Statement of Purpose

Study Rationale: Neovascular glaucoma (NVG) is an aggressive secondary glaucoma that occurs in patients with underlying retinal diseases. In NVG, the blood flow to the eye is impaired, so abnormal blood vessels (neovascularization - NV) grow in the eye to bring more oxygen. However, NV can grow into the angle (NVA) and block aqueous outflow through the conventional outflow pathway. This causes the intraocular pressure to rise, which left untreated can cause permanent glaucomatous optic neuropathy and vision loss. The retina specialist treats the underlying retinal disease by injecting anti-vascular endothelial growth factor (anti-VEGF) to regress the vessels and performing panretinal photocoagulation (PRP) to ablate the ischemic retina to destroy the angiogenic signal so the vessels do not grow back. However, even when NVA regresses, it can sometimes result in permanent synechae in the angle (peripheral anterior synechaie – PAS), which continues to block the conventional aqueous outflow pathway, with resultant high IOP. The standard of care for neovascular glaucoma involves a glaucoma drainage implant (GDI) to bypass the blocked conventional outflow pathway. GDIs have a host of lifetime risks and complications, and it would be preferable if we could develop a technique to salvage the eye's conventional aqueous outflow pathway and avoid a GDI. To our knowledge, there have not been any trials or techniques which attempt to salvage the conventional outflow pathway in NVG, because it is widely known that NVG is extremely aggressive and NVA is generally expected to recur and re-scar the angle.

Hypothesis: Gonioscopy-assisted transluminal trabeculotomy (GATT) is a minimally invasive glaucoma surgery (MIGS) which uses a catheter to tear through the trabecular meshwork and restore aqueous outflow in eyes with open angles and dysfunctional or clogged trabecular meshworks. GATT is typically not used in eyes with peripheral anterior synechiae, as in the case of neovascular glaucoma. I have tried GATT in 3 patients with acute neovascular glaucoma after the NVA has been regressed with anti-VEGF, with excellent short-term results (restored aqueous outflow and lower IOP), but as expected, the NVA recurred because the underlying retinal disease was not treated aggressively enough. The retina standard of care is to perform additional injections or lasers when the NV recurs, but there is no widely accepted concensus protocol for prophylactic injection or laser to prevent NV recurrence. I propose that we should develop a more aggressive NVG treatment protocol, with the goal of preventing NVA recurrence, because every time the NV recurs and regresses, they leave behind more fibrosis and synechiae in the angle. Preventing NVA recurrence would give us a chance to salvage the conventional pathway and avoid a glaucoma drainage implant. I propose that the glaucoma specialist can perform GATT to restore aqueous outflow in NVG eyes, even when there are already some peripheral anterior synechae. The glaucoma specialist must also collaborate with the retina specialist to deliver a novel treatment protocol where these NVG eyes will receive the same aforementioned injections and lasers, but on a preventative and scheduled basis, to prevent the vessels from recurring, rather than only treating after the NV recurs.

Specific Objectives: The purpose of this project is to pilot a novel multidisciplinary treatment protocol for NVG with the purpose of salvaging the conventional outflow pathway and avoiding the implantation of an artificial glaucoma drainage implant whenever possible.

Clinical Relevance: NVG is an extraordinarily aggressive disease which requires close collaboration between the glaucoma and retina specialist. However, there is currently no interdisciplinary consensus about how to treat NVG patients, and many NVG eyes progress to profound vision loss either due to uncontrolled IOP, uncontrolled retinal disease, or both. In the modern era of anti-VEGF and MIGS, there is an opportunity for glaucoma and retina specialists to offer a more aggressive prophylactic treatment protocol for NVG patients with the goal of salvaging the conventional outflow pathway, avoiding GDIs, and achieving stricter control of the underlying retina disease.

Preliminary Data

I have performed GATT for NVG in 3 eyes. In the past year, there have been 3 patients who presented with acute NVG who all received prompt anti-VEGF, and after the NVA regressed, their IOP remained elevated, and their angle had some extent of peripheral anterior synechiae (PAS). In all 3 eyes, I successfully performed GATT to restore the conventional outflow pathway, and IOP initially improved in all 3 cases. These 3 eyes all received at least one session of PRP before the GATT. However, in all 3 cases, the anti-VEGF was not repeated on a strict every-4-week schedule, either due to the patient missing an appointment, or the retina provider not recommending a strict every-4-week dosing, and these eyes did not have full PRP coverage yet, so the NVA unsurprisingly recurred in all 3 cases, and the IOP rose again.

In one case, the angle had already become completely synechially closed and the visual potential was poor, so CPC was performed. In another case, the angle had multiple areas of broad PAS, but some areas were still open, so a repeat GATT was attempted, but eventually a Baerveldt 350 implant in the sulcus was needed. In the third case, the recurrent NVA was detected early, anti-VEGF was promptly resumed every-4-weeks strictly regardless of visible NV, more fill-in PRP was performed, and this eye did not develop any subsequent recurrent NVA or high IOP. At post op month 9 after the GATT, this eye had an IOP of 18 on 0 medications.

This is the first case report of an eye with acute NVG (with some PAS in the angle) that was successfully treated with GATT in combination with aggressive anti-VEGF and PRP. This case example serves as a proof of concept that GATT combined with an aggressive prophylactic anti-VEGF and PRP schedule may offer the potential to salvage the conventional outflow pathway in NVG eyes, which historically would have required artificial glaucoma drainage implants.

In collaboration with the retina service, we are initiating a new best-practices protocol, which we are also formally going to investigate as a trial called Salvaging Conventional Outflow Pathway In Neovascular Glaucoma (SCOPING) whereby all patients with a new diagnosis of NVA will received anti-VEGF every-4-weeks for 6 doses, with at least 3 scheduled session of PRP in between the injections, in attempt to rapidly regress the NVA and prevent any NVA recurrence before full PRP is achieved. If IOP lowering surgery is needed, GATT will be attempted before moving on to a GDI, whenever possible.

Our SCOPING protocol is currently undergoing IRB approval to be a formal prospective clinical trial, but we are already treating our NVG patients this way, since the injections and lasers are not experimental, and are considered standard medical care which is billable to insurance, and we believe that this strict schedule with increased frequency of injection, laser, and angle surveillance represents clinical best practices.

Since October 2020, there have been 2 NVG patients that presented with NVA and angles completely synechially closed, one underwent CPC and one underwent Baerveldt 350 tube in the sulcus, both are receiving the SCOPING protocol despite the fact that their conventional outflow pathway is already unsalvageable. There have been 5 other NVG patients who presented with NVA and angles largely still open, all 5 of these patients started receiving the SCOPING protocol and none have required an IOP lowering surgery so far. There have also been 2 other who presented with NVI without NVA yet, and they also started receiving the SCOPING protocol, and neither of these two patients have elevated IOP or NVA since starting the protocol.

Research Plan

The study protocol is that we will treat NVG patients with anti-VEGF injection every 4 weeks for 6 doses, with scheduled sessions of PRP laser in between the injections, for at least 3 sessions, until full laser is achieved. The purpose is to prevent NVA from recurring, rather than re-treat after it has recurred. The primary outcome measures are NVA recurrence, need for glaucoma surgery (GATT, tube, CPC).

Inclusion criteria : Age > 18, Neovascularization in the angle seen on gonioscopy.
Exclusion criteria : Pregnant, History of glaucoma drainage implant or trabeculectomy, LP or NLP vision

Study Title: Salvaging Conventional Outflow Pathway In Neovascular Glaucoma (SCOPING Trial)
Sponsor: The University of Chicago
Protocol #: IRB20-1486
Investigator: Dr. Mary Qiu

Time and Events Schedule

Procedures	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22
See Glaucoma Provider	X		X		X		X		X		X	
See Retina Provider	X	X	X	X	X	X	X	Only if needed	X	Only if needed	X	Only if needed
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics/Socioeconomic History	X											
Medical and Procedural History (Injections, lasers, surgeries)	X											
Vision and IOP (scheduled)	X	X	X		X		X		X		X	
Vision and IOP (only if needed)				X		X		X		X		X
Anterior Segment Exam (NVI, NVA, PAS) (Glaucoma Provider)	X		X		X		X		X		X	
Fundus Exam (Retina provider)	X		X		X		X		X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Bevacizumab injection scheduled	X		X		X		X		X		X	
PRP Laser scheduled		X		X		X						
PRP Laser only if needed								X		X		X

Statistical Plan
We will perform descriptive statistics to describe the demographics of the study participants, their clinical data (vision, IOP, anterior segment exam, posterior segment exam) on the day of diagnosis and each injection and laser visit. We will calculate the proportion of patients that had recurrent NVA and / or needed subsequent glaucoma surgery, and which procedure. We will also track a secondary measure which is success/failure to follow the protocol, and identify risk factors for failure to follow the protocol, which we hypothesize could be related to socioeconomic status, language barriers, transportation issues, poor medical literacy. If the patients missed a visit, we will contact them to inquire about the reason.

Anticipated Results
We anticipate that patients who enroll in the SCOPING protocol will be more likely to achieve complete NVA regression and avoid recurrent NVA and accordingly will keep their IOP under control and avoid subsequent glaucoma surgery. Patients who do end up requiring glaucoma surgery will also start with the minimally invasive GATT procedure instead of glaucoma drainage implant, so we anticipate that intervening aggressively with injection and laser will spare some NVG patients a glaucoma drainage implant.

Pitfalls
This treatment protocol is aggressive and time intensive, requiring every 2 week visits to the ophthalmologist in the first few months, so we expect that some patients will not be able to come back to the eye clinic every 2 weeks despite our best efforts to counsel them about the critical nature of this follow-up. We also anticipate that despite receiving adequate aggressive treatment, some patients disease severity will still be too advanced upon initial presentation, and their conventional outflow pathway will already be unsalvageable despite the most aggressive treatment protocol. We also anticipate that some patients with very aggressive disease may still progress to total synechial angle closure despite a very aggressive injection/laser schedule in attempt to salvage the angle.

Alternative Strategies
Patients who indicate from the day of presentation that they absolutely cannot keep up with the frequent follow-up visits may want to have a GDI instead of a GATT. These patients should also have as much PRP in the first session as possible, if poor followup is anticipated to be an issue.

Timeline
I will enroll every patient who presents with documented neovascularization in the angle for a 12 month period. I will then follow them all for 12 months. I will report my results at 6 months, 12 months, and 24 months.