ORIGINAL ARTICLE

SHORT-TERM EFFICACY OF INTRAVITREAL BEVACIZUMAB IN TREATMENT NAIVE PATIENTS- REAL WORLD EVIDENCE IN PAKISTAN

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Background: Anti-VEGF agents have been proven to be effective in treating macular oedema secondary to a multitude of pathological conditions. However, in large clinical trial settings, the results may be overstated. This study aimed to evaluate the short-term efficacy of intraocular Bevacizumab in consecutive patients with macular oedema being treated in a 'real-world' setting in Pakistan. **Methods:** A prospective study was conducted at Amanat Eye Hospital, Rawalpindi from August 2018 to November 2019. Thirty-five eyes of 29 patients with macular oedema were treated with monthly intravitreal Bevacizumab injections for three consecutive months. Best-corrected visual acuity (BCVA), and OCT parameters including central retinal thickness (CRT) and macular volume were assessed prior to the injections and then 4 weeks post the final injection and compared. **Results:** BCVA improved from 1.00±0.44 at baseline to 0.83±0.48 four weeks after the third intravitreal injection. CRT decreased significantly from 492.77±192.31 at baseline to 362.91±126.11 (p<0.05), and macular volume decreased significantly from 11.61±2.39 at baseline to 9.87±1.68 (p<0.05) four weeks after the third intravitreal injection. No systemic or ocular complications were observed during the course of the study. **Conclusion:** Treatment with intravitreal Bevacizumab injections was found safe and resulted in clinically and statistically significant improvement in SD-OCT parameters and visual acuity in patients with macular oedema secondary to various retinal pathologies. However, the improvement in a real-world setting was sub-optimal in comparison to larger clinical trials for specific diseases in the developed world.

Keywords: Bevacizumab; Macular Oedema; Diabetic Retinopathy; Macular Degeneration; Retinal Vein Occlusion

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INTRODUCTION

The introduction of anti-vascular endothelial growth factor (anti-VEGF) injections such as Bevacizumab, Ranibizumab and Aflibercept has revolutionized the treatment of macular edema and is one of the most promising approaches to the management and prevention of its possible detrimental effects.[1,2] While anti-VEGF agents such as Ranibizumab and Aflibercept are FDA (Food and Drug Administration) approved drugs for retinal pathologies including neo-vascular age-related macular degeneration (nAMD), diabetic retinopathy (DR) and retinal vein occlusion (RVO)[3–5], Bevacizumab (Avastin®; Genentech, San Francisco, California, USA) was approved by FDA for the treatment of metastatic colorectal carcinomas, renal carcinomas and glioblastoma multiforme of the brain in 2004[4]. However, owing to its VEGF inhibiting properties, easy availability and substantially lower cost as opposed to other anti-VEGF agents, it is being used off-label for treatment of neo-vascular age-related macular degeneration (nAMD), diabetic retinopathy, retinal venous occlusions and iris neovascularization.[4] In fact, the use of Bevacizumab in eye care surpasses that of licensed anti-VEGF drugs especially in the developing countries.[6]

Numerous studies have established the efficacy of Bevacizumab for treating macular oedema in varied pathologies. However, these recommended a strict regimen for their administration on regular intervals and excluded many cases with concomitant ocular and systemic factors that may negatively influence the outcome. In our study, we prospectively evaluated the efficacy of Bevacizumab in a real world setting in patients with various retinal pathologies and various degrees of severity/complications that warranted anti-VEGF.

MATERIAL AND METHODS

This was a prospective interventional study. The study was conducted at Amanat Eye Hospital in Rawalpindi between August 2018 and November 2019.

All cases in this study were Pakistani individuals between the ages of 33 and 79 years. We

included 35 eyes of 29 patients with various symptomatic treatment naive retinal pathologies including diabetic retinopathy, retinal vein occlusion, and choroidal neovascularization (CNV) which provided an indication for treatment with anti-vascular endothelial growth factor (anti-VEGF) injections.

The study group was composed of individuals who met the inclusion and exclusion criteria. The inclusion criteria included patients with treatment naive retinal pathologies with subretinal fluid (SRF) or intraretinal fluid (IRF) observed on optical coherence tomography (OCT) or leakage on fluorescein angiography. Exclusion criteria encompassed 1) Patients with NVE (Neovascularization Elsewhere) and PDR (Proliferative Diabetic Retinopathy) with no macular edema; 2) patients who switched to alternative anti-VEGF compounds prior to the completion of three consecutive monthly injections of Bevacizumab or switched to treatment options other than VEGF inhibitors such as Ozurdex® (dexamethasone intravitreal implant, Allergan, Inc., Irvine, CA) and 3) those who received any other treatment, including thermal laser photocoagulation, submacular surgery, photodynamic therapy or any other anti-VEGF intravitreal drugs prior to receiving the Bevacizumab treatment.

Ethical approval was obtained from the medical ethics board at Amanat Eye Hospital. This study adhered to the tenets of the Declaration of Helsinki and informed written consent was obtained before the investigation began.

All patients were consented for the study. Clinical record was maintained and included duration and severity of diabetes, underlying nephropathy, cardiac disease, hyperlipidaemias and history of stroke. A thorough clinical examination was conducted including best corrected visual acuity (BCVA measurements were converted to logarithm of the minimum angle of resolution [logMAR]), intraocular pressure (IOP) and anterior and posterior segment findings. Prior surgery and retinal laser were documented in the data sheet. Baseline OCT parameters were recorded, namely central retinal thickness (CRT) and macular volume.

Every patient received 0.05 ml of Bevacizumab via intravitreal injection (using 30-gauge needle) under sterile conditions every four weeks for three consecutive months. BCVA, CRT and Macular Volume were then recorded 04 weeks post the third injection. If further injections/laser were required on the post-operative visit, the patients were counselled and managed accordingly. The data was analysed by using SPSS version 23. The descriptive variables were presented as frequencies, percentages, mean and standard deviation. The BCVA, CRT and macular volume were compared before and after intravitreal Bevacizumab injection by using Paired *t*-test. At 95% confidence interval, the p value <0.05 was considered as showing statistically significant results.

RESULTS

In total, 35 eyes of 29 patients were analysed. The patients had a mean age ±SD of 59.7±8.9 years and comprised of 14 (40%) males and 21 (60%) females. Twenty-six (74.2%) patients had concomitant co-morbidities, including 20 (57.1%) patients with hypertension, 3 (8.6%) with hypercholesterolemia, 4 (11.4%) suffering from nephropathy and 5 (14.3%) from ischemic heart disease. Of concomitant ocular diseases, 7 (20%) patients had glaucoma accompanying their retinal pathology and 8 (22.8%) had epiretinal membranes or abnormal vitreomacular interaction, 27 (77.1%) patients underwent prior intervention pertaining to their ocular disease, including 18 (51.4%) patients who underwent panretinal photocoagulation (PRP), 4 (11.4%) who underwent grid macular laser (at least 06 months prior to initiation of anti-VEGF therapy), and 25 (71.4%) had cataract surgery.

Of the 35 treated eyes, 24 (68.6%) exhibited DR with diabetic macular edema (DME), 9 (25.7%) had RVO, and 2 (5.7%) showed evidence of CNV. Mean BCVA (logMAR) at baseline was 1.00. On OCT, the mean CRT at baseline was 492.77 microns and the mean macular volume at baseline was 11.61 mm3.

A Paired t-test was conducted to compare BCVA before and after intravitreal Bevacizumab injections. The mean BCVA assessed 4 weeks after the third intravitreal Bevacizumab injection was 0.83. A statistically significant vision gain was observed from baseline as 0.17 ($p<0.05$). Vision gain from baseline is presented in table-1. The BCVA improved in 17 (48.5%) of patients, stabilized in 10 (28.6%) patients, and deteriorated in 8 (22.9%) patients.

A Paired t-test was conducted to compare CRT before and after intravitreal Bevacizumab injection. The mean CRT values 4 weeks after the third intravitreal Bevacizumab injection were 362.9 microns. As shown in table-2, the mean CRT decreased significantly ($p<0.05$) compared with the baseline 492.8 microns.

A Paired t-test was conducted to compare macular volume before and after intravitreal Bevacizumab injection. The mean macular volume 4 weeks after the third intravitreal Bevacizumab

injection was 9.87 mm3, and exhibited a significant decrease in trend (p<0.05) compared with the baseline 11.61 mm3as shown in table-3.

One hundred and thirty-one injections were administered to the patients in total. Twenty-seven patients (77.1%) did not require additional injections, whereas 8 patients (22.9%) required additional injections. Among them, 1 eye required 6 more injections, 1 required an additional 5 injections, 3 eyes required 3 extra injections, and the remaining 3 eyes needed 2 extra injections of Avastin. Treatment of 8 (22.9%) patients is still continuing.

No patient was observed to develop ocular complications including endophthalmitis, rhegmatogenous retinal detachment, intraocular pressure elevation, cataracts or ocular haemorrhage. A single patient with a large fibrovascular pigment epithelial detachment (PED) developed a retinal pigment epithelium (RPE) tear after the second injection. No incidence of systemic side effects including cerebrovascular accident (CVA), myocardial infarction or allergic reactions was noted.

Table-1: BCVA before and after intravitreal Bevacizumab injection

BCVA	Mean±SD	t (df)	*p*-value
Before intravitreal Bevacizumab injection	1.00±0.44	2.51 (34)	0.017
After third intravitreal Bevacizumab injection	0.83±0.48		

Table-2: Central retinal thickness before and after intravitreal Bevacizumab injection

CRT	Mean±SD	t (df)	*p*-value
Before intravitreal Bevacizumab injection	492.77±192.31	3.74 (34)	0.001
After third intravitreal Bevacizumab injection	362.91±126.11		

Table-3: Macular volume before and after intravitreal Bevacizumab injection

Macular Volume	Mean±SD	t (df)	*p*-value
Before intravitreal Bevacizumab injection	11.61±2.39	4.12 (34)	< 0.001
After third intravitreal Bevacizumab injection	9.87±1.68		

DISCUSSION

The results of this prospective study establish that treatment with intravitreal Bevacizumab injections provided clinically and statistically significant improvement in SD-OCT parameters and visual acuity (VA) in patients with macular oedema secondary to various retinal pathologies in a 'real-world' clinical setting in Pakistan. However, the results are suboptimal if compared to larger controlled clinical trials in the developed world.

In our analysis, the mean average change in BCVA post intravitreal Bevacizumab injections was 0.17. The average reduction in CRT is 129.86 microns and average reduction in macular volume is 1.74 mm^3. Importantly, it is observed that in 14 cases a significant decrease in CRT was noted without a significant improvement in vision. This lack of improvement in visual acuity could be owing to other concomitant ocular diseases such as cataract, glaucoma, macular ischemia, taut posterior hyaloid or epiretinal membranes.

Our findings are consistent with various studies that have been conducted on Asian populations with regards to the effectiveness of Bevacizumab. Tareen et al. conducted a study at the Retina Clinic in Al-Ibrahim Eye Hospital, and Isra Postgraduate Institute of Ophthalmology in Karachi to establish the efficacy of intravitreal Bevacizumab in patients with diabetic macular oedema by assessing the improvement in BCVA and CRT on OCT[7]. The study yielded positive results (the mean CRT measurement improved from 452.9±143.1 µm at baseline to 279.8±65.2 µm on the final visit, and BCVA improved from 0.42±0.14 at baseline to 0.16±0.14 on the final visit), and these results were comparable to our study.[7] Also consistent with our observation, another study conducted at Combined Military Hospital (CMH) Kharian to ascertain the efficacy of intravitreal Bevacizumab in patients with branch retinal vein occlusion (BRVO) found that the mean CRT was 559 microns at baseline which improved to 380 micron at 3rd month, and mean baseline acuity was logMAR = 0.70 and at three months was logMAR=0.40.[8]

Similarly, visual and anatomic improvements with Bevacizumab treatment in our set up were comparable to an interventional retrospective case series conducted at the Department of Ophthalmology, PSG Institute of Medical Sciences and Research in India on patients with CNV secondary to angioid streaks which found a statistically significant decrease in the CRT from 324.40 µm at baseline to 265.53 µm at the final visit and improved or stabilized VA in 73.33% of the eyes.[9]

The absolute values of CRT and macular volume are comparable to the DRCR protocol 'T' (a

multi-center randomized controlled trial to assess the efficacy of anti-VEGF compounds in patients with center involving diabetic macular oedema) which showed significant improvement in VA from baseline (+10 letters) and decrease in the central subfield thickness of 101±121 μm with Bevacizumab at the 1-year visit.[10] However, it is important to note here that the average baseline CRT for patients in the Bevacizumab group in DRCR was much lower and therefore there was much less room for improvement and the percentage improvement is actually higher in DRCR. Furthermore, the average HbA1c of patients in the DRCR group was 8.4 which is considerably lower than our patient group indicating a better state of glycaemic control. It is observed that patients involved in larger clinical trials tend to be more educated and aware of their disease and risk factors as well as more regular with clinic visits as opposed to patients treated in our clinics.

The BERVOLT study was a retrospective non-comparative case series conducted to assess the efficacy of Bevacizumab in patients with macular oedema secondary to branch retina vein occlusion (BRVO) and central retinal vein occlusion (CRVO). The study reported a mean change in BCVA of 0.25 LogMAR and -0.118 LogMAR in the BRVO and CRVO groups respectively. Our study yielded a statistically significant mean change in BCVA of 0.17 LogMAR, (worse than BRVO group and better than CRVO group of the BERVOLT study).[11] The subgroup of patients in BERVOLT study were exclusive to only one pathology. It is evident from the BERVOLT study alone that the pathological process under study can influence the response to treatment.

The BRAVO and CRUISE trials highlighted the efficacy of Ranibizumab in the treatment of foveal center involving macular oedema secondary to BRVO and CRVO respectively. In the BRAVO trial, central foveal thickness (CFT) decreased by a mean of 337 microns (0.3 mg) and 345 microns (0.5 mg) with Ranibizumab at month 6[12], whereas in the CRUISE trial it decreased by a mean of 434 microns (0.3 mg) and 452 microns (0.5 mg).[13] Though the mean change observed in these studies using Ranibizumab was greater than what we observed with Bevacizumab, this could be due to the possibility of these trials following patients over a longer time frame and injecting more doses. These improvements are significantly higher than the result of our study due to several reasons. Firstly, Ranibizumab is a smaller molecule and seems to penetrate better within retinal tissue. Indeed, significantly better results were reported for Ranibizumab in DRCR studies for macular oedema in comparison to Bevacizumab. Secondly, in BRAVO and CRUISE studies, patients were injected at 4 weekly intervals for 6 months and even longer as compared to three months and were followed for a longer period of time. Further, the prognosis of retinal vascular occlusions is generally better due to spontaneous resolution of oedema in the first 6 months and especially when concomitant co-morbidities have been further excluded. Therefore, to expect these results in real life settings or to quote them to patients would be unrealistic.

A major strength of our study was its prospective study design encompassing most of the common retinal pathologies that lead to macular oedema. In addition, the study provided real-life data in Pakistani patients on Bevacizumab and established its efficacy in treating various retinal disorders. We included treatment naive patients only, and analysed OCT parameters which are directly influenced by the effects of Bevacizumab, thereby providing an objective measure of outcome. We also established that the results in clinical settings may be suboptimal when compared to research trial settings. The analysis was limited, however, by lack of a control group, limited sample size and the fact that it was single-centered. Despite these limitations, our study supports the current data available regarding the short-term effectiveness of intravitreal Bevacizumab and proved that Bevacizumab can safely and successfully be used instead of the licensed anti-VEGF compounds in the management of macular edema and producing positive visual outcomes. Further avenues of growth in this direction will include the possibility of a multicenter trial, more extended follow up than present, and comparison with other anti-VEGF molecule results.

CONCLUSION

In conclusion, Bevacizumab significantly improved visual acuity and anatomical morphology in Pakistani patients with visual impairment due to macular oedema secondary to various retinal pathologies. However, results in an actual clinical setting across all patients with retinal diseases are suboptimal (negatively influenced by concomitant ocular and systemic comorbidities). Therefore, to expect these results in real life settings or to quote them to patients in our set up would be unrealistic.

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Conflicts of Interest
The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

HAM, RS, MK, MA: Data collection, conceptualization of study design, literature search, write-up. MA: Data analysis and interpretation, write-up. HK, AA: Interpretation of OCT scans, data collection, critical review of write-up.

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