGF, Vascular endothelial growth factor.

Five eyes presented with anterior segment neovascularization and a completely open angle without any peripheral anterior synechiae (PAS). Among these, 2 eyes had normal IOP and NVA while 3 eyes had elevated IOP and NVA. These 5 eyes all achieved and/or maintained physiologic IOP without IOP-lowering surgery to date. Notably, 3 of the 5 eyes underwent subsequent IVB beyond the 6-month SCOPING protocol period: one for cystoid macular edema secondary to PDR, one for vitreous hemorrhage secondary to PDR, and one for recurrent NVA and elevated IOP in the setting of ocular ischemic syndrome.⁴ These 3 angles remained completely open with the resumption of serial anti-VEGF therapy.

Among the 4 eyes (eyes #6-9) with partial angle closure at the time of presentation, 1 eye (eye #6) was still partially open after completion of the SCOPING protocol and has not required any further procedures. The other 3 eyes (eye #7-9) underwent further procedures.

Eye #7 underwent a GATT between IVB #1 and #2 for elevated IOP on 4 medications. Although GATT is typically contraindicated in eyes with PAS, it can be completed¹⁴ and was successfully performed in eye #8 with NVG and PAS.¹⁵ After GATT, eye #7 received anti-VEGF injections with a local retina specialist but there was a lapse in retina follow-up, and this eye did not receive anti-VEGF injections for 82 days. Due to this lapse, this eye subsequently developed recurrent NVI and NVA with total synechial angle closure and elevated IOP and underwent a Baerveldt-350 in the sulcus 5 months after SCOPING protocol completion. This was likely due to incomplete PRP as this patient had only 1 session.

Similarly, eye #8 also underwent GATT 35 days after NVG presentation. Eye #8 subsequently achieved medication-free IOP control for 9 months while undergoing monthly anti-VEGF injections before subsequently becoming lost to follow-up. This eye developed recurrent disease with subsequent total synechial angle closure, requiring Baerveldt-350 in the sulcus 9 months after completing the SCOPING protocol.¹⁵ In eyes #7 and #8 with progressive synechial closure, the anti-VEGF had ample time to take effect in regressing anterior segment neovascularization since the angle was partially open on presentation, so GATT could be performed after regression. Eye #9, despite initially being an anatomic candidate for GATT, underwent Baerveldt-350 in the sulcus 8 days after NVG presentation as the patient elected for an aqueous shunt instead.

Discussion

Our results demonstrate the value of prompt and aggressive anti-VEGF treatment for anterior segment neovascularization with completely open or partially open angles. IVB leads to immediate regression of NVI and NVA which is maintained while serial injections keep neovascularization at bay. Under the coverage of monthly IVB, interspersed sessions of PRP exert a long-lasting effect beyond the completion of injections. Once sufficient PRP has been completed, serial monthly injections can be stopped. However, it is important to realize that sufficient PRP is difficult to define. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined sufficient PRP as 1200 to 1600 burns which should extend to the edge of an oval area including the disc and macula, and anteriorly to or beyond the equator.¹⁶

Of the eyes that had recurrence after completion of the study protocol (eyes #5-8), eye #7 only had 1 session of PRP which was insufficient according to this definition. The other 3 eyes (eyes #5, #6 and #8) did have greater than 1600 burns documented. It is possible that these 3 eyes also did not have sufficient PRP but it is also possible that despite maximal PRP, they had persistent neovascularization from uveal ischemia which would not be addressed by PRP.¹⁶ Indeed, there are some choroidal vascular changes that have been documented in PDR and DME, including decreased combined thickness of the choriocapillaris and medium choroidal vessel layers.¹⁷

Once PRP is completed, one could consider obtaining a fluorescein angiogram to assess for areas of persistent leakage, or OCT angiography to assess for choroidal ischemia. With prompt control of neovascular drive, there may be a window of opportunity to salvage the angle medically or surgically, if necessary.

Our results reflect the importance of stratifying eyes with anterior segment neovascularization by angle status as described above. For eyes that present with anterior segment neovascularization with a completely open angle, this protocol may allow them to maintain or achieve physiologic IOP without any subsequent IOP-lowering surgery. For eyes that present with partial synechial angle closure, this protocol allows rapid regression of anterior segment neovascularization and temporary improvement of IOP so that any subsequent IOP-lowering surgery can be considered only after anterior segment neovascularization has fully regressed. Microinvasive glaucoma surgeries such as GATT may be attempted to surgically salvage and/or restore the conventional outflow pathway in select eyes if the patient and team are committed to close follow-up and ongoing treatment.

Of the 4 patients who had NVI/NVA with elevated IOP and PAS with partial synechial closure, 3 required IOP-lowering surgery as described above. The patient who elected to have primary BGI 350 did not have recurrence of neovascularization (eye #9). However, the other 2 patients (eyes #7 and #8) who elected to try GATT first may have had insufficient PRP during the 6-month window of anti-VEGF to completely regress their neovascular drive. Thus, while their IOP was controlled during their monthly anti-VEGF in the protocol period, they developed recurrent NVA with subsequent progressive synechial angle closure requiring additional IOP-lowering surgery with BGI-350 in the sulcus. These 2 patients demonstrate that the angle can be salvaged as long as the neovascular drive is controlled. Crucially, sufficient PRP must be completed while patients are receiving short-term coverage with anti-VEGF in order to allow long term control once the injections are stopped. If they do not get full PRP within this period of coverage, neovascularization may recur if there is a break in regular injections.

Each of the patients in this pilot study had at least a partially open angle. In NVG eyes with total synechial closure (defined as more than 270° of synechial closure) and active anterior segment neovascularization, prompt cyclophotocoagulation with anti-VEGF was recommended as the primary intervention, and we have published our outcomes for those patients separately.⁵ In such patients, IOP would not be expected to improve with regression of anterior segment neovascularization as the angle is already synechially closed.⁹

Our study has limitations. First it is a retrospective pilot study with small sample size. Additionally, as it is based on 9 individual patients, there is variability in compliance with treatment and follow up. However, we offer a novel and unique protocol to treat neovascular glaucoma which is valuable given the limited guidelines currently available.

Conclusion

The SCOPING protocol may be utilized to salvage the conventional outflow pathway for patients with any anterior segment neovascularization regardless of IOP when the angle is completely or partially open. Further directions include comparison of outcomes in patients with neovascular glaucoma treated prior to the development of the SCOPING protocol.

Data Sharing Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Patient Consent

Consent to publish personal information and case details was obtained verbally from the patients included in this report. No individual patients are identifiable by their case description.

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Disclosure

Mary Qiu reports personal fees from Lantrek, personal fees from New World Medical, personal fees from Abbvie, personal fees from Nova, outside the submitted work. The authors report no other conflicts of interest in this work.

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