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STUDY ON INTRAVITREAL AVASTIN(BEVACIZUMAB) IN BRVO WITH MACULAR EDEMA

Dr. Mohd. Ayaz Bhat*, Dr. Waseem Raja and Dr. Rafia[1]

*Consultant Ophthalmology, J&K Health Services.
[1]Junior Resident, GDC, Srinagar.

***Corresponding Author: Dr. Mohd. Ayaz Bhat**
Consultant Ophthalmology, J&K Health Services.

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ABSTRACT

Purpose: To evaluate efficacy and safety of intravitreal injections of bevacizumab(avastin) in the treatment of macular edema due to branch retinal vein occlusion (BRVO). **Methods:** Retrospective, consecutive case series. Study was done on 52 eyes of 52 patients. Outcome measures include: Best corrected visual acuity (BCVA), central macular thickness (CMT) by spectral domain optical coherence tomography, and complications. **Results:** BCVA improved by a mean of 3.2 lines from an initial mean BCVA: 0.1 (counting fingers: 1 m-0.3) to a mean BCVA 0.4 (0.05-0.8) over the follow-up period of 6.9 months (4-12 months). CMT was reduced from an initial mean of 613 (401-959 µ) to the mean of 400 µ (274-623 µ) at the end of the follow-up period. This was achieved through a mean number of injections: Four with a range (3-6 injections). **Conclusion:** IVB is an effective treatment for ME secondary to BRVO. There was a significant improvement of VA and significant reduction in macular thickness in many cases, but not in all cases.

KEYWORDS:

INTRODUCTION

The circulation to the inner retina derives from the central retinal artery and central retinal vein. The central retinal vein forms at the nerve head by the confluence of tributaries of retinal veins and accompanies the central retinal artery, which emerges out of the nerve. Usually there are 2 main contributors, a superior and an inferior branch. Sometimes the 2 retinal veins remain separate until uniting within the substance of the nerve.[1] Within the retina, the retinal arteries and veins follow roughly the same paths and cross extensively. At crossings, the 2 vessels share a common wall and adventitial sheath.[2] With BRVO, the site where the artery and vein are proximate and the lumen of the vein is impinged by the more robust arterial wall is at an arteriovenous (AV) crossing.[3] This occurs more frequently when the artery overlies the vein, more often in the superior temporal quadrant.[4] Branch retinal vein occlusions have perhaps less opportunity for collateralization.[5] Bevacizumab (Vascular endothelial growth factor) is a vasoactive protein made by many tissues both physiologically for tissue maintenance and pathologically in response to various drivers, such as ischemia and resulting hypoxia. VEGF is required for normal development, and reduction of VEGF during embryogenesis causes defects in the development of the cardiovascular system in mice.[6] VEGF has 5 isoforms. VEGF 165 has been shown to be associated with human pathologic responses while having less effect on physiologic responses.[7] However, when selectively blocked, VEGF 165 had less effect on choroidal neovascularization than when VEGF 121 was also blocked.[8,9]

The rationale for use of an intravitreally injected antivascular endothelial growth factor (VEGF) drug to treat BRVO is that vascular occlusion induces upregulation of VEGF, resulting in increased vascular permeability and subsequent macular edema.[10,11,12] Prospective studies of ranibizumab (Lucentis, Genentech, Inc., South San Francisco, California, USA), a humanised, affinity-matured VEGF antibody fragment that neutralises all isoforms of VEGF-A and their biologically active degradation products in treatment-naïve eyes with ME following BRVO, found that ranibizumab was effective at 2 years after treatment of ME caused by BRVO.[13]

MATERIAL AND METHODS

This study was an open-label, single-arm, single-centre trial that was conducted in GMC Srinagar in year 2016. The off-label use of bevacizumab was explained to all patients before study enrolment, and all patients provided informed consent. Patients with a decimal VA between 0.8 (20/25 Snellen VA) and 0.05 (20/400 Snellen VA) as a result of macular edema secondary to BRVO were eligible if the foveal thickness was 250 µm or more and

none of the following were present: possible permanent visual loss in the study eye (atrophy or prominent pigmentary macular changes); vitreomacular traction or an epiretinal membrane; a history of vitreous surgery and intravitreal injection of a VEGF antagonist or steroids; or macular edema in the study eye due to causes other than BRVO, such as diabetic retinopathy.

Eligible patients were evaluated at least every 3 months or more frequently. At each study visit, patients could receive an intravitreal bevacizumab injection (1.25 mg/0.05 mL) if the foveal thickness was 250 µm or more or if there was persistent or recurrent macular edema that affected the VA based on the investigator's evaluation. Thus, even if the foveal thickness was less than 250 µm, an intravitreal injection was administered in eyes in which macular edema around the fovea persisted or recurred. Patients were examined 1 month after each intravitreal bevacizumab injection, and if additional treatment was not required, the next visit was planned for 2 months later. Bevacizumab injections were administered under sterile conditions in the operating room. At baseline and every visit during the follow-up period, all patients underwent a complete ophthalmologic examination, including measurement of the best-corrected VA (BCVA) using a Landolt ring VA chart, intraocular pressure (IOP) measurement and macular evaluation with optical coherence tomography (OCT) (OCT 3000, Zeiss Humphrey Instruments, Dublin, California, USA). Six radial line scans through the centre of the foveal lesion were used to determine if fluid was present in the macula. The foveal thickness was defined as the average foveal thickness measured on the vertical and horizontal scans. Fluorescein angiography (FA) was performed in all patients from 3 to 6 months after study entry when most retinal haemorrhages had cleared sufficiently to allow appropriate evaluation of the retinal vascular findings.

Statistical analysis was performed using the SPSS software package (SPSS Inc., Chicago, Illinois, USA). The BCVA measured using a Landolt ring chart was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analyses. The VA and foveal thickness were compared using the paired Student t test. $p<0.05$ was considered significant.

RESULTS

52 eyes of 52 patients were treated at GMC srinagar. They were 36 males (69.2%) and 16 females (31.8%). The mean age was 52 years, (range: 34-67 years). BRVO was ST in 28 cases (53.9%) and IT in 24 cases (46.1%). 42 cases were hypertensive (80.7%). 2 had systemic lupus and Reiter syndrome. 30 had diabetes mellitus (57.7%), 10 of them showed nonproliferative diabetic retinopathy changes and the other 20 cases showed no signs of diabetic retinopathy. 14 had glaucoma (26.9%). The mean initial BCVA was 0.1 (standard deviation [SD]: 0.08) (range: counting fingers [CF] 1 m-0.3). The mean initial CMT was 613 µ (SD: 174) and (range: 401-959 µ).

Best corrected visual acuity improved from an initial mean 0.1 (with a range of CF 1 m-0.3) to mean 0.4 (with a range of 0.05-0.8) at the final follow-up visit. The average lines of improvement in VA at final follow-up visit were 3.2 lines (0-6 lines). 8 cases had no improvement in BCVA (16%). The lines of improvement in BCVA were inversely proportional to the initial BCVA. The better the initial BCVA, the less final lines of improvement of BCVA. There was no statistically significant difference between lines of improvement of vision in both IT BRVO (mean 3.3, range: 1-6) and ST BRVO cases (mean 3.0, range: 0-6). Three or more lines of improvement of vision were observed in 36 eyes (69% of eyes) and 8 cases (16% of eyes) had an improvement of ≤2 lines. The following table illustrates the mean change in lines of BCVA over the follow-up period. The changes in lines of BCVA at 3 and 6 months were compared with baseline BCVA.

Lines of change in BCVA

Date	Mean lines	Range
Baseline	0	0
3 months	3.46	0-6
6 months	2.76	0-6
Final follow up	2.6	0-6

Mean CMT was reduced from an initial 613 (range: 401-959 µ) to 473 µ (range: 362-719 µ) at 3 months (1 month after the initial IVB loading) ($P < 0.001$). Mean CMT was further reduced to 400 µ (range: 274-23 µ) at the final follow-up ($P < 0.001$). The mean CMT reduction was 226 µ (SD: 125, range: 19-443 µ), which is 43.5% at final follow-up.

DISCUSSION

This study demonstrates the early and clinically relevant benefits of bevacizumab injection for macular edema due to BRVO. In this prospective case series, we found that intravitreal injections of bevacizumab led both to a significant reduction of foveal thickness, as well as to an improvement of visual acuity in patients with BRVO. A beneficial effect of intravitreal bevacizumab was observerd as early as the first week and over a 6-month follow-up period The intravitreal use of bevacizumab may provide anatomical and functional amelioration of the macula in patients with macular edema due to BRVO. The electrical responses in the fovea and parafovea of the multifocal electroretinography recording depict a significant improvement at 1 and 3 months after the injection (Moschos and Moschos 2008). The use of anti-VEGF agents in retinal disease has become increasingly common since the approval (in 2004 and 2006, respectively) of pegaptanib and ranibizumab for age-related maculopathy. These agents are currently being studied for their efficacy against macular edema due to BRVO. The anti-VEGF agent most studied in regard to BRVO is bevacizumab. Off-label intravitreal

injection of bevacizumab was first reported in 2005 to represent a potential therapy for macular edema secondary to BRVO (Rosenfeld et al 2005b). Our results suggest a possible short-term benefit for macular architecture and VA; however, it is also clear that such benefits are transient. Continuous VEGF suppression may be required to sustain beneficial effects observed in the short term and the risks associated with multiple intravitreal injections need to be considered. Our data suggest that patients may require several injections to maintain efficacy. The changes observed throughout the present study may provide important clues about drug effects and duration. Favorable macular changes, documented by OCT, were evident as soon as day 7 post-injection. While these improvements were maintained at post-injection week 4, there was a clear tendency for macular edema to recur around week 12; this suggests, therefore, that reinjections might be considered at some point during this period when a 1.25 mg dose regimen is used. We had 69% of eyes gaining three or more lines of vision as compared to Ehlers *et al*.[14] who had only 26% of eyes gaining three or more lines and 49% of eyes gaining one or more lines, but 7.5% of eyes gaining six or more lines. The mean lines of improvement in this study were 3.2 and in that of Ehlers was 1.6. In Ehlers's study, the inclusion criteria was BRVO with presence of ME, treatment with at least one IVB injection, with a reduction of VA ≤20/25, and previous treatment with laser or IVTA was allowed ≥4 months before the IVB treatment. It did not follow the Prager protocol, nor had any loading doses. The number of injections, interval between injections, and retreatment criteria was dictated by physician preference, and reasons for retreatment included recurrence of ME on OCT, decreased VA or new intraretinal hemorrhage. However, the follow-up period in this study was shorter than others, 6.9 months compared to 9 months in Ehlers *et al*.'s study,[14] Our study proves the efficacy of Prager style intravitreal bevacizumab in the treatment of macular edema secondary to BRVO. During the follow-up duration of 6 months, our mean number of injections was four. This is similar to 3.4 injections which were given over 6 months in the study done by Ahn *et al*.[15]

CONCLUSION

Intravitreal bevacizumab is an effective treatment for macular edema secondary to BRVO. There was a significant improvement of VA and significant reduction in macular thickness in many cases.

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