COMPARISON OF RANIBIZUMAB AND BEVACIZUMAB IN DIABETIC MACULAR EDEMA

Sanaullah Khan,[1] Zahid Mahmood,[1] Muhammad Saeed[2]

ABSTRACT

Background: Diabetic retinopathy is one of leading causes of blindness. **Objective:** To compare the efficacy of ranibizumab and bevacizumab in the treatment of diabetic macular oedema. **Material and Methods:** Study Design: Prospective, randomised trial evaluating efficacy of ranibizumab and bevacizumab in diabetic macular oedema (DME). Place and duration of study: Study was done at Nawaz Sharif Social Security Hospital Lahore / University of Lahore, from 1st January 2012 to 31st December 2013. Thirty two eyes were included in the study consisting of twenty eight patients. They were classified into 2 groups; Group A where 16 eyes received monthly intravitreal injections of Ranibizumab and Group B: Where 16 eyes received monthly intravitreal injections of Bevacizumab for the treatment of DME. Patients were followed on monthly basis. **Results**: Twenty eight patients (32 eyes) completed 48 weeks of follow-up. At baseline, mean best-corrected visual acuity (BCVA) on snellens chart was (20/100) in the bevacizumab group and (20/120) in the ranibizumab group. A significant improvement in mean BCVA was seen in both groups at subsequent follow up visits, post treatment BVCA was 20/160 and 20/200 in Group A and Group B as compared to pretreatment BVCA of 20/120 and 20/100 respectively. **Conclusion:** Bevacizumab and ranibizumab are both effective antivascular endothelial growth factor drugs preferred in the treatment of DME. Our comparison of both therapies suggested that the effect on BCVA was not statistically different in both groups.

Key words: Diabetic macular edema, Bevacizumab, Antivascular endothelial growth factor, Diabetic retinopathy, Ranibizumab

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INTRODUCTION

Diabetic retinopathy is a leading cause of visual loss and blindness in under developed countries.[1] DR is related to 1% of all cases of blindness worldwide. The main cause of vision impairment in diabetic patients is diabetic macular edema (DME). The presence of DME varies directly in proportion with the duration and stage of diabetic retinopathy. It is prevalent 3% in mild non-proliferating retinopathy, 38% in moderate-to-severe non-proliferating retinopathy and 71% with proliferative retinopathy. Macular edema is divided into two types:1) Focal DME, which is caused by accumulation of fluid from leaking micro-aneurysms.[2] Diffuse DME which is caused by accumulation of excessive amount of extracellular fluid in the macula due to disruption of the inner blood-retinal barrier, and abnormal permeability of blood vessels.[3] Recent work has found elevated levels of Vascular endothelial growth factor (VEGF) in ocular fluids of patients with proliferative diabetic retinopathy(PDR) and DME.[3] This VEGF has been found to be an endothelial cell-specific mitogen and cause angiogenesis in a variety of in vitro and in vivo models. It also causes increase in retinal vessels permeability by increasing the phosphorylation of tight junction proteins. Furthermore, injection of VEGF into normal primate eyes induces the same pathological processes seen in diabetic retinopathy, including microaneurysm formation and increased vascular permeability.[4,5]

Available treatments for DME include macular laser photocoagulation therapy to cauterize leaking blood vessels, intravitreal corticosteroid, and intravitreal anti-vascular endothelial growth factors (anti-VEGF) to prevent blood vessel growth and leakage. Successful laser treatment reduces moderate visual loss. However, it mainly preserves vision rather than restoring it, and some patients do not respond well to this therapy.[6,7] Intravitreal triamcinolone works via a number of mechanisms including reducing vascular permeability and down regulating VEGF. It may moderately improve visual acuity, but there is risk of increased IOP and cataract formation in phakic eyes. Observing that VEGF intraocular levels are increased in DME, it was hypothesized that alternative or adjunct therapies using anti-VEGF could be beneficial in reversing vision loss from macular edema. These anti-VEGF have been widely used in age related macular degeneration, and their use in diabetic macular oedema is growing. These have been proved not only in preserving vision but also in improving it. Therefore, at present, treatment

1. Department of Ophthalmology, University College of Medicine, University of Lahore, Pakistan.
2. Department of Ophthalmology Azra Naheed Medical College, Superior University Lahore, Pakistan.

Correspondence: Dr Sanaullah Khan, Associate Professor of ophthalmology, University college of medicine/University of Lahore.

Phone: +92-333-4275690 **Email:** ksanaullah@gmail.com

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with anti-VEGF agents such as ranibizumab, bevacizumab, and pegaptanib, are one of the most promising approaches for the treatment of vision loss due to DME .[8,9,10,11]

Bevacizumab is not FDA approved and is used off-label for the treatment of DME. Documented adverse effects of anti-VEGF include transiently elevated intraocular pressure (IOP) and endopthalmitis and retinal detachment. In a two year retrospective study of bevacizumab treatment for diabetic macular oedema, Arevalo et al found the rate of cardiovascular events to be only 1.7%.[12] Systemic effects associated with anti-VEGF injection include rise in blood pressure, thrombo-embolic events, myocardial infarction (MI), transient ischemic attack and stroke.[12] This study was conducted to compare the efficacy of ranibizumab and bevacizumab in treatment of diabetic macular edema.

MATERIALS AND METHODS

After obtaining approval by the institutional board, a prospective study was done to compare the efficacy of intravitreal bevacizumab and ranibizumab for the treatment of DME. The participants of the study were recruited between 1st January 2012 to 31st December 2013 at ophthalmology department of Nawaz Sharif Social Security Hospital Lahore / University of Lahore. Each patient underwent complete ophthalmological examination, including BCVA measurement, anterior and posterior segment slit lamp evaluation, indirect ophthalmoscopy and intraocular pressure measurements. Blood pressure and blood sugar measurements were also done at each visit. Confirmation of DME with fluorescein angiography was done at start of study.

Inclusion Criteria: Ages 40 years and older of either sex, diabetes mellitus (Type 1 or 2), macular oedema secondary to diabetes mellitus (DME) involving the center of the fovea seen on clinical examination or FFA, best corrected visual acuity (BCVA) score in the study eye of 20/40 to 20/200 Snellen chart, and decrease in vision primarily due to the result of DME and not to other causes.

Exclusion Criteria: History of vitreoretinal surgery in the study eye, history of previous Panretinal photocoagulation (PRP) or macular laser photocoagulation, history of previous use of intraocular corticosteroids like triamcinolone, proliferative diabetic retinopathy (PDR) at initial examination, iris neovascularization, vitreous hemorrhage, traction retinal detachment, or epiretinal membrane, subretinal fibrosis, or organized hard-exudate plaque at macula. Aphakia or posterior capsule rent, history of glaucoma or previous filtration surgery. Uncontrolled blood pressure or diabetes mellitus or renal failure, history of cerebral vascular accident or myocardial infarction within 3 month prior to anti-VEGF therapy and history of allergy to fluorescein or anti-VEGF.

The visual acuity (Snellens chart) and IOP were checked before and after two hours of injection. All patients were explained about possible adverse effects after intravitreal injection. All injections were given by experienced surgeons in operating room under strict aseptic measures. Each eye was prepared in a standard fashion 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 or 0.3 mg(0.05 ml) ranibizumab was performed 3.5 to 4 mm posteriorto the limbus, through the inferotemporal/superotemporal pars plana with a 30-gauge needle under topical anesthesia. After the injection, V.A, IOP and retinal artery perfusion were checked, and patients were instructed to administer topical antibiotics for 7 days. If a visually significant cataract developed during the follow up, we performed cataract surgery with IOL implantation. We divided all patients into two groups. Group A 16 eyes of 13 patients received three consecutive monthly intavitreal injections of Ranibizumab 0.3mg/0.05ml and then as needed basis. Group B 16 eyes of 15 patients received three consecutive monthly intavitreal injections of Bevacizumab 1.25mg/0.05ml and then as needed basis. Then all these patients were followed up on monthly basis and snellen chart, IOP measurements and fundoscopy was done. The data was entered and analyzed by using SPSS version 15.

RESULTS

Best-corrected visual acuity (BCVA) was obtained every month using the Snellen chart. Patients also underwent an ophthalmic examination, including a slit-lamp evaluation and fundus examination, as well as FFA if needed.

The mean BCVA on snellens chart was 20/120 in

Bevacizumab group at base line and post treatment BCVA was 20/160 and 20/200 respectively

Table I: Comparison of both groups

	Group A (n=13) (Ranibizumab)	Group B (Bevacizumab)
Male	8	9
Total Eyes	16	16
Age	54.7 ± 6.11	57.3 ± 5.32
Pre Treatment BCVA	20/120	20/100
Post Treatment BCVA	20/160	20/200
Pre treatment IOP	16 mmHg	15 mmHg
Post treatment IOP	15 mmHg	14 mmHg

A gain of more than two lines on snellens chart was observed in 46% of eyes with Ranibizumab group and 40% of eyes with Bevacizumab group at week 20-28, which has increased to 69% in Ranibizumab group and 58% in iv Bevacizumab group at week 44-48. A gain of >3 lines was observed in about 15% of eyes with Ranibizumab group and 10.5% of eyes with Bevacizumab group at week 48.

No significant long term increase was found in IOP from base line 15 and 14 to 16 and 15 after treatment in both groups. No case of endophthalmitis was seen during this study as all injections were given in an operating room following recommended aseptic practices. No patient experienced myocardial infarction, stroke or GIT bleeding.

DISCUSSION

Diabetic retinopathy, a vision threatening pathology of diabetes mellitus, is a serious global public health problem that impairs the quality of life. The number of people worldwide who are at risk for developing vision loss from diabetes, is predicted to double over the next 25 years. So a regular screening examinations is mandatory in reducing the magnitude of DR related visual impairment in the community especially in underdeveloped countries.

The management protocol for DR include, strict metabolic control of hyperglycemia, good blood pressure control, normalization of serum lipids, weight reduction, regular exercise, prompt retinal laser photocoagulation. Focal and grid laser photocoagulation are the primary treatments for DME. However, the ETDRS[4] demonstrated that immediate focal photocoagulation reduced moderate visual loss by 50%, 12% of treated eyes still lost 15 ETDRS letters at the 3-year follow-up interval, and 24% of immediately treated eyes had thickening involving the center of the macula at 36 months.[6] In addition, laser treatment of eyes with diffuse macular edema has been disappointing.[7] Our results indicate that intravitreal bevacizumab/ ranibizumab injections have a beneficial effect on macular thickness and VA, independent of the type of macular edema that is present (focal vs. diffuse). Therefore, in the future this new treatment modality could replace or complement focal/grid laser photocoagulation. Bevacizumab is a full-size, humanized, recombinant monoclonal immunoglobulin G antibody that inactivates all VEGF isoforms. It is approved as an anti-VEGF agent for the systemic treatment of metastatic colorectal cancer, but it has been widely used off-label as an intravitreal treatment for diabetic macular oedema.[11] Ranibizumab is a fragment of the same parent molecule as bevacizumab, and it has been approved by FDA for management of DME but it is considerably more expensive than bevacizumab. Intravitreal-bevacizumab (IVB) has been more widely utilized, primarily due to its low cost, safety and positive clinical effects in case studies and retrospective studies.[12]

CONCLUSION

Our clinical trial has suggested that bevacizumab could be used as a safe and efficacious alternative to ranibizumab for treatment of DME and because of its availability and lower cost, despite the lack of FDA approval for this indication.

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