ORIGINAL ARTICLE

Role of Intravitreal Avastin (Bevacizumab) in Anterior Segment Iris Neo- Vascularization (INV) and Neovascular Glaucoma (NVG) in our population

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ABSTRACT

Objective: To assess the efficacy of intravitreal Avastin in regressing iris and anterior chamber angle neovascularization and improving outcome of secondary neovascular glaucoma.
Study design: Prospective, consecutive, interventional case series.
Materials and methods: The study was conducted in the department of ophthalmology CMH Lahore and CMH Khuzdar for duration of 2 years from May 2010 to May 2012. Fifteen patients (15 eyes) with INV or NVG secondary to ischemic retinal disorders were included in the study. The study group included eleven males (73.33%) and four females (26.66%) aged 27 to 72 years (average, 59 years). Out of 15 cases, 10 had proliferative diabetic retinopathy and remaining five cases were secondary to ischemic central retinal vein occlusion (CRVO).Baseline complete ophthalmic evaluations was carried out included assessment of visual acuity by snellen charts, slit-lamp biomicroscopy of the anterior segment, gonioscopy, applanation tonometry, indirect ophthalmoscopy.
Results: Satisfactory regression of Iris (rubeosis) and anterior chamber angle neovascularization was observed in all eyes after one to four injections repeated at monthly intervals. In eight eyes, neovascularization recurred during the follow-up period. The intraocular pressure remained adequately controlled in one eye only. Six eyes were managed with addition of antiglaucoma therapy.
Conclusions: Intravitreal bevacizumab seems to be effective in regressing and stabilizing iris neovascularization, and lowering IOP in patients with INV alone and early NVG without angle closure. In advanced cases, Intravitreal bevacizumab cannot control IOP alone but may be used adjunctively to other procedures. However it is likely to extend our therapeutic options in managing neovascular glaucoma in patients with proliferative retinal vasculopathies.
Keywords: Bevacizumab, avastin, iris neovascularization, neovascular glaucoma

INTRODUCTION

Neovascular glaucoma (NVG) is characterized by rubeosis irides with secondary angle closure glaucoma[1]. Historically, it has been referred to as hemorrhagic glaucoma, thrombotic glaucoma, congestive glaucoma, rubeotic glaucoma, and diabetic hemorrhagic glaucoma. Various ocular and systemic diseases that predispose patients to retinal hypoxia and ischemia with subsequent release of angiogenesis factors can cause NVG. Neovascular glaucoma (NVG) is classified as a secondary glaucoma in which pathologic fibro vascular tissue grows on the iris and angle structures including the trabecular meshwork. Contraction of this tissue leads to progressive angle closure and elevation of intraocular pressure (IOP) eventually leading to a glaucoma and frequently results in variable visual loss[2]. Although Ischemic retinal disorders are the most prevalent conditions leading to NVG, other pathophysiologic mechanisms such as inflammation, retinal detachment, tumors and irradiation may also lead to this condition[3]. Studies have shown that iris neovascularization (INV) is highly related with retinal ischemia which stimulates the production of vascular endothelial growth factor (VEGF),a key mediator in ocular neovascularization[4]. Since role of VEGF in ocular neovascularization was established from various studies, inhibition of this mediator seems to be a possible therapeutic tool for regression of anterior segment neovascularization and management of NVG[2,5].

Avastin (Bevacizumab) a humanized monoclonal antibody to VEGF, in a series of studies was reported to have a potential and beneficial response in regressing retinal and iris neovascularization due to diabetic retinopathy, [6-9] in iris neovascularization due to central retinal vein occlusion (CRVO)[9,10] and neovascular glaucoma of various etiologies[11]. The aim of our study was to assess the efficacy of intravitreal Avastin (bevacizumab) in regressing and stabilizing iris and anterior chamber neovascularization and as an adjunct procedure in the management of neovascular glaucoma in our population.

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MATERIAL AND METHODS

Fifteen patients with INV or NVG secondary to ischemic retinal disorders were included in the study. The study group included 11(73.33%) males and 4(26.66%) females (Table 1) aged 27 to 72 years (average, 59 years). Out of the 15 cases, 10(66.66%) had proliferative diabetic retinopathy and remaining 5(33.33%) cases were secondary to ischemic central retinal vein occlusion (CRVO) (Table 2). Baseline complete ophthalmic evaluations was carried out included assessment of visual acuity by snellen charts, slit-lamp biomicroscopy of the anterior segment, gonioscopy, applanation tonometry, indirect ophthalmoscopy and finally fluorescein angiography of iris neovascularization. Diagnosis of NVG was established on the basis of iris neovascularization/ angle neovascularization/ ectropion uveae and raised IOP. Disc evaluation could not be performed in every patient due to hazy media and therefore was not taken as diagnostic criteria. Also, visual field examination could not be done in any of our patients due to poor visual acuity. Avastin (Bevacizumab) was applied at a stage of iris neovascularization with an elevation of IOP, in the dose of 1.25mg/0.05ml intravitreal inj after taking written informed consent. NVG was then managed medically or surgically. Follow up was carried out for 7-9 months.

RESULTS

Out of 15 patients who were identified to have rubeosis and neovascular glaucoma, NVG was secondary to PDR in 10(66.66%) cases and to CRVO in 5(33.33%)cases. 11(73.33%) patients were males and 4(26.66%) were females. The mean age of the patients was 59 years, with a range from 27-72 yrs. The mean follow up period was 7-9 months. Pre operative visual acuity ranged from 6/60 to perception of light with acceptable projection. Mean IOP before IVB treatment was 30-50mmHg with or without medication. Iris neovascularization was grade-4 clinically in 10 patients and grade 3 in remaining 5 patients. Gonioscopy showed closed angles with 360 degrees peripheral anterior synechiae (PAS) in 3 patients, 270 degrees PAS in 4 and PAS involving one quadrant in 2 patients. The angle was open with excessive pigmentation and angle neovascularization involving two quadrants in 3 patients while the hazy cornea in 01 patient obscured the gonioscopic findings. Disc exam. showed a CD ratio of 0.4-0.9 in 12 pts & in the remaining, discs could not be adequately visualized due to hazy media.

An average 1-4 injection of bevacizumab was given per patient (Table 3). Marked regression of the iris neovascularization was seen clinically in almost all eyes. In eight eyes, neovascularization recurred during the follow-up period. The intraocular pressure remained adequately controlled in one eye only. Six eyes were managed with addition of antiglaucoma therapy. A cyclodestructive procedure was planned in three eyes. Ahmet drainage valve were implanted in five eyes. The average IOP at the end of the follow-up period was 15 mmHg (range 12 to 30 mmHg).

It is usually seen that results of filtration surgery were not good in such patients but in our case those patients who received Avastin the bleb remained well formed and works reasonably well during our limited follow-up period.

Table 1: Socio demographic profile of subjects

Gender	Frequency	%age
Male	11	73.33
Female	04	26.66

Table 2: Disease responsible for neovascularization

Etiology	Frequency	%age
Diabetes Mellitus	10	66.66
CRVO	05	33.33

Table 3: Patient data on presentation

Case no	gender	eye	etiology	IOP mm of hg	INV Grade	PAS	Avastin inj
1	M	OS	DM	30	3	NO PAS	+
2	M	OD	CRVO	44	4	3	+++
3	F	OS	DM	45	4	4	++
4	M	OS	DM	40	3	2	+
5	M	OD	CRVO	34	4	1	++
6	M	OD	DM	42	4	3	++
7	M	OS	DM	43	4	Hazy Cornea	+++
8	F	OD	CRVO	38	4	NO PAS	+
9	M	OS	DM	45	4	4	++++
10	M	OS	DM	37	4	3	++
11	M	OD	CRVO	40	3	2	+
12	F	OS	DM	38	4	2	+
13	M	OD	DM	50	4	4	+++
14	M	OS	CRVO	46	4	3	+
15	F	OD	DM	32	3	1	+

Table 4: Treatment and final results

Case no	Reoccurrence of neovascularization	Final IOP mm of Hg	Final treatment
1		18	Drainage Valve
2	reoccurs	16	drops
3		10	drops
4	reoccurs	17	Drainage Valve+drops
5		15	Cyclodestruction
6	reoccurs	11	drops
7	reoccurs	18	Drainage Valve+drops
8		14	drops
9	reoccurs	24	Cyclodestruction
10		13	Drainage Valve
11	reoccurs	15	drops
12		12	Nothing
13	reoccurs	30	Drainage Valve+drops
14		14	drops
15	reoccurs	19	Cyclodestruction

DISCUSSION

The visual rehabilitation and management of patients with iris and angle neovascularization and secondary NVG still remains a challenge despite recent advances. Rapid diagnosis of the disease, followed by immediate and aggressive treatment, is essential. NVG is a potentially devastating glaucoma, where delayed diagnosis or poor management can result in complete loss of vision or even loss of the globe itself. The vital factor in improving treatment outcome of NVG patients is early detection of iris and angle neovascularization and addressing the underlying pathological process responsible for the rubeosis[2]. Although PRP remained the standard treatment for retinal ischemia, the best alternative method is still yet to be worked out. Consideration of visual potential is also an important because if visual status is poor the management plan changes and the goal of therapy becomes patient comfort. It is necessary to treat both the elevated intraocular pressure (IOP) and the underlying etiology for better prognosis.

Intraocular inj of Avastin (bevacizumab) had been used as an adjunct management modality in anterior segment neovascularization of various etiologies[6,8,9] and benefit of intraocular injection on iris neovascularization and IOP was already subject of discussion in past literature[12,13,14]. Chilov reported three cases of angle closure secondary to neovascularization (with elevated IOP in two cases) treated with intravitreal inj of bevacizumab (Avastin). In all three cases there was rapid resolution of neovascularization and control of intraocular pressure[15]. In a series of 3 pts with NVG reported by Mason et al, IVB resulted in total regression of INV with control of IOP surgically in one case and medically in 2 cases[10]. In our study 9 eyes were managed with addition of antiglaucoma therapy due to inadequate IOP control while Ahmet drainage valve were implanted in six eyes and 4 eyes were planned for a cyclodestructive procedure.

In another randomized controlled trial included 26 eyes of 26 patients with NVG, Intravitreal injections of bevacizumab demonstrated significant reduction in NVI and IOP from a mean baseline value[16]. Yet In another case series study of six patients with NVG secondary to CRVO by Iliev et al, a single inj of intravitreal Avastin (bevacizumab) resulted in a marked regression of iris and anterior chamber angle neovascularization and relief of symptoms with no side effects[13]. In our study significant to marked regression of the iris neovascularization was seen clinically in almost all eyes after 1-4 injections repeated at monthly intervals. Our results also suggest that IVB is well tolerated and can be tried as an adjunct treatment of choice for INV that is not adequately responsive to conventional procedures alone. Our study also throws light that response differs among different patients with some cases requiring more injections than others. So, the appropriate frequency of its use needs to be standardized by further trials.

In a pilot study of 6 patients Intracameral inj of bevacizumab (Avastin) as the first line maneuver before pan retinal photocoagulation and/or filtering surgery resulted in a rapid regression of the iris and angle neovascularization, thus halting the progression of PAS formation[17]. Moreover a single injection of bevacizumab can regress or reduce leakage from rubeotic vessels and may reduce the risk of Intracameral bleeding during surgery[7]. Our current study also demonstrates that bevacizumab has a role in the resolution of neovascularization of the iris and by reducing leakage from rubeotic vessels it decreases chances of intraoperative complications. In advanced neovascular glaucoma, intravitreal bevacizumab could not control IOP but could be used adjunctively to improve subsequent

surgical results[18]. Our study also suggests that Intravitreal bevacizumab (Avastin) has better prognostic outcome in patients with INV alone as compared to advanced disease, where IVB cannot adequately control IOP alone but may be combined with other surgical procedures.

To conclude, our study agrees with all these past reports in terms of beneficial effect of Avastin in regressing anterior segment neovascularization in our patients. Although the best protocol for management can only be determined through thorough future case trial studies, our limited research suggests that Intravitreal Avastin (bevacizumab) definitely has a favorable role in stabilizing the neovascular process and it seems to open a new therapeutic era in which future surgical intervention can be carried out successfully for visual salvation and IOP control in a more stable eye with low chances of hyphema,haemorrhaage, less operative time, decreased risk of complications and early recovery and rehabilitation period. However how much time regression of neovascularization will last is unknown, but still a positive response could be of benefit as a surgical adjuvant as it provides time to prepare the patient for filtering surgery/other procedure for NVG.

CONCLUSIONS

Intravitreal bevacizumab (Avastin) is usually well tolerated, seems to be effective in regressing and stabilizing INV activity, and lowering IOP in patients with INV alone and in NVG without synechial angle closure. In advanced disease, IVB cannot adequately control IOP alone but may be used adjunctively to other conventional procedures. However it is likely to extend our therapeutic options in the management of neovascular glaucoma in patients with proliferative retinal vasculopathies. In early rubeosis bevacizumab has a preventive effect and arrests the progression of disease. The treatment of the causative ischemic stimulus must be addressed in every individual separately. Eyes must be monitored closely after initial injection of intravitreal bevacizumab, regardless of initial angle status, as many may still require further medical or surgical intervention to lower IOP or repeat injection of intravitreal bevacizumab.

REFERENCES

1. Chen KH, Wu CC, Roy S, Lee SM et al. Increased Interleukin-6 in Aqueous Humor of Neovascular Glaucoma. Invest Ophthalmol Vis Sci. 1999;40:2627.
2. Sivak-Callcott JA, O'day DM Evidence-based Recommendations for the Diagnosis and Treatment of Neovascular Glaucoma. Ophthalmol. 2001;108:1767.
3. Glaucomas associated with disorders of the retina, vitreous and choroids. In: Allingham RA, Damji KF, Freedman S, Moroi SE, Shafranov G, Shields MB, eds. Shields' textbook of glaucoma. 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005:328-346.
4. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of Iris Neovascularization After Intravitreal Injection of Bevacizumab in Patients With Proliferative Diabetic Retinopathy. Am J Ophthalmol 2006;142:155–7.
5. Ng WME, Anthony AP. Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Can J Ophthalmol 2005;40:352.
6. Paula S, Jorge R, Costa A, Rodrigues Mde L, Scott IU. Short-term results of intravitreal bevacizumab (Avastin®) on anterior segment neovascularization in neovascular glaucoma. *Acta Ophthalmol Scand*. 2006;84:556–557.
7. Grisanti S, Biester S. Intracameral bevacizumab for iris rubeosis. *Am J Ophthalmol*. 2006;142:158–160.
8. Avery R. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina*. 2006;26:351–354.
9. Davidorf F, Mouser G, Derick R. Rapid improvement of rubeosis iridis from a single bevacizumab (Avastin®) injection. *Retina*. 2006;26: 354–356.
10. Mason J, Albert M, Mays A, Vail R. Regression of neovascular iris vessels by intravitreal injection of bevacizumab. *Retina*. 2006;26: 839–841.
11. Hasanreisoglu M, Weinberger D et al. Intravitreal bevacizumab as an adjunct treatment for neovascular glaucoma. *Eur J Ophthalmol*. 2009;19:607–612.
12. Martínez-Carpio PA, Bonafonte-Márquez E, Heredia-García CD, Bonafonte-Royo S. Efficacy and safety of intravitreal injection of bevacizumab in the treatment of neovascular glaucoma: systematic review]. *Arch Soc Esp Oftalmol.* 2008;83:579–588.
13. Iliev M, Domig D, Wolf-Schnurrbursch U. Intravitreal Bevacizumab (Avastin) in the treatment of neovascular glaucoma. *Am J Ophthalmol*. 2006;142: 1054 –1056.
14. Andrijevic´-Derk B, Vatavuk Z, Bencic´ G, Novak-Laus K, Mandic´ Z. Intravitreal bevacizumab for neovascular glaucoma. *Acta Clin Croat.*2008;47:175–179.
15. Chilov MN, Grigg JR, Playfair TJ. Bevacizumab (Avastin) for the treatment of neovascular glaucoma. Clin Experiment Ophthalmol. 2007 Jul;35(5):494-6.
16. Yazdani S, Hendi K, Pakravan M. Intravitreal bevacizumab for neovascular glaucoma: a randomized controlled trial. J Glaucoma. 2009 Oct-Nov;18(8):632
17. Duch S, Buchacra O, Milla E Intracameral bevacizumab (Avastin) for neovascular glaucoma: a pilot study in 6 patients. J Glaucoma. 2009; 8(2):140-3.
18. Wakabayashi T, Oshima Y et al. Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal diseases in 41 consecutive cases. Ophthalmology. 2008;115:1571.