Aflibercept as Adjunctive Treatment for Filtration Surgery in Neovascular Glaucoma

Naris Kitnarong, M.D., MBA., Janyawassamon Kittipiriyaakul, M.D., Anuwat Jiravarnsirikul, M.D.
Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT
Objective: To investigate intravitreal aflibercept (IVA) injection as an adjunctive treatment to trabeculectomy with mitomycin C (TMC) and panretinal photocoagulation (PRP) for neovascular glaucoma (NVG).

Materials and Methods: PRP and IVA (2 mg/0.05 ml) injection were given, and TMC was performed within 2 weeks after IVA. Additional PRP, laser suture lysis, subconjunctival 5-fluorouracil injection, and bleb needling were performed after TMC if indicated. Best corrected visual acuity (BCVA), intraocular pressure (IOP), surgical complications, and number of anti-glaucoma medications were collected.

Results: Five eyes from 5 consecutive patients were included. Two eyes had proliferative diabetic retinopathy (PDR), 2 central retinal vein occlusion, and 1 ocular ischemic syndrome (OIS) (mean initial IOP: 46.8±6.8 mmHg). NVI regression occurred in one eye after PRP alone, and in one eye after PRP and IVA resulting in a good IOP control with topical medical therapy. The other 3 underwent TMC. The preoperative IOP was 34 (OIS), 54 (PDR), and 50 (PDR) mmHg. The 3-month postoperative IOP decreased to 8, 8, and 4 mmHg, respectively, and to 21, 10, and 6 mmHg, respectively, at the last visit. Only the one OIS eye required postoperative topical IOP-lowering medications. Final BCVA was improved, unchanged, and decreased in 2, 2, and 1 eye, respectively. No intraoperative/postoperative complications or NVI recurrence were observed (mean follow-up: 10.7 months).

Conclusion: Intravitreal aflibercept was shown to be a potentially effective additional treatment to PRP and TMC in patients with NVG.

Keywords: Aflibercept; adjunctive treatment; filtration surgery; neovascular glaucoma (Siriraj Med J 2022; 74: 27-33)

INTRODUCTION
Neovascular glaucoma (NVG) is a devastating secondary glaucoma characterized by the development of neovascularization of the iris (NVI) and anterior chamber angle (NVA), which causes obstruction of aqueous outflow and increased intraocular pressure. It is estimated that 97% of NVG patients develop neovascularization as a result of posterior segment ischemia.1,2 The common causes of this condition include proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), and ocular ischemic syndrome (OIS).1,3 Ocular ischemia leads to the production of pro-angiogenic factors that diffuse into the anterior segment and cause NVI, NVA, and fibrovascular membranes.4 Vascular endothelial growth factor (VEGF) is one of the pro-angiogenic factors found in the ocular fluids of both PDR patients and NVG patients.4 Panretinal photocoagulation (PRP) is a standard treatment for retinal ischemic conditions that is combined with treatment of the underlying disease.5 However, PRP causes the death of healthy retinal cells, permanently diminishes visual fields, and gradually regresses the neovascularization. The use of...
anti-VEGF, such as bevacizumab and ranibizumab, has been reported to rapidly reduce the ischemic process, reverse neovascularization, and limit ocular tissue damage. Treatment of NVG with combination PRP, intravitreal anti-VEGF, and trabeculectomy with mitomycin C (TMC) was reported to reduce intraoperative bleeding and improve surgical outcomes. In 2011, the US Food and Drug Administration approved aflibercept (Eylea®; Regeneron, New York / Bayer, Berlin, Germany) for the treatment of neovascular age-related macular degeneration (AMD). Aflibercept is a novel recombinant fusion protein that is made up of portions of vascular endothelial growth factor receptor 1 (VEGFR 1) and VEGFR 2 fused to the Fc portion of human immunoglobulin G1 and VEGF-receptor ligand binding elements. Aflibercept exhibits higher affinity for VEGF-A/-B compared to previously-known anti-VEGF molecules, and binds to all of the VEGF isoforms (VEGF-B and -C, placental growth factor-1/-2). The aim of this study was to investigate the effects of intravitreal aflibercept (IVA) injection as an adjunctive treatment to TMC and PRP in patients with NVG.

MATERIALS AND METHODS
This prospective study included NVG patients who consecutively presented at the Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during November 2018 to October 2019. The study protocol was reviewed and approved by the Siriraj Institutional Review Board (SIRB) (certificate of approval number Si726/2018). Written informed consent was obtained from all study patients prior to participation. All patients received PRP and maximum tolerated IOP reduction, including systemic acetazolamide. Aflibercept was injected intravitreally (2 mg in 0.05 ml) through the pars plana in the operating theater within 1 week after the first session of PRP if NVI still persisted. TMC was carried out within 2 weeks after IVA in eyes with intraocular pressure (IOP) greater than 21 mmHg with maximal anti-glaucoma medications.

Surgical technique
All surgeries were performed by NK. The operated eye was draped and then a lid speculum was placed. Xylocaine hydrochloride 2% was injected subconjunctivally at the superonasal quadrant. A fornix-based conjunctival flap was created by disinsertion of the conjunctiva and Tenon’s capsule at the 2-3 o’clock position. Oblique relaxing incisions at one side facilitated adequate scleral exposure. Diathermy was applied to control the hemostasis of the incisions at one side facilitated adequate scleral exposure. Capsule at the 2-3 o’clock position. Oblique relaxing was created by disinsertion of the conjunctiva and Tenon’s superonasal quadrant. A fornix-based conjunctival flap hydrochloride 2% was injected subconjunctivally at the was draped and then a lid speculum was placed. Xylocaine all surgeries were performed by NK. The operated eye was draped and then a lid speculum was placed. Xylocaine hydrochloride 2% was injected subconjunctivally at the superonasal quadrant. A fornix-based conjunctival flap was created by disinsertion of the conjunctiva and Tenon’s capsule at the 2-3 o’clock position. Oblique relaxing incisions at one side facilitated adequate scleral exposure. Diathermy was applied to control the hemostasis of the sclera. A no.15 surgical blade was used to create a partial thickness triangular scleral flap 3.5 (base) x 3.5 (height) mm. The cellulose sponge soaked with mitomycin C (MMC) 0.4 mg/ml was placed over the sclera under the Tenon’s capsule and the conjunctiva for 2-3 minutes. The duration of MMC application was based upon the preoperative evaluation of potential risks for surgical failure, including the status of the conjunctiva over the operating area and the patient’s age. Generally, a thicker Tenon’s capsule and/or a younger age underwent a longer application of MMC. The MMC at the surgical area was then extensively washed out with balance saline solution (BSS).

A 20-gauge needle was used to performed paracentesis at the nasal or temporal clear cornea. The sclerotomy was done using a 15-degree blade. A Kelly Descemet’s punch may be needed to widen the sclerotomy for an adequate size. Peripheral iridectomy was performed then the scleral flap was sutured with 10-0 nylon sutures at its apex and sides. The number and the location of sutures were customized for each patient to facilitate optimal aqueous outflow. The fornix-based conjunctival flap was repositioned to the limbus, tightly anchored with round needle 10-0 nylon sutures, and the relaxing incisions were closed with a continuous suture. The surgical area was tested for leaks before the injection of subconjunctival dexamethasone.

Postoperative procedure
A combination of topical 1% prednisolone and antibiotics were administered 4-6 times a day for 7 days. A topical eye drop containing a combination of antibiotics and dexamethasone was applied 4 times a day for the following 1 month, and then reduced to twice a day thereafter. Best corrected visual acuity (BCVA), IOP, number of anti-glaucoma medications, and the present of NVI were compared between pre- and post-IVA, and before and after TMC. The intraoperative and postoperative complications were also noted. The patients were scheduled for follow-up at 1 day, 1 week, and every 4-8 weeks. Each postoperative visit involved a full eye examination and Seidel test for the presence of bleb leak. Postoperative interventions such as laser suture lysis, 5-fluorouracil (5-FU) injection, bleb needling, or any other procedures were performed under surgeon (NK) consideration.

RESULTS
Five eyes from 5 patients with a mean age of 70.8 years were enrolled in this study during the November 2018 to August, 2019 study period. One patient was male and 4 patients were female. The underlying causes of NVG
included 2 eyes with PDR, 2 eyes with CRVO, and 1 eye with OIS. The eye with OIS underwent several sessions of PRP before participation. The partial regression of NVI had been observed. The mean IOP at presentation was 46.8±6.8 mmHg. After the first session of PRP in eyes without prior PRP, regression of NVI observed in one eye with CRVO, and the IOP was controlled with topical anti-glucoma medications. The remaining 4 eyes received IVA due to the minimal regression and the persistence of NVI. The mean IOP among those 4 eyes was 37.9 mmHg before IVA, and 36.1 at 1 week after IVA. There was no observed complication related to IVA. Iris neovascularization was absolutely regressed within 1 week in all 4 eyes after IVA. Intraocular pressure was controlled in 1 eye with CRVO after PRP and IVA with maximal topical therapy. The remaining 3 eyes (2 PDR, 1 OIS) underwent TMC. The preoperative IOP of each patient was 34 (OIS), 54 (PDR), and 50 (PDR) mmHg (mean: 46 mmHg). Postoperatively, the IOPs decreased to 8, 8, and 4 mmHg (mean: 6.7 mmHg), respectively, at 3 months, and to 21, 10, and 6 mmHg (mean: 12.3 mmHg), respectively, at the last visit. Only the eye with OIS required postoperative medications. The mean follow-up among all five operated eyes was 10.7 months. No intraoperative or postoperative complication was noted. The BCVA was improved in 2 eyes, unchanged in 2 eyes, and decreased in 1 eye. There was no recurrence of NVI or significant symptoms in any of the 5 study eyes. Pre- and post-procedural characteristics compared among the 5 study eyes/patients are shown in (Table 1). Change in IOP over time from baseline compared among the 5 cases in our series, regression of NVI occurred after PRP alone in one eye, and after combination PRP and IVA in one eye. IOP could be controlled in these 2 eyes with topical IOP lowering medications alone. This may be explained by the fact that prompt treatment in the early stage of the disease to eliminate the progression of ocular neovascularization can prevent further ocular complications. The effects of intraocular administration of anti-VEGFs in NVG included rapid regression of neovascularization, IOP reduction, and improved surgical outcome.6,8-11 In several previous reports, the regression of NVI usually observed within 1 week after administration of anti-VEGF.14,15 This effect may persist for several weeks (4 to 28 weeks). According to the half-life of anti-VEGFs and their transitory effects, multiple injections may be needed. The transient effect of anti-VEGF underscores the demand for a simultaneous treatment to eradicate the source of angiogenic factors, such as retinal photocoagulation. The combined treatment of intravitreal anti-VEGF and retinal ablation to control the retinal ischemic condition is theoretically more effective.36 Anti-VEGF rapidly, but transiently reduces neovascularization in the early treatment stage, whereas PRP prolongedly controls ischemia of the retina over the long-term. In addition, intravitreal anti-VEGFs have demonstrated their benefit as an alternative treatment for NVG patients in whom retinal ablation could not be applied due to inadequate visualization. We considered administering anti-VEGF as soon as possible, especially in eyes in which the status of the ocular media contraindicates retinal treatment. Our group previously reported that application of PRP and anti-VEGF may be considered simultaneously during the same visit to expedite the regression of neovascularization.11 Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, USA) is a recombinant humanized monoclonal antibody to VEGF. It is approved as an anti-angiogenic agent for the treatment of metastatic colorectal cancer in combination with chemotherapy.17,18 Off-label use of intraocular injection of bevacizumab has been reported as a treatment for macular degeneration, PDR, retinal vascular occlusive disorder, and NVG.6,7,19 Ranibizumab (Lucentis®; Genentech) is a recombinant humanized antibody antigen-binding fragment (Fab) that was approved for the treatment of neovascular AMD by the US Food and Drug Administration due to its ability to neutralize all active forms of VEGF-A.20,21 Intravitreal bevacizumab (IVB) and intravitreal ranibizumab (IVR) have been reported as adjunctive treatment in NVG not only to reduce rubeosis iridis, but also to improve the surgical outcome of glaucoma surgeries.8-11 Afibercept is the most recently introduced anti-VEGF for the treatment of neovascular AMD.22,23 According to our review of the literature, afibercept has not yet been widely studied as a treatment for NVG. The additional effect of this anti-VEGF compared to the previous anti-VEGFs is that it has a longer half-life, and a higher binding affinity for
TABLE 1. Pre- and post-procedural characteristics compared among the 5 study eyes/patients.

<table>
<thead>
<tr>
<th>Case number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80</td>
<td>73</td>
<td>78</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Lateralization</td>
<td>RE</td>
<td>LE</td>
<td>RE</td>
<td>LE</td>
<td>LE</td>
</tr>
<tr>
<td>Underlying condition</td>
<td>CRVO</td>
<td>CRVO</td>
<td>OIS</td>
<td>PDR</td>
<td>PDR</td>
</tr>
<tr>
<td>Initial BCVA (logMar)</td>
<td>1.0</td>
<td>1.6</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Initial IOP (mmHg)</td>
<td>42</td>
<td>52</td>
<td>36</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>No. of medications</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Lens</td>
<td>IOL</td>
<td>NS2+</td>
<td>IOL</td>
<td>IOL</td>
<td>IOL</td>
</tr>
<tr>
<td>Interventions</td>
<td>PRP</td>
<td>PRP/IVA</td>
<td>PRP/IVA/TMC</td>
<td>PRP/IVA/TMC</td>
<td>PRP/IVA/TMC</td>
</tr>
<tr>
<td>Days between PRP and IVA</td>
<td>-</td>
<td>1</td>
<td>272</td>
<td>4</td>
<td>Same day</td>
</tr>
<tr>
<td>BCVA at last visit (logMar)</td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
<td>0.3</td>
<td>3.0</td>
</tr>
<tr>
<td>IOP at last visit (mmHg)</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Numbers of medications at last visit</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>6.0</td>
<td>1.1</td>
<td>31.6</td>
<td>20.2</td>
<td>17.0</td>
</tr>
</tbody>
</table>

**Abbreviations**: RE, right eye; LE, left eye; CRVO, central retinal vein occlusion; OIS, ocular ischemic syndrome; PDR, proliferative diabetic retinopathy; BCVA, best-collected visual acuity; logMar, logarithm of the minimum angle of resolution; IOP, intraocular pressure; IOL, intraocular lens; NS2+, mild nuclear sclerosis cataract; PRP, panretinal photocoagulation; IVA, intravitreal aflibercept; TMC, trabeculectomy with mitomycin C.

**Fig 1.** Change in intraocular pressure (IOP) over time from baseline compared among patient 3 (ocular ischemic syndrome [OIS]), patient 4 (proliferative diabetic retinopathy [PDR]), and patient 5 (PDR) (Abbreviations: mmHg, millimeters of mercury; TMC, trabeculectomy with mitomycin C).
VEGF-A. The use of aflibercept can, therefore, decrease the frequency of injections.\textsuperscript{24} Often times, IOP may not be adequately controlled with anti-glaucoma medications alone in recalcitrant NVG despite the regression of ocular neovascularization. This may due to permanent damage to the aqueous drainage channel. When this happens, surgical intervention is required. Three eyes in our series subsequently underwent TMC due to uncontrolled IOP after PRP and IVA. Our study demonstrated that aflibercept injected intravitreally before TMC resulted in prompt regression of NVI, which resulted in reduced intraoperative bleeding and good postoperative IOP control. Moreover, there was no recurrence of NVI during the mean follow-up of 10.7 months, and no complication related to IVA and TMC was observed. The eye with OIS had localized filtration bleb resulted in occasional IOP spike compared to the eyes with PDR. The OIS eye underwent bleb needling with 5-FU injection 3 times. This difference in IOP control and the filtration bleb morphology may due to the nature of underlying disease. Trabeculectomy has long been the gold standard surgical treatment for glaucoma.\textsuperscript{25,26} In NVG, the success of filtration surgery needs both the neovascularization control and wound healing modulation at the filtering site. Several studies have reported frequent intraoperative complications, subsequently poor surgical success of TMC in NVG, especially in eyes with persistent ocular neovascularization.\textsuperscript{2,27} The management of NVG with a combination treatment of PRP, intravitreal anti-VEGF injection, and TMC has been reported as an alternative option.\textsuperscript{8,11} In addition to its anti-VEGF property, anti-VEGF may provide an additional effect on the wound-healing modulation at the filtering area. Anti-VEGF influenced an inhibitory effect on fibroblast activity and wound healing response that may improve the surgical success of trabeculectomy in NVG.\textsuperscript{28,29} Our findings have shown the potential of IVA as an adjunctive treatment in filtration surgery for NVG. In 3 patients who underwent TMC, IVA induced preoperative regression of NVI, which minimized intraoperative bleeding and postoperative inflammation, and this resulted in the enhanced success of TMC. There were no significant local or systemic side effects associated with IVA in our series. That said, the side effects and complications from the use of anti-VEGF include central retinal arterial occlusion, endophthalmitis, retinal detachment, increased intraocular pressure, conjunctival hemorrhage, and cataract.\textsuperscript{30-33} Several studies reported short-term or long-term IOP elevation after intravitreal anti-VEGF injection.\textsuperscript{34,35} There was no clinically significant change in IOP observed in our study. The surgical result was encouraging in terms of IOP control and visual outcome. At last visit, all eyes had IOP under 21 mmHg with or without topical IOP lowering medications, and had improved or preserved visual acuity. Moreover, recurrence of neovascularization was not detected during the follow-up period (range: 16-62 weeks). We hypothesized that in addition to reduced VEGF production from PRP and anti-VEGF injection, VEGF had a new drainage channel via trabeculectomy. The new VEGF drainage channel may explain the non-recurrence of neovascularization, the favorable surgical outcome, and the need for repeat anti-VEGF injection. However, owing to the short-term follow-up period in this study, the possibility of long-term recurrent neovascularization still exists. All eyes in our study demonstrated benefits from IVA and filtration at the last follow-up, including being symptom-free. Most of the eyes had retained visual acuity and had good IOP control.

Preoperative IVA combined with TMC appears to be a safe and effective management for IOP controlling in NVG. Although its effect is temporary, aflibercept may provide an adjunctive effect to PRP because of its swift and dramatic biologic effect. The application of IVA may also be considered before performing the glaucoma drainage device surgery. The long-term outcome of this technique is still undetermined. The repeated application of IVA may be needed to achieve a long-term effect.

Limitations and strengths
Despite the small sample size, the short-term study period, and the lack of a control group, this is the first study to report a series of NVG eyes who underwent TMC after IVA. Further study with a larger sample size, a longer follow-up period with a control group should be conducted to evaluate the safety profile and the long-term efficacy of this technique.

CONCLUSIONS
Preoperative intravitreal administration of aflibercept was shown to be a potentially effective additional treatment to PRP and TMC in patients with NVG. Moreover, IVA was found to be safe and effective for controlling IOP and preserving visual acuity. The rapid regression of NVI minimized intraoperative complications during trabeculectomy, and may have improved the short-term surgical result after TMC. All eyes in this series remained symptom-free, preserved their visual acuity, and had good IOP control. A further study with a long-term follow-up in a larger study population needs to be conducted to evaluate the long-term outcomes.
ACKNOWLEDGEMENTS

The authors gratefully acknowledge the patients who participated in this study.

Conflict of interest declaration

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Funding disclosure

This was an unfunded study.

REFERENCES


