INTRAVITREAL BEVACIZUMAB (AVASTIN) FOR PROLIFERATIVE DIABETIC RETINOPATHY

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ABSTRACT
Objective: *To determine the efficacy of intravitreal injections of bevacizumab (Avastin) for the treatment of proliferative diabetic retinopathy (PDR).*
Study Design: *Quasi-Experimental.*
Setting & Duration: *Department of Ophthalmology, Civil Hospital, Karachi. Liaquat National Hospital and Sindh Government Qatar Hospital Orangi Town from January 2007 to February 2009.*
Methodology: *One hundred and fifty eyes of 102 patients with proliferative diabetic retinopathy (PDR). Patients with proliferative diabetic retinopathy (PDR) were included in the study with detail history, and clinical examination using necessary instruments and investigations. After all aseptic measures, all patient received intravitreal Avastin (1.25mg/0.05ml) as base line, followed by two additional injections at six weeks interval. Intravitreal injection of Avastin was given 3.5mm away from the limbus in phakic and 3mm away in Pseudopahkic eyes. The efficacy of intravitreal Avastin were measured by changes in visual acuity (VA), intra ocular pressure (IOP), funds photographs, fluorescein angiographic lesion characteristics and ocular or systemic side effects were noted.*
Results: *One hundred and fifty eyes of 102 patients with PDR participated in the study. The mean age of patient was 55 years (range: 25-85 years).One hundred and twelve eyes 112(75%) had previous pan retinal photocoagulation (PRP). Ninety eyes 90(60%) showed total regression of retinal neo-vascularization (RNV) on fundus examination with absence of flourecien leakage, 41 eyes (27.3%) demonstrated partial regression of RNV on fundus examination and 18 eyes (12.6%) of patients showed no regression of RNV.Follow-up had a mean of 36 weeks (range from 28 to 48 weeks).Best corrected visual acuity (BCVA) demonstrated improvement (P<0.0001).No significant side effects were observed.*
Conclusion: *Intravitreal injections of Bevacizumab (Avastin) 1.25mg is found very effective in preventing visual loss, improved mean visual acuity and reduction in fluorescein angiographic leakage in patients with proliferative diabetic retinopathy.*

KEYWORDS: *Avastin, Bevacizumab, Intravitreal Injections, Proliferative Diabetic Retinopathy, Retinal Neo-Vascularization*

INTRODUCTION

The incidence of diabetes mellitus (DM) has increased rapidly in the last few decades throughout the world.[1] It affects 3% of global population and about 2% of the population in developed countries.[2] It has become a major global public health problem. Its complications such as Diabetic Retinopathy (DR) remains a major threat to sight in the working age population in the developed world and developing countries like Pakistan.[3] It is the leading cause of worldwide preventable blindness in working age adults. Proliferative diabetic retinopathy (PDR) is a major cause of visual loss in diabetic patients. In PDR, the growth of new vessels from the retina or optic disc is thought to occur as a result of vascular endothelial growth factor (VEGF) release into the vitreous cavity as a response to ischemia.[4]

Bevacizumab (Avastin) is a complete full-length huma-

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nized antibody that binds to all subtypes of VEGF and is successfully used in tumor therapy as a systemic drug.[5] Recent studies have demonstrated the usefulness of an intravitreal injection of bevacizumab in the reduction of vascular permeability and fibro vascular proliferation, RNV secondary to PDR.[6] The Pan retinal photocoagulation (PRP) is the gold standard for PDR, unless the patient already has extensive vitreous hemorrhage, which would preclude the possibility of laser photocoagulation. Neovascularization on and around the optic disc (NVD) and vitreous hemorrhage were found to be more frequently associated with severe visual loss despite PRP in the Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS).[7] Long intervals between PRP sessions and the variable amount of time required for a favorable response may increase the incidence of complications due to the progression of PDR.[8] In fact, a single episode of PRP or shorter intervals between PRP episodes, although desirable in severe PDR and when the patient must travel long distances for treatment, are often associated with acute visual disturbances due to exeudative choroidal detachment, retinal detachment, and macular edema.[9]

The purpose of this prospective study was to evaluate the effectiveness of intravitreal bevacizumab on RNV in patients with PDR as a base for future studies in which bevacizumab may be used as an adjuvant treatment to PRP for PDR.

METHODOLOGY

This prospective study was conducted on 150 eyes of 102 patients with RNV in patients with PDR, who were treated with off-label intravitreal bevacizumab from January 2007 to February 2009. Informed consent was obtained from all patients for this study at three institutions. The off-label use of the drug and its potential risks and benefits were discussed thoroughly with all patients. Clinical data including age, sex and duration of diabetes mellitus were obtained. Clinical findings such as best-corrected visual acuity (BCVA), applanation tonometery, fundus examination and fundus fluorescein angiography (FFA) were recorded. Eyes that were previously treated with scatter photocoagulation, and previous intravitreal triamcinolone injection were included in the study if any of those therapies had been performed at least 6 months before intravitreal bevacizumab. Commercially available bevacizumab 1.25mg in a tuberculin syringe was used for each patient. Before administration of injection the eye had been prepared in a standard manner using 5% povidone/iodine. An eyelid speculum was used to stabilize the eyelids, and the injection of 1.25 mg (0.05 ml) of bevacizumab was given 3.5-4 mm posterior to the limbus, through the inferno-temporal pars plana with a tuberculin syringe (30-gauge needle) under topical anaesthesia. After the injection, intraocular pressure and retinal artery perfusion were checked, and patients were instructed to administer topical antibiotics for 7days.

Patients were examined at 1, 2 weeks and 1 month after the first injection and monthly thereafter. One, three and six months after initial injection, patient evaluation was performed using ophthalmic examination with slit-lamp biomicroscopy, and FFA. Patients were included in this consecutive series if there was a minimum of 6-months follow-up. The main outcome measure was the change in RNV defined as the change in the area of vitreous leakage from NVD and new vessels elsewhere (NVE) in the late phase of FFA. Patients received reinjections only if RNV was not totally resolved on ophthalmic examination or FFA. The systemic conditions monitored included myocardial infarction, stroke, systemic hypertension, thromboembolic diseases, and death. Blood pressure was measured prior to bevacizumab injection and at 1 and 2 weeks following each injection.

RESULTS

The study included 102 patients with PDR from January 2007 to February 2009. A total number of 150 eyes were treated with injection intravitreal bevacizumab. The clinical records of all patients (150 eyes) were reviewed. Patients had a mean follow up of 36 weeks (range from 28 to 48 weeks). These patients had a mean age of 55 years (range from 25 to 85 years), and 51% were female (50 men and 52 women). Seventy diabetic patients (69.5%) were insulin dependent (Table I), the mean duration of the diabetes was 17 years (range from 1 to 30 years).

One hundred and nineteen eyes (79.3%) were treated with an intravitreal injection of 1.25mg of bevacizumab and thirty one (20.7%) with two additional injections 1.25mg of bevacizumab intravitreal at four to six weeks interval in poor response. Of the 112 eyes (75%) that were previously treated with scatter photocoagulation, 54 had prior focal/grid laser photocoagulation and 6 patients had a previous intravitreal triamcinolone injection (Table II). Sixty seven eyes had clinical significant macular edema (CSME) at biomicroscopy non-contact fundus examination with a 78-D. Ninety eyes (60%) showed total regression of RNV on fundus examination with absence of fluorescien leakage (Fig.1), 40 eyes (27.3%) demonstrated partial regression of RNV on fundus examination and 18 eyes (12.3%) of patients showed no regression of RNV (Table III). The mean baseline BCVA was log MAR=1.21 and the final mean

Gender	No.	Insulin Dependent	Non-Insulin Dependent
Male	50	33	17
Female	52	37	15
Total	102	70	32

Table I. Distribution of Diabetes & Gender

BCVA was log MAR=0.70 (P<0.0001). Among all eyes BCVA remained stable in 30.5%, improved in 56% and decreased two or more ETDRS lines of BCVA in 13%. Final BCVA analysis by subgroups of patients with CSME demonstrated that 52 eyes (77.4%) improved two or more ETDRS lines of BCVA.

DISCUSSION

Various Studies has shown that RNV may be due to more than one factors[10] VEGF is an important, if not the most important factor involved.[11] VEGF increases vessel permeability leading to deposition of proteins in the interstitial that facilitate the process of angiogenesis. There are several reports published on the intravitreal administration of anti-VEGF compounds for RNV in diabetic retinopathy.[12,13] In addition, there are five case reports on the use of intravitreal bevacizumab in RNV in diabetic retinopathy demonstrating regression of RNV in PDR.[14] This study demonstrated that intravitreal bevacizumab resulted in marked regression of RNV on fundus examination and FFA in patients with PDR and previous PRP. Furthermore, a rapid resolution of vitreous hemorrhage in three naïve (no previous PRP) eyes was also seen.

To determine the effect of an intravitreal injection of bevacizumab on actively growing new vessels, the change in vitreous leakage from RNV was chosen as our primary outcome. The detection of NVD and NVE on FFA allowed the use of a systematic anatomical approach to monitor the area of leaking new vessels over time.

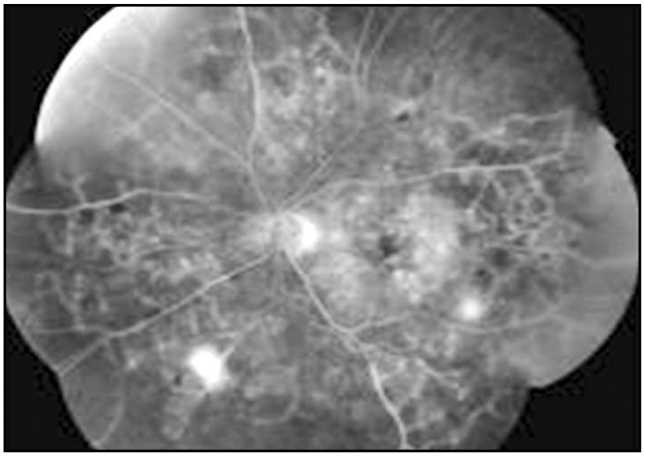

Fig. 1. Showing pre IVT Bevacizumab

Regression of neovascularization and decrease of retinal thickening occurred in some injected eyes as soon as 15-30 days after the intravitreal injection of bevaciaumab. Thirty one eyes (20.7%) needed a second injection due to recurrence of neovascularization at a mean of 4 weeks, and seven eyes needed a third injection due to recurrence of neovascularization at a mean of 8.3 weeks Our clinical impression is that the effect of intravitreal bevacizumab on RNV may be more lasting than in eyes with other pathologies such as choroidal neovascularization or macular edema; however, the cause is not known.

Our results suggest an overall VA gain as well as a reduced risk of VA loss in eyes with diabetic macular edema (as recognized on fundus exam.) treated with intravitreal bevacizumab. Avery[15] reported similar results to the present study in 45 eyes of 32 patients with retinal and/or iris neovascularization secondary to diabetes mellitus who had received intravitreal injections of 6.2mg-1.25mg of bevacizumab. They demonstrated that all patients with neovascularization had complete or at least partial reduction in leakage of the neovasculari-zation within 1 week after the injection. Pan-retinal photocoagulation has been the mainstay for the treatment of PDR, and its suppressive effect on RNV has been well documented.[16] However, substantial

Table II. Distribution of eyes according to prior treatment

Prior Treatment	1.25mg IVT Bevacizumab	Re. Inj. 1.25mg IVT Bevacizumab	Total of Eyes
PRP	42	16	58
PRP + Grid	30	12	42
PRP + Focal	8	4	12
IVT Trimcinolone	4	2	6
Total of Eyes	84	34	118

RNV Regression	Neovascularization with previous PRP		Naive Neovascularization		Total Eyes
	1st Inj. 1.25mg	Next Inj. 1.25mg	1st Inj. 1.25mg	Next Inj. 1.25mg	
Total	**61**	**4**	**25**	**--**	**90(60%)**
Partial	**24**	**10**	**--**	**7**	**41(27.3%)**
No	**10**	**9**	**--**	**--**	**19(12.6%)**
Total Eyes	**95**	**23**	**25**	**7**	**150**

Table III. Results of 1.25mg IVT Bevacizumab

IVT, intravitreal; naive, no previous PRP; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; RNV, retinal neovascularization.

regression of new vessels may take weeks after completion of PRP, and in up to one-third of cases, new vessels continue to grow despite initial PRP[17] In these cases, vitreous hemorrhage may induce visual loss and prevent complete laser. Moreover, macular edema may increase after PRP and cause transient or persistent visual loss.[18]

This study demonstrates multiple benefits of intravitreal bevacizumab on PDR and in the future this new option could be an adjuvant agent to PRP so that more selective therapy may be applied. In addition, bevacizumab may allow long intervals between PRP sessions to avoid the development of macular edema and other complications.[19] The current study has several definite limitations, like a relatively small sample size and a shorter duration of follow-up. However the results of the study confirms the hypothesis that at least some eyes with PDR, such as those with pre-existing macular edema or rapidly growing new vessels, may benefit from intravitreal bevacizumab. In addition, it can safely assume with a 95% confidence, that the true rate of systemic complications are very low as other study reports < 9 of side effects.[20]

CONCLUSION

Intravitreal bevacizumab appears to be a promising treatment for PDR, minimizing the risk for exeudative complications, progression of RNV, vitreous hemorrhage, and decreased vision caused by macular edema. Therefore intravitreal bevacizumab may be used as an adjuvant agent to PRP for PDR.

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