

Intravitreal ranibizumab for neovascular glaucoma: an interventional case series

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Abstract

Objective: To evaluate the efficacy of ranibizumab in treating neovascular glaucoma.

Design: Prospective interventional case series.

Participants: Six eyes of 6 patients.

Method: Six eyes with refractory neovascular glaucoma were treated with one dose of 0.5 mg intravitreal ranibizumab followed by laser panretinal photocoagulation. Patients were divided into 2 groups based on angle status for comparison. Recurrence was defined as re-emergence of iris neovascularization, and an intraocular pressure of more than 21 mm Hg after stabilization.

Results: The patients' mean age was 59 years and the mean follow-up 23 weeks. Three eyes had open-angle glaucoma, and three had a closed-angle configuration glaucoma. In 5 (83%) of the eyes, neovascularization completely regressed within the first 48 hours of intravitreal ranibizumab injection. Overall mean intraocular pressure dropped from 27.0 mm Hg pre-treatment to 18.3 mm Hg 1 week post-intravitreal ranibizumab. The mean anti-glaucoma drop usage decreased from 4.2 pre-treatment to 2.2 one month later. There was no recurrence throughout the initial 3 months, but 2 eyes with closed-angle configuration glaucoma recurred, with a mean time to recurrence of

14 weeks.

Conclusions: These results suggested that intravitreal ranibizumab is a useful and safe adjunct in the management of neovascular glaucoma.

Key words: Antibodies, monoclonal; Glaucoma, neovascular; Light coagulation; Retinal neovascularization; Vascular endothelial growth factor

Introduction

Neovascular glaucoma (NVG) is a serious complication of ischemic retinal disorders, such as vascular occlusions, and proliferative diabetic retinopathy.¹ The hallmark of NVG is the formation of new vessels in the iris (NVI), which progress to form a fibrovascular membrane on the surface of the iris. This membrane contracts slowly and closes the anterior chamber angle, thus impeding aqueous outflow and resulting in an elevation in intraocular pressure (IOP), which is difficult to control and often leaves the patient with a painful blind eye.

The etiology of NVG is related to the production of vascular endothelial growth factor (VEGF) by the underlying ischemic retina, which in turn stimulates neovascularization.^{2,3} In primates, injection of recombinant VEGF produces NVI and NVG; inhibition of endogenous VEGF prevents retinal ischemia and NVG formation.^{4,5} To date, the gold standard in treatment of NVG is laser

panretinal photocoagulation (PRP).¹ Retinal ischemia is reduced after PRP, which in turn decreases the level of VEGF and control of NVG. Nevertheless, sometimes PRP may be difficult, for example in eyes with media opacities like cataract or vitreous hemorrhage. PRP is also less effective in rapidly progressing NVG.

Recently, case series employing anti-VEGF agents in the treatment of NVG have been described.⁶⁻¹¹ They mainly entailed the use of bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), which is a full-length humanized monoclonal antibody that binds all isoforms of VEGF.¹² Results so far have been promising in terms of NVI regression and IOP control. To date, however, the US Food and Drug Administration has not yet approved bevacizumab for intraocular use.

Ranibizumab (Lucentis®; Novartis, Basel, Switzerland) is a fragment of the full-length bevacizumab antibody that has been engineered for intraocular use.¹³ We are not aware of any prior human studies with topical ranibizumab. Here

we present our case series injected with ranibizumab in the treatment of NVG.

Patients and methods

This prospective interventional case series was approved by the Ethics Committee of the Hong Kong East Cluster of Hospital Authority. Protocols were in accordance with the Declaration of Helsinki. Six consecutive patients with NVG in 6 eyes were recruited from the Eye Clinic of the Department of Ophthalmology, Tung Wah Eastern Hospital between October 2007 and September 2008, Hong Kong. The causes of NVG were diabetic retinopathy (n=3), central retinal vein occlusion (n=1), central retinal arterial occlusion (n=1), and radiation retinopathy (n=1).

Inclusion criteria were: (1) elevated IOP ≥ 21 mm Hg despite use of maximum anti-glaucoma medication, (2) presence of NVI, and (3) NVG refractory to other conventional treatment (i.e. laser PRP). Exclusion criteria were: (1) any prior anti-VEGF treatment, (2) systemic or local contraindications

Table. Demographic details of 6 patients in the study.

	All (n = 6)	OAG (n = 3)	CAG (n = 3)	p Value
Age (years)				
Mean \pm SD	59.0 \pm 12.1	57.5 \pm 12.0	53.0 \pm 4.0	0.264
Range	49-80	49-80	49-57	
Sex (male:female)	3:3	2:1	0:3	
Ischemic retinal disease, No. (%)				
PDR	3 (50%)	0 (0%)	3 (100%)	
CRVO	1 (17%)	1 (33%)	0 (0%)	
CRAO	1 (17%)	1 (33%)	0 (0%)	
Radiation retinopathy	1 (17%)	1 (33%)	0 (0%)	
Presenting feature (%)				
Iris rubeosis	6 (100%)	3 (100%)	3 (100%)	
Pain	6 (100%)	3 (100%)	3 (100%)	
Red	6 (100%)	3 (100%)	3 (100%)	
Duration of rubeosis (days)	15.5	14.3	16.7	
Area of ischemia on angiogram (disc diameter at $\sim 1500 \mu\text{m}$)	>10	>10	>10	
Presence of media opacity	0	0	0	
Baseline intraocular pressure (mm Hg)				
Mean \pm SD	30.0 \pm 5.6	29.3 \pm 6.9	28.0 \pm 4.4	0.291
Range	25-40	28-40	25-33	
Medications used at presentation (types)				
Mean	4.2	4.0	4.3	0.101
Range	3-5	3-5	4-5	
Required oral acetazolamide	4 (66%)	2 (66%)	2 (66%)	
Prior treatment received				
Laser panretinal photocoagulation (range) [sessions]	2.5 (2-3)	2.3	2.6	
Follow-up (weeks)				
Mean \pm SD	23.0 \pm 8.2	15.7 \pm 2.5	30.3 \pm 1.5	
Range	13-32	13-18	29-32	

Abbreviations: OAG = open-angle glaucoma; CAG closed-angle glaucoma; SD = standard deviation; PDR = proliferative diabetic retinopathy; CRVO = central retinal vein occlusion; CRAO = central retinal artery occlusion.

to ranibizumab injection (high risk for cerebrovascular accident, bleeding tendency, ocular infection), and (3) pre-existing glaucoma or angle closure status.

After obtaining informed consent, a standard dose of 0.05 ml (0.5 mg) ranibizumab was injected intravitreally in the operating theatre, under aseptic conditions, via a 30-gauge needle. Anterior segment fluorescein angiogram (ASFA) documentation of the NVI and IOP measurements were performed at baseline, within the first 48 hours after the injection, and at 1 week, 1 month, and 3 months after the injection. Both eyes were examined. The ASFA images were graded according to the method reported previously.^{4,5,9} IOP measurements were performed using a Goldmann applanation tonometry. The conventional treatment regimen was resumed as soon as practical after the intravitreal ranibizumab (IVR) injection. Sessions of PRP were undertaken if needed to stabilize the condition. If necessary, drainage procedures, vitrectomy, and other procedures were allowed as before. Researchers were blinded to the eye's angle status to prevent bias.

After IVR, patients were monitored in terms of (1) IOP control, (2) NVI regression, (3) rate of recurrence, (4) need for laser PRP or further surgical procedures. Recurrence was defined as re-emergence of NVI, and IOP higher than 21 mm Hg after stabilization. In addition, for better comparison of outcomes we divided our cases into 2 groups, those having open-angle glaucoma (OAG) or closed-angle glaucoma (CAG). Angle status was defined as open if at least 270° of the angle was open; the angle was defined as closed if open angle was <270° due to peripheral anterior synechiae.

Student's *t* tests were used for statistical comparison where appropriate. A *p* value of less than 0.05 was considered significant.

Results

Of the 6 patients recruited, 3 were male and 3 were female. Their mean \pm standard deviation (SD) age was 59 ± 12 (range, 49-80) years. The mean \pm SD follow-up duration was 23 ± 8 (range, 13-32) weeks. Of the 6 eyes, 3 had OAG, while the remaining 3 had a CAG. Patient demographics are detailed in the **Table**.

In 5 (83%) out of 6 eyes, NVI completely regressed within the first 48 hours after IVR injection. The patient in whom NVI did not completely regress belonged to the CAG group, and although his NVI did not regress completely, the vessels became less prominent and did not leak when an ASFA was performed. Mean ASFA grading before IVR was 5.0, which decreased to 0.17 by postoperative 1 week (0.0 for OAG group, 0.33 for CAG group). For the OAG group, the mean grading remained 0.0 throughout the 3-month follow-up; for the CAG group, it increased to 2.33. At all visits, differences between the 2 subgroups were not statistically significant (**Figure 1**).

Overall the mean IOP dropped from 27 mm Hg pre-IVR to 18 mm Hg at the 1-week follow-up (17 mm Hg and 18 mm Hg for the OAG and CAG groups, respectively). Mean IOP for the OAG group remained below 21 mm Hg (17 mm Hg) at the end of the 3-month follow-up period but that for the CAG group increased to 21 mm Hg. Difference between

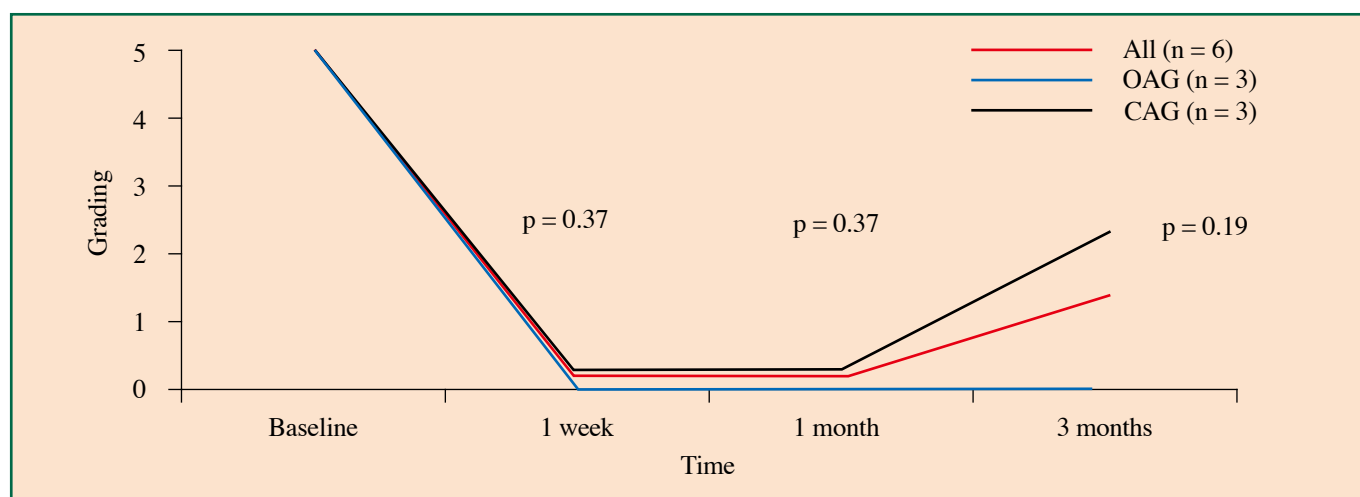


Figure 1. Anterior segment fluorescein angiogram grading of all 3 groups decreased from baseline (5) to almost 0 after ranibizumab injection. After 1 month, grading increased in the CAG group while the OAG group remained unchanged.

Grade 0: Vessels may or may not be visible. If seen, appear radial and do not leak.

Grade 1: Vessels appear more tortuous and discontinuous than normal but still do not leak.

Grade 2: The vessels are non-radial and leak minimally on angiogram.

Grade 3: The vessels are identifiable individually, and leak early in angiogram (20-30 sec).

Grade 4: Individual vessels cannot be delineated in the early frames due to leakage.

Grade 5: Grade 4 plus hyphema, glaucoma, or ectropion uveae.

Abbreviations: OAG = open-angle glaucoma; CAG = closed-angle glaucoma.

the two subgroups was not statistically significant before treatment ($p = 0.29$), and remained not significant at all visits ($p > 0.05$), as shown in **Figure 2**.

Overall the mean items of antiglaucoma drugs used decreased from 4 pre-IVR to 2 one month later. The number of drops being used in the OAG group remained static but in the CAG group usage increased towards the end of the 3-month period. Differences between the two subgroups were not statistically significant before treatment ($p = 0.10$), remained non-significant at the 1-month follow-up ($p = 0.13$), but was significant at the 3-month follow-up ($p = 0.01$). Details are plotted in **Figure 3**.

Recurrence of NVG, as defined by either (1) NVI leakage on ASFA or as seen on slit-lamp examination, or (2) IOP

increase to ≥ 21 mm Hg, did not ensue in the OAG group throughout the follow-up period. There were also no recurrences in the CAG group in the first 3 months, but 2 out of 3 cases had recurrences later. In these 2 cases, after initial IVR the recurrences ensued after 13 and 15 weeks.

During the initial 3-month follow-up, a mean of 2.5 laser PRP sessions were performed per eye, on average slightly more in the CAG than the OAG group (3 vs 2). One CAG case underwent extraction of a mature cataract 4 weeks post-IVR. The cataract was noted to increase in density progressively in the 4th week post-IVR and surgical extraction was considered necessary. As it had remained relatively stable in the initial weeks after IVR, it was thought to be unrelated to the procedure. No other procedures or re-treatment with IVR were carried out in the initial 3 months,

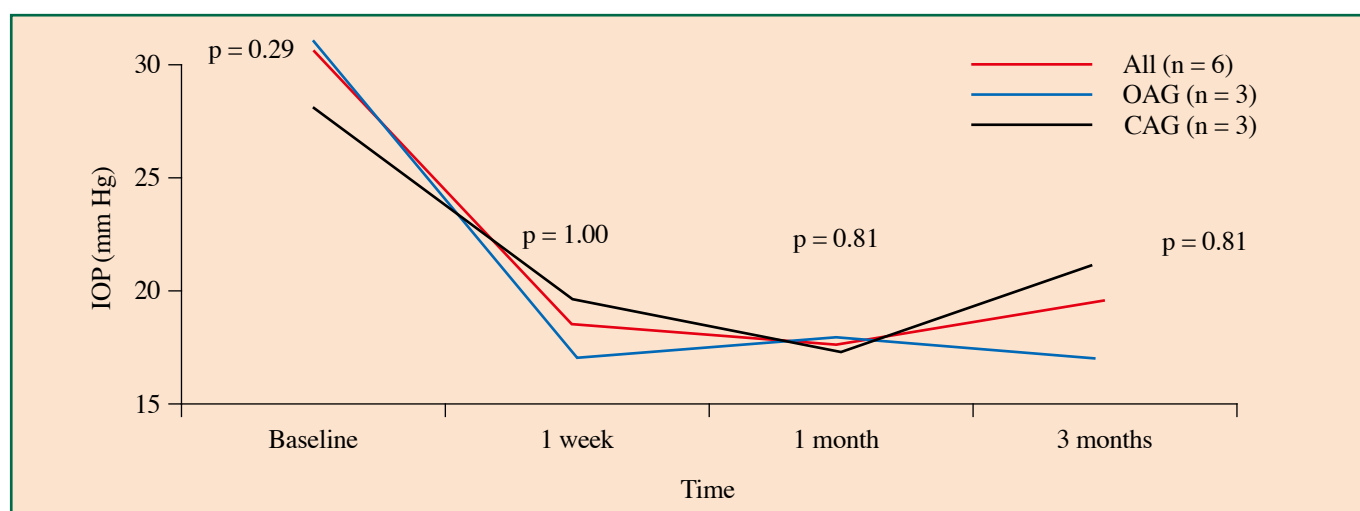


Figure 2. Intraocular pressure (IOP) reduced from baseline (mean, >30 mm Hg) to below 20 mm Hg 1 week after ranibizumab. Abbreviations: OAG = open-angle glaucoma. CAG = closed-angle glaucoma.

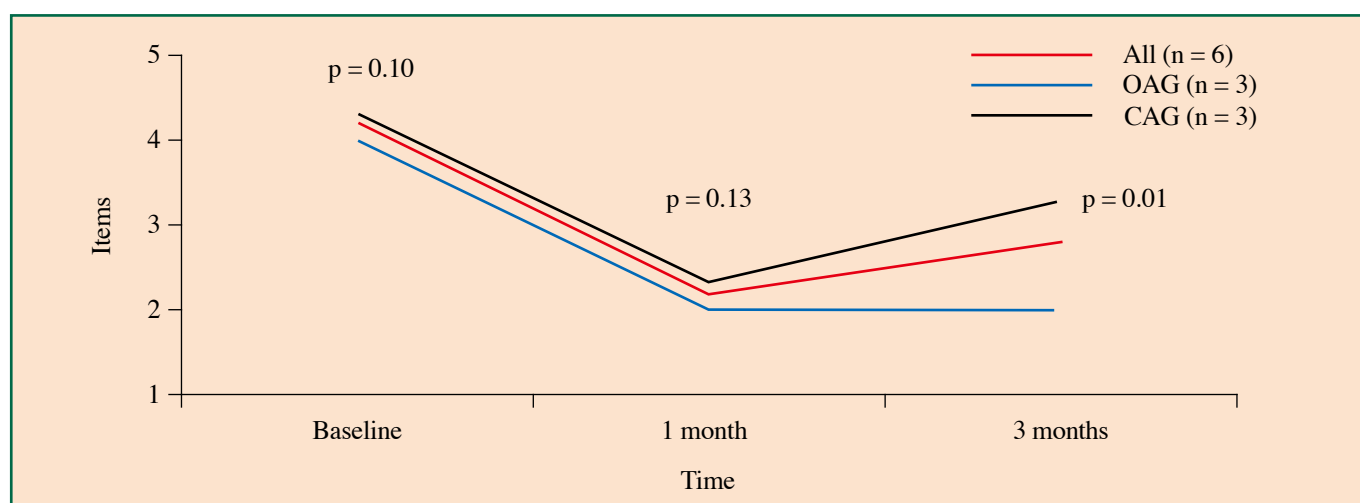


Figure 3. Mean items of antiglaucoma drugs used reduced from over 4 at baseline after ranibizumab. The number of drugs used remained static in the OAG group whereas in the CAG group it increased after 1 month from initial ranibizumab.

No. of antiglaucoma drug refers to classes employed in the order: Topical beta-blockers, e.g. timolol; Topical carbonic anhydrase inhibitor, e.g. brinzolamide; Topical alpha-2 adrenergic agonists, e.g. brimonidine; Topical prostaglandin analogues, e.g. lantanoprost; Oral carbonic anhydrase inhibitor, i.e. acetazolamide.

Abbreviations: OAG = open-angle glaucoma; CAG = closed-angle glaucoma.

but one CAG case required vitrectomy and endolaser due to vitreous hemorrhage at 6 months, and another CAG eye was deemed to require a glaucoma implant for refractory IOP rise at 6 months. Both of these cases had re-treatment with IVR 1 week prior to their respective surgeries.

There were no local or systemic complications arising from the IVR injection throughout the follow-up period.

Discussion

To our knowledge this may be the first report of ranibizumab in the treatment of NVG. The concept of counteracting VEGF with anti-VEGF agents appears attractive given the successes of recent small case series using bevacizumab.⁶⁻¹¹ Being almost 3 times larger in molecular size than ranibizumab, in theory bevacizumab can stay in the eye (especially the vitreous) longer as it takes longer time to penetrate the retina.¹⁴⁻¹⁶ In rabbit studies, Bakri et al¹⁴ have found a longer vitreous half-life of 4.3 days for bevacizumab, as compared to 2.8 days for ranibizumab. In NVG, VEGF production is ongoing as long as retinal ischemia is not fully treated. If this is the case, it is therefore possible that bevacizumab may be more advantageous. However, a recent report comparing the ability of bevacizumab and ranibizumab to antagonize VEGF showed that both can neutralize VEGF equally well at clinical doses, but diluted ranibizumab was more efficient.¹⁷ This finding may compensate for the shorter half-life of ranibizumab. Furthermore, ranibizumab lacks an Fc portion, hence it may cause less inflammation within the eye. In an already inflamed NVG eye, this could well be beneficial. Nevertheless, there are no definite reports of a head-to-head comparison of these agents, even in a small case series. To the best of our knowledge, this is the first prospective interventional study to report the efficacy of ranibizumab in the treatment of NVG. In the current study, 6 eyes with refractory NVG were monitored prospectively regarding their response after IVR.

In the current study, throughout the 3-month follow-up period the overall results were satisfactory. In the natural history of NVG, the anterior chamber angle is open in the early stage. As the disease progresses, NVI forms a fibrovascular membrane over the surface of the iris and closes the angle. Wakabayashi et al¹¹ pointed out that this is one of the anatomical break points during the disease course. Therefore we have divided the analyses into those with an open angle and those with a closed angle. All 3 OAG eyes enjoyed marked regression of NVI within the first 48 hours, both clinically and angiographically, after a single shot of ranibizumab. Normalization of IOP was achieved in all eyes, antiglaucoma drop usage decreased, there were no recurrences, and the IOP remained stable with an average of 1.7 PRP laser sessions per month. This suggests that progression to angle closure, a single shot of ranibizumab combined with adequate laser PRP may stabilize previously refractory NVG. The reason for failure of conventional treatment was likely to be due to coexisting intraocular

inflammation and retinal ischemia. A rising IOP may also be due to intraocular inflammation and exudation. After IVR, intraocular haze and retinal edema were reduced; hence laser energy is more effectively absorbed, even when the same level of energy is used.

In the CAG group, marked regression of NVI was also noted in 2 out of 3 eyes. Although one did not achieve complete regression, NVI did reduce in caliber and did not show leaks on the angiogram. IOP normalization was achieved in all cases and antiglaucoma drop usage also decreased within the first month. Towards the end of the 3-month follow-up period, however, the IOP was re-elevated and antiglaucoma drop usage had also increased. The IOP increase was likely due to impedance of aqueous outflow by angle closure due to contraction of the fibrovascular membrane on the iris surface. As the disease progresses into the angle closure state, IVR was not able to reverse structural damage, so that the pressure continues to rise even when intraocular inflammation is controlled. Beyond the initial 3-month cut-off, recurrence was noted in 2 (67%) out of the 3 patients. Despite having almost twice the average sessions of laser PRP after IVR (3 in the CAG vs 1.7 in OAG groups), recurrence still occurred among CAG cases. Thus the combination of a single shot of IVR and laser PRP seemed inadequate, such that 2 out of the 3 eyes had to undergo further surgeries (glaucoma implant, vitrectomy and endolaser). Nevertheless, IVR did achieve temporary control. Furthermore, re-injecting IVR 1 week prior to surgery may have reduced intraoperative complications, such as bleeding. Therefore, in CAG cases, though surgical procedures may be necessary eventually, IVR may provide temporary control if immediate surgery is not feasible.

Although not currently studied, other factors might also have an important role in recurrence. These include: baseline level of retinal ischemia, carotid patency status, presence of coexisting systemic diseases such as hypertension and hyperlipidemia. Such factors may all contribute to the occurrence and / or recurrence of NVG despite treatment, and further study into these areas is required.

Using ranibizumab, we were able to achieve comparable results to studies using bevacizumab. In a recent study, in which 41 NVG eyes were treated with intravitreal bevacizumab, Wakabayashi et al¹¹ achieved a 71% complete regression of NVI while our rate was 83%. In their study, Wakabayashi et al¹¹ found a recurrence rate of 58% in their OAG subgroup of up to 6 months. In our study, no recurrence was noted in OAG eyes, though at 3 months 66% had recurrence in the CAG subgroup, whilst no comparable data were available in the study by Wakabayashi et al.¹¹ The seemingly lower recurrence rate in our study may be explained by the differences in study end-points. Both studies had 100% IOP normalization in OAG cases. In their study too, there were no complications.

The concern about injecting IVR into an eye with an already elevated IOP is understandable, as central retinal

artery occlusion is possible. In all our cases, however, a small amount of vitreous fluid refluxed from the injection site when performing the procedure, which may have compensated for the increased intraocular content (IOP increase), thus reducing the risk of central retinal artery occlusion. Furthermore, as noted on indirect biomicroscopy immediately after the injection, disc perfusion remained good in all cases. Other than no local side-effects, no systemic side-effects were observed in our series.

Our results suggest that ranibizumab could be an adjunct to the management of NVG. Being engineered for intraocular use only and lacking the Fc portion, theoretically ranibizumab may possibly supersede bevacizumab.

Limitations to our study include the relatively small sample

size and short follow-up period. A small sample size may reflect the rarity of this disease in modern practice, as adequate prophylactic PRP is usually done early in most cases. Moreover, a longer follow-up may not be necessary to explore the effect of ranibizumab in this condition given its relatively short half-life in-vivo. There was no control arm in our study because the number of cases we encountered was so small, and to further divide the patients into treatment and sham arms would have lowered the significance of the current series. Finally, there was no bevacizumab arm in our study, mainly because its use was prohibited due to its off-label status.

In conclusion, we report an interventional case series using ranibizumab for treating NVG. IVR is a useful and safe adjunct in the management of this condition.

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