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Intracameral Avastin dramatically resolves iris neovascularization and reverses neovascular glaucoma

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PURPOSE. *To report the biologic effect of intracameral bevacizumab in patients with iris neovascularization secondary to proliferative retinal vasculopathies.*

METHODS. *Sixteen eyes of 15 patients with iris neovascularization associated with or without neovascular glaucoma secondary to proliferative retinal vasculopathies received intracameral bevacizumab (1.25 mg). Ophthalmic evaluations included Snellen visual acuity (VA), complete ophthalmic examination, fluorescein iris angiography, and slit lamp photography. Main outcome measure was change in degree of iris neovascularization. Secondary outcomes included fluorescein iris angiographic leakage, control of intraocular pressure, and changes in VA.*

RESULTS. *All patients with neovascularization demonstrated by slit lamp photography and fluorescein angiography (16/16 eyes) had complete (or at least partial) reduction in leakage of the neovascularization within 3 weeks after the injection. Leakage from iris neovascularization resolved in 12 of 16 (75%) eyes. In two cases recurrent leakage was seen as early as 4 weeks necessitating repeat injection. Intraocular pressure was controlled with maximum medical therapy in eight of nine eyes reducing the need for glaucoma surgery. Visual acuity improved from a median of hand motions to 20/200.*

CONCLUSIONS. *In summary, intracameral bevacizumab was effective in reversing iris neovascularization in the majority of patients. It also facilitated intraocular pressure control in patients with associated glaucoma. (Eur J Ophthalmol 2008; 18: 255-62)*

KEY WORDS. *Intracameral Avastin, VEGF, Neovascular glaucoma*

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INTRODUCTION

Vascular endothelial growth factor (VEGF) is elevated in aqueous of patients with neovascular glaucoma (NVG) secondary to proliferative vasculopathies such as proliferative diabetic retinopathy (PDR) and central retinal vein occlusion (CRVO) (1). Reduction of VEGF levels was noted after successful laser treatment of PDR (2). Injection of VEGF in primates produces a retinopathy similar to diabetic retinopathy as well as iris neovascularization (INV) (3). Furthermore, inhibition of VEGF can prevent iris neovascularization in primates (4).

Pegaptanib, an aptamer that binds VEGF165, has demonstrated its benefit in reducing diabetic macular edema, and it has been noted to induce regression of small areas of retinal neovascularization (5). Bevacizumab (Avastin, Genentech, San Francisco, CA) is a humanized recombinant antibody that binds all isoforms of VEGF. It has been approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer. Accessed December 28, 2005. Intravitreal bevacizumab is well tolerated in the short term and efficacious in the treatment of neovascular age-related macular degeneration (6). Intravitreal administration of bevacizumab was effective in reducing INV associated with PDR (7-10). Given the overwhelming evidence for VEGF's role in proliferative

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vasculopathies, intracameral bevacizumab was offered to patients with INV secondary to PDR, CRVO, and central retinal artery occlusion (CRAO).

METHODS

Between November 2005 and October 2006, 16 eyes of 15 consecutive patients were reviewed retrospectively (Tab. I) after Institutional Review Board approval. These patients included six women and nine men, aged 41–85 years (mean 54 years), with neovascularization of iris complicating PDR (10 patients), CRVO (3 patients), CRAO (1 patient), and proliferative vitreoretinopathy (1 patient).

Visual acuity ranged from no light perception to 20/30. Patients were followed for a minimum of 6 months with a range of 6–36 weeks with a median of 24 weeks. Neovascular glaucoma was present in 9/16 (56%) patients. Mean baseline intraocular pressure (IOP) was 51 mmHg ± 14.5.

Patients with active INV, who were unresponsive to traditional treatment, were considered for bevacizumab treatment. Patients were not offered treatment if they had uncontrolled hypertension or a recent myocardial infarction or cerebrovascular accident. The off-label use of the drug and its potential risks (especially the possibility of thromboembolic events and uveitis) and benefits were discussed extensively with all patients. Each patient signed a comprehensive consent form before administration of the intracameral bevacizumab.

An 0.12-mL aliquot of commercially available bevacizumab (25 mg/mL) was prepared for each patient and placed in a tuberculin syringe by a compounding pharmacy using aseptic techniques. The bevacizumab was refrigerated until it was used (within 14 days). After the eye had been prepared in a standard fashion using 5% povidone/iodine and topical antibiotics, 0.1 cc of aqueous was aspirated to reduce IOP. A total of 0.05 mL of undiluted bevacizumab was injected intracamerally through limbus. After the injection, IOP and retinal artery perfusion were assessed, and patients were instructed to administer topical antibiotics (moxifloxacin) for 3 days.

Injection was repeated after a month if recurrence of INV was noted. Patients with established NVG were treated with medical and/or surgical therapy as needed. Patients were interviewed 1 day after injection and were reexamined weekly by an ophthalmologist.

Patients were examined weekly until resolution of iris neovascularization and optimal control of NVG. Ophthalmic evaluations included nonstandardized Snellen visual acuity, complete ophthalmic examination including degree of INV and IOP, iris angiography, and slit lamp photography. The patients' records were reviewed to record patient demographics and clinical data. Iris angiograms were evaluated in a nonmasked fashion.

Iris neovascularization was graded clinically as described by Teich and Walsh (11) (Tab. II). Similarly angiography was graded as described by Ehrenberg et al (12) (Tab. III). The response in fluorescein leakage after injection was graded as complete (no leakage, only minimal staining), partial (definite reduction in intensity of leakage), or persistent (no change in intensity of leakage).

RESULTS

Follow-up data were available for all the eyes. No significant ocular or systemic adverse events were observed. The injection was well tolerated in all patients. Specifically no evidence of corneal toxicity was noted. None of the patients developed uveitis, endophthalmitis, ocular toxicity, or any obvious systemic adverse event. Blood pressure was monitored before initial injection and at each follow-up, and no significant elevation was observed over the course of the study.

TABLE I - CHARACTERISTICS OF PATIENTS

Subject no.	Age, yr	Gender	Eye	Clinical diagnosis
1	68	F	Right	PDR
2	57	M	Right	PDR
3	32	M	Left	PVR
4	39	M	Right	PDR
5	54	F	Right	PDR
6	53	M	Right	PDR
7	61	M	Right	CRVO
8	46	M	Left	CRAO
9	58	M	Right	PDR
10	46	F	Both	PDR
11	85	M	Left	CRVO
12	50	F	Left	PDR
13	65	F	Left	PDR
14	53	F	Left	CRVO
15	48	M	Right	PDR

PDR = Proliferative diabetic retinopathy; PVR = Pproliferative vitreoretinopathy; CRVO = Central retinal vein occlusion; CRAO = Central retinal artery occlusion

Follow-up ranged from 6 to 36 weeks, with mean and median follow-up of 24 weeks. The majority (12/16 [75%]) of eyes had received prior panretinal photocoagulation for active retinal or INV associated with diabetic retinopathy or CRVO. All patients with neovascularization demonstrated by iris angiography (12/16 eyes) had complete (or at least partial) reduction in leakage of the neovascularization within 4 weeks after the injection. Complete resolution of INV was noted in 15 of 16 (94%) eyes. Iris neovascularization was noted to diminish as early as 24 hours. In addition to the reduction in angiographic leakage, the neovascularization clinically appeared to involute in many patients with a reduction in the caliber or presence of perfused blood vessels. In two patients, recurrence of INV was observed at 1 month and needed reinjection of medication.

Nine of 16 (56%) eyes had established NVG (>24 mmHg). Intraocular pressure control varied. Eight of 9 (89%) were managed with maximum medical therapy. Despite reduction in neovascularization, one eye (11%) needed shunt surgery.

Iris neovascularization

Dramatic regression of INV was noted in 9/16 eyes (56%) in 7 days, 14/16 eyes (88%) in 14 days, and 15/16 eyes (94%) in 21 days. Two eyes (12%) had recurrence and were injected after a month (Figs. 1 and 3-6).

Iris angiography

In four eyes, hyphema or corneal edema precluded preoperative fluorescein angiography, but in all other eyes, at least a partial reduction in fluorescein leakage was seen after treatment. Six (50%) eyes showed complete resolution, 4 (33%) eyes showed two grade difference, and 2 (17%) eyes showed one grade difference (Figs. 2, 3, and 6).

Visual acuity

Visual acuity improved from a median of hand motion to 20/200 after intracameral injection as noted at the most recent visit with a median follow-up of 24 weeks.

Intraocular pressure

Intraocular pressure control (<24 mmHg) was achieved in 89% of the eyes and correlated to the initial degree of INV (R = 0.9) with maximal medical ther-

TABLE II - GRADING OF IRIS NEOVASCULARIZATION

Grade	Iris neovascularization
Grade 0	No iris neovascularization
Grade 1	Fine surface neovascularization of the pupillary zone of the iris involving less than two quadrants
Grade 2	Surface neovascularization of the pupillary zone of the iris involving more than two quadrants
Grade 3	In addition to neovascularization of the pupillary zone, neovascularization of the ciliary zone of the iris and/or ectropion uveae involving one to three quadrants
Grade 4	In addition to neovascularization of the pupillary zone, neovascularization of the ciliary zone of the iris and/or ectropion uveae involving more than three quadrants

TABLE III - GRADING OF IRIS FLUORESCEIN ANGIOGRAPHY

Grade	Iris fluorescein angiography findings
Grade 0	No fluorescein leakage
Grade 1	Mild fluorescein leakage in one or two quadrants of the pupillary sphincter
Grade 2	Mild fluorescein leakage in three or four quadrants of the pupillary sphincter
Grade 3	Pupillary-sphincter leakage in three or four quadrants combined with leakage in one or two quadrants of the iris stroma.
Grade 4	Pupillary-sphincter leakage in three or four quadrants combined with leakage in at least three quadrants of the iris stroma.

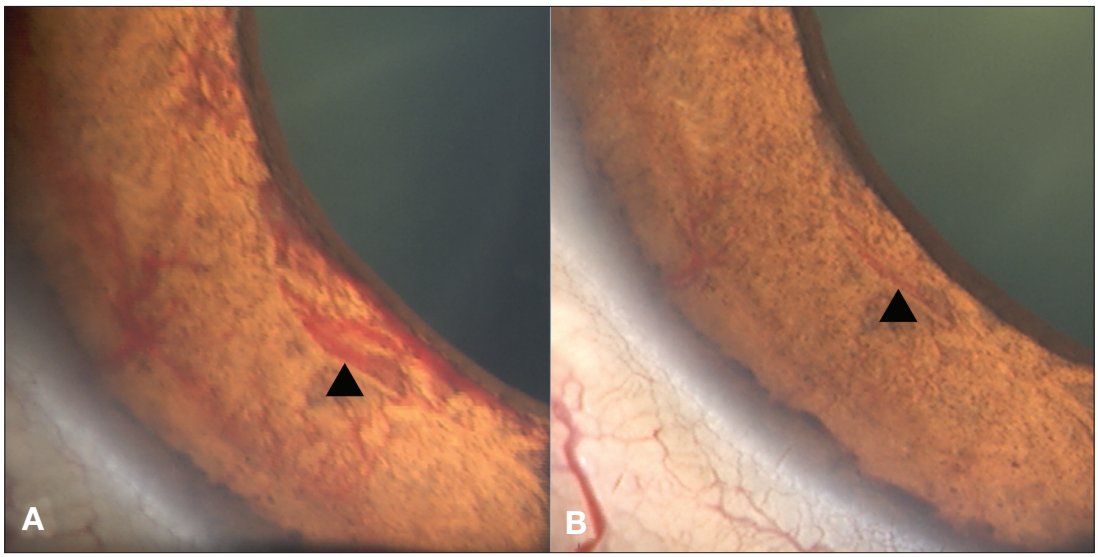

Fig. 1 - (A) *Pre-bevacizumab: anterior segment photograph of section image of iris showing neovascularization.* **(B)** *Four weeks post-bevacizumab: anterior segment photograph showing complete resolution of neovascularization of iris.*

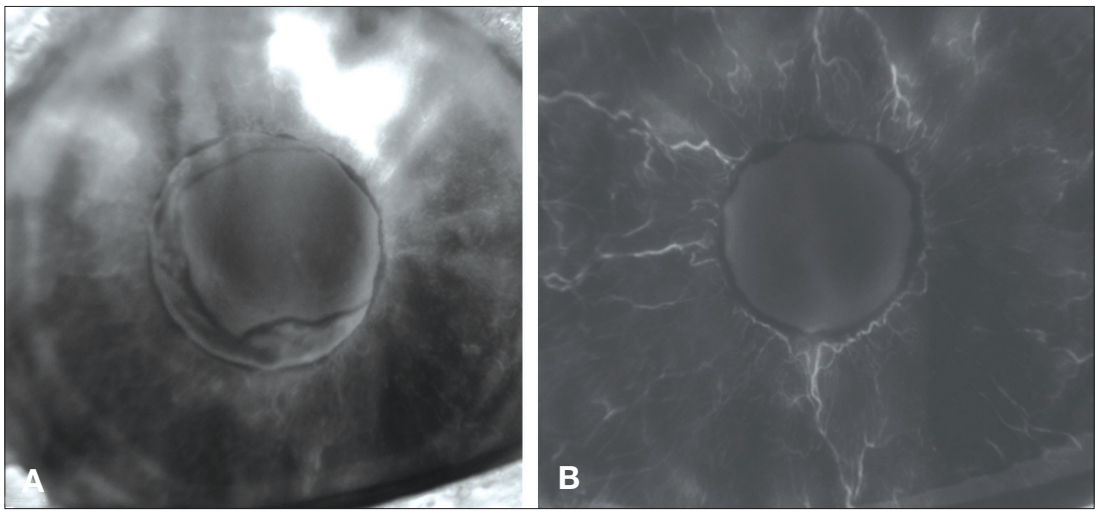

Fig. 2 - (A) *Iris fluorescein angiogram pre-bevacizumab: showing leakage from iris neovascularization.* **(B)** *Two weeks post-bevacizumab: showing marked decreased in leakage from iris neovascularization.*

apy. The mean IOPs decreased from a preoperative value of 51±14.5 mmHg (n=9) to 25.6±2.2 mmHg (n=8) ($p<0.001$).

Six patients underwent planned vitrectomy after intracameral injection of bevacizumab, which was given between 8 and 12 days before surgery. One had placement of a pars plana Baerveldt implant for NVG, and 5 underwent vitrectomy for vitreous hemorrhage and/or traction retinal detachment.

DISCUSSION

Iris neovascularization with secondary angle-closure glaucoma is a serious sequela of a number of disease processes affecting the eye. Clinical studies indicate that diabetic retinopathy, retinal venous obstruction, and sickle cell disease are leading etiologic factors for the development of NVG (1, 2). The common feature present in these diseases is believed to be retinal ischemia, which stimulates the production and secretion of an angiogenic factor as proposed by Michaelson in 1948 (13). Recent evidence obtained from both animal and human studies has indicated that VEGF or vascular permeability factor (VPF) is the most likely candidate for Michaelson's hypothetical molecule (2, 14-18). Neutralization of the VEGF either through reversal of original underlying process or through neutralization with monoclonal antibody shall reverse the

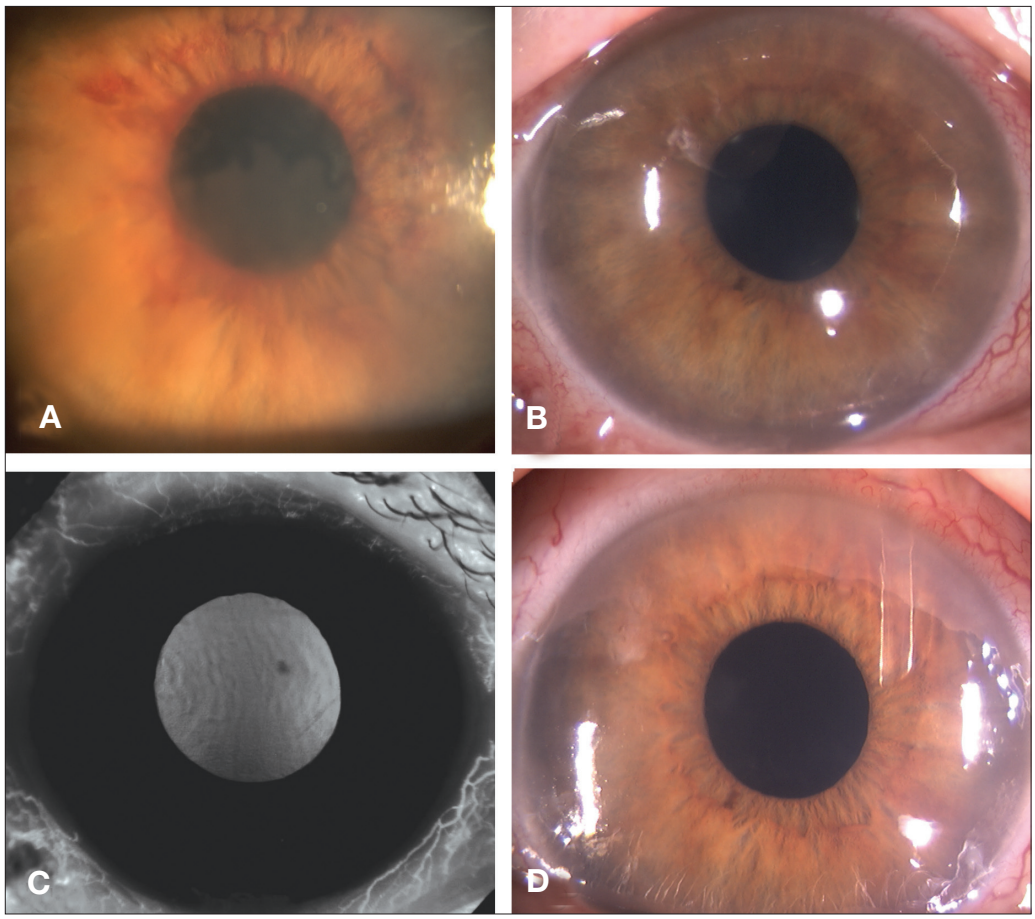

Fig. 3 - *Patient 1.* **(A)** *Pre-bevacizumab: anterior segment photograph showing grade 4 neovascularization of iris (NVI) and corneal edema due to neovascular glaucoma secondary to proliferative diabetic retinopathy.* **(B)** *Post-bevacizumab at 1 week: anterior segment photograph showing clear cornea and complete regression of NVI.* **(C)** *Iris angiogram at 3 weeks showing complete absence of leakage.* **(D)** *Post-bevacizumab at 20 weeks: anterior segment photograph showing complete regression of NVI and presence of shunt for control of intraocular pressure.*

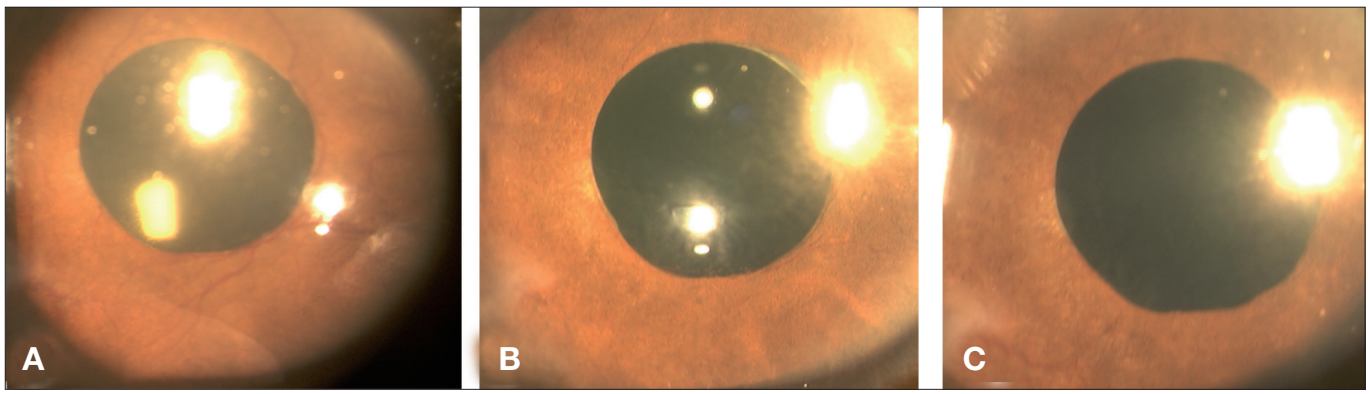

Fig. 4 - *Patient 2.* **(A)** *Pre-bevacizumab: anterior segment photography showing grade 4 neovascularization of iris (NVI) and corneal edema due to neovascular glaucoma secondary to proliferative diabetic retinopathy.* **(B)** *Post-bevacizumab at 1 week: anterior segment photograph showing clear cornea and regressed NVI with few involuted vessels.* **(C)** *Post-bevacizumab at 2 weeks: anterior segment photograph showing complete regression of NVI with few ghost vessels.*

process of INV and ameliorate associated glaucoma. Initial degree of neovascularization and iris angiography were good predictors of response to intracameral bevacizumab. Response was immediate and measurable. However optimal dose is not yet defined and it is reasonable to assume that the response will be dose dependent and correlate with levels of VEGF in the anterior chamber. Pharmacodynamics of anti VEGF

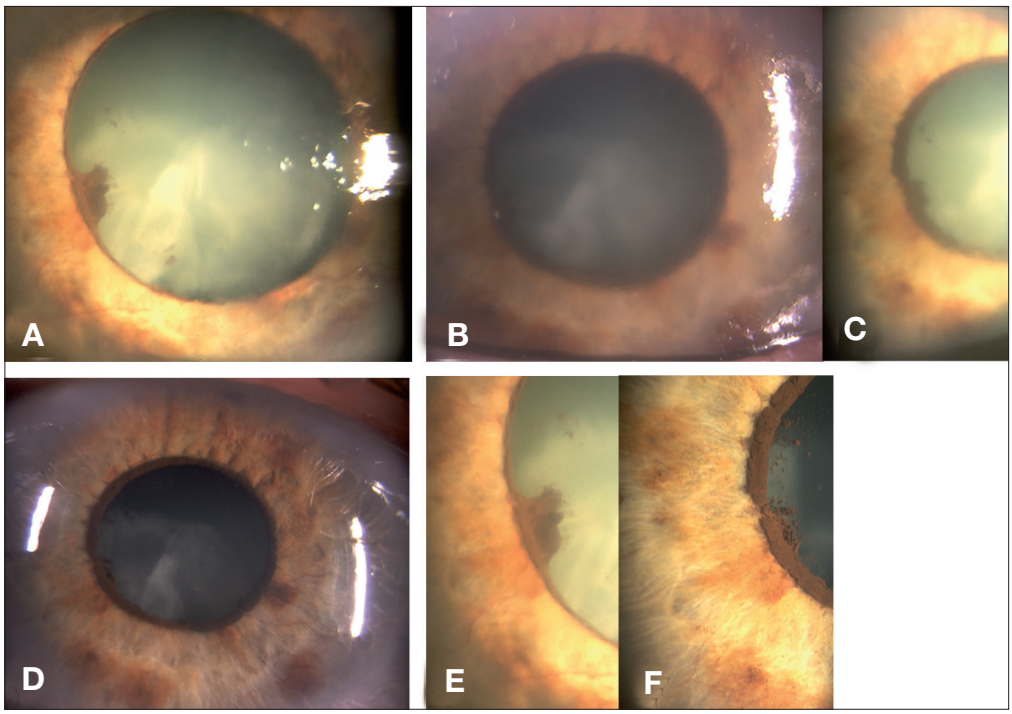

Fig. 5 - *Patient 11.* **(A)** *Pre-bevacizumab: anterior segment photograph showing grade 4 neovascularization of iris (NVI) and corneal edema due to neovascular glaucoma (NVG) secondary to central retinal vein occlusion.* **(B, C)** *Post-bevacizumab at 1 week: anterior segment photograph showing near complete regression of NVI with corneal edema; section image of iris showing regressed NVI and corneal edema.* **(D)** *Post-bevacizumab at 4 weeks: anterior segment photograph showing clear cornea and regressed NVI. Few faint vessels are seen in the nasal quadrant. Section image of iris pre-bevacizumab* **(E)** *and post* **(F)** *at 4 weeks showing complete regression of NVI.*

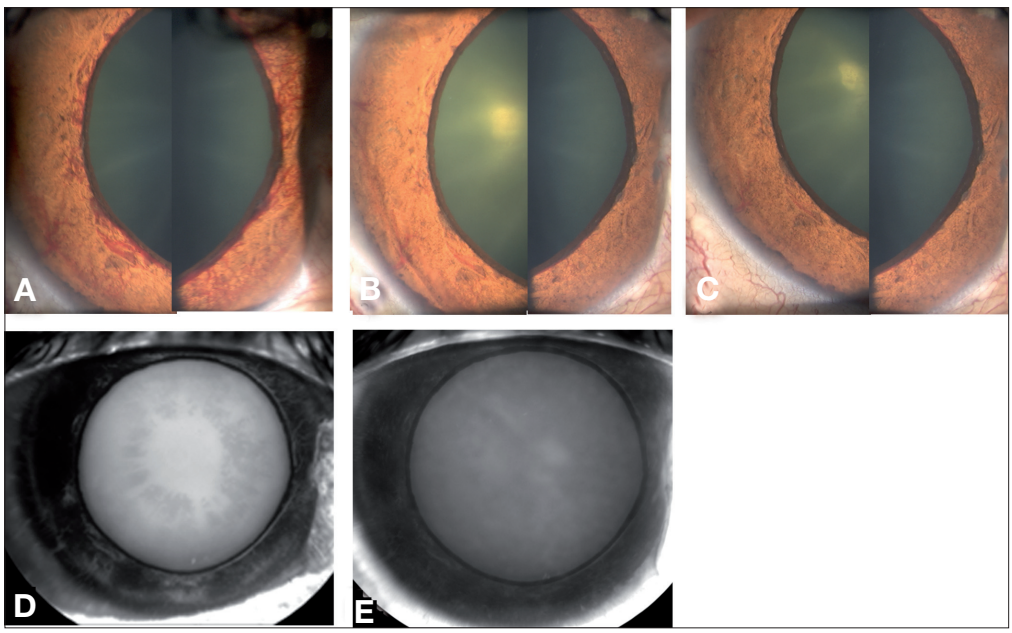

Fig. 6 - *Patient 15.* **(A)** *Pre-bevacizumab: anterior segment photograph showing grade 4 neovascularization of iris (NVI) with neovascular glaucoma (NVG) secondary to proliferative diabetic retinopathy.* **(B)** *Post-bevacizumab at 1 week: anterior segment photograph showing near complete regression of NVI with few persistent vessels.* **(C)** *Post-bevacizumab at 4 weeks: anterior segment photograph showing completely regressed NVI.* **(D)** *Iris angiogram at 1 week showing minimal leakage.* **(E)** *Iris angiogram at 4 weeks showing complete absence of leakage.*

antibodies depend on the rate of aqueous turnover, patency of the angle, status of vitrectomy, and presence or lack of a shunt. Further study is needed to define these parameters.

Standard treatment for INV through the years has been panretinal photocoagulation (PRP), and in cases where IOP rises to an extent where topical drops alone cannot control the pressure, glaucoma tube drainage procedures or ciliary body ablations are performed (19). In some cases, PRP alone does suppress proliferation of vasculature. In other cases, neovascularization recurs after PRP. Corticosteroids have been

used periocularly and intravitreally to treat many ocular conditions including neovascularization (12, 20). Bevacizumab inhibits VEGF, which has been implicated as a major angiogenic stimulus responsible for neovascularization. Bevacizumab has been used intravitreally to treat choroidal neovascularization in patients with age-related macular degeneration as well as an adjunct in treating INV-associated NVG (6-8, 10).

In the present study, after intracameral injection of bevacizumab, each patient had total regression of INV. One patient required a tube drainage procedure, and the other eight patients were treated with topical IOP-lowering drops alone. The shunt procedure was performed without bleeding complications secondary to regression of the iris and angle neovascularization. This resulted in less operative procedure time, decreased risk of hemorrhage, and quicker recovery for the patient.

The observation of the clinical tolerability and the efficacy of intracameral bevacizumab should stimulate further research on the clinical use of this agent for intraocular neovascularization. In addition, intracameral bevacizumab may be used to treat those patients who, despite prior PRP, have developed INV, recurrent hemorrhage from INV, and NVG. Subsequent tube drainage procedures for these patients may be less complicated with less intraoperative bleeding (19-21). Many patients may potentially avoid tube drainage procedures by undergoing an intracameral bevacizumab injection, which may cause immediate regression of iris and angle neovascularization, thus allowing for IOP to be controlled by concomitant administration of topical anti-IOP agents. Repeated injections of bevacizumab may be necessary in the event of recurrence.

Intracameral bevacizumab delivers anti VEGF therapy directly to neovascular tissue and promotes rapid resolution. Additionally, direct visualization of the needle at all times limits potential posterior segment complications associated with intravitreal injections (retinal detachment, damage to the lens, vitreous hemorrhage). However, rapid drainage from the anterior chamber may necessitate more frequent administration or increased dosage compared to intravitreal therapy.

Long-term results are not known, and therefore, caution should be exercised until the numerous outstanding questions with regard to safety, dosing, efficacy, and duration of effect can be answered by prospective clinical trials.

In summary, intracameral bevacizumab was effective in reversing INV in a majority of patients. It also facilitated IOP control in patients who had associated glaucoma. Visual acuity improved from a median of hand motion to 20/200. Shortcomings of this study include its retrospective nature, limited follow-up (24 weeks), nonstandardized visual acuities, limited knowledge of required intracameral dosage of bevacizumab, and relatively small number of patients.

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