

Visual Results Following Intravitreal Bevacizumab in Neovascular Age-Related Macular Degeneration

Kashif Iqbal, Jamil Baig, Ahmad Zeeshan Jamil, Hannan Jamil, Khurram Mirza and Tariq Khan

ABSTRACT

Objective: To determine the visual and anatomic outcome of intravitreal Bevacizumab injection in the treatment of neovascular age-related macular degeneration (AMD).

Study Design: Quasi-experimental study.

Place and Duration of Study: Layton Rahmatulla Benevolent Trust Eye Hospital (LRBT), Lahore, from January to July 2010.

Methodology: Patients who received, one or more intravitreal Bevacizumab injections (1.25 mg per 0.05 ml) for exudative AMD were included in the study. Outcome measures included standardized visual acuity, optical coherence tomography (OCT), macular thickness, intraocular pressure, and blood pressure at 24 or more weeks follow-up. Descriptive statistics were obtained.

Results: Fifty eyes with exudative AMD were observed for six months. The mean VA improved from 0.21 ± 0.11 before injections to 0.43 ± 0.11 after injections at six months. Overall, mean OCT macular thickness decreased by 99 micron at last follow-up. At last follow-up, all eyes received an average of 3.28 ± 0.85 injections. There was no incidence of severe vision loss or adverse effects like endophthalmitis or retinal detachment.

Conclusion: Intravitreal Bevacizumab has the potential for improvement of vision in exudative AMD for at least 6 months.

Key words: Age-related macular degeneration. Bevacizumab. Choroidal neovascularization. Vascular endothelial growth factor.

INTRODUCTION

Choroidal neovascularization (CNV) is the primary cause of vision loss in wet age-related macular degeneration (AMD).¹ AMD is the most common cause of irreversible visual loss in the developed world in individuals over 50 years of age.² In USA, at least 10% of individuals between the ages of 65 and 75 have some visual loss due to AMD.² Amongst those above 75, 30% are affected to some degree.² Up regulation of vascular endothelial growth factor (VEGF), stimulates angiogenesis, which is the principle mechanism behind neovascularization.³ VEGF increases vascular permeability and promotes endothelial cell growth, growth mediator release, and leukocyte recruitment.⁴ In animal models, anti-VEGF therapy has been shown to prevent the formation of CNV and decrease leakage from existing CNV.⁵

Pegaptanib is the only anti-VEGF agent which is approved for the treatment of exudative AMD.⁶ It is an aptamer that binds specifically to the VEGF165 isoform and its intravitreal use has been shown to delay visual loss at 1 year.⁶ Ranibizumab, is an anti-VEGF antibody fragment that binds all isoforms of VEGF-A.⁷

Ranibizumab and Bevacizumab are derived from a common murine antibody.^{7,8} Bevacizumab, the full-length anti-VEGF antibody, is approved for intravenous use in metastatic colon cancer.^{7,8} In a pilot study, patients with wet AMD who were treated with intravenous Bevacizumab demonstrated visual improvement at 12 weeks.⁹ Avery and associates reported improved visual acuity after intravitreal Bevacizumab in a series of patients in whom the majority had prior Pegaptanib and/or photodynamic therapy (PDT) with Verteporfin.¹⁰ The intravitreal injection is easy to administer unlike PDT which requires a comprehensive setting and laser unit.

The objective of this study was to determine the visual and anatomic outcome of intravitreal Bevacizumab injection in the treatment of neovascular age-related macular degeneration (AMD).

METHODOLOGY

Fifty patients were selected who came for fundus Fluorescein angiography (FFA) in outpatient department of LRBT Hospital, Lahore. The patients were selected on the basis of FFA who demonstrated the presence of neovascular AMD, aged 40 years or above regardless of gender. They were classified on their angiographic features as classic CNV, occult CNV or retinal pigment epithelium detachment (PED). These patients were studied from January to June 2010.

Exclusion criteria comprised glaucoma, previous retinal surgery, myopia, choroiditis, trauma, angioid streaks,

Department of Ophthalmology, Layton Rahmatulla Benevolent Trust Eye Hospital (LRBT), Lahore.

Correspondence: Dr. Kashif Iqbal, 40A/195, Allaudin Road, Lahore Cantt.

E-mail: kashifmd@hotmail.com

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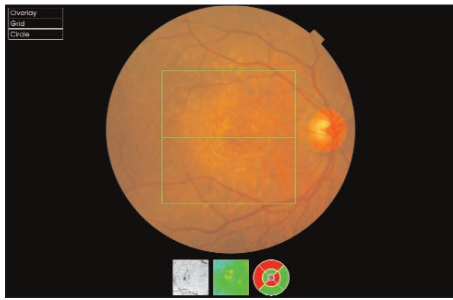


Figure 1: Right eye shows AMD with drusens.

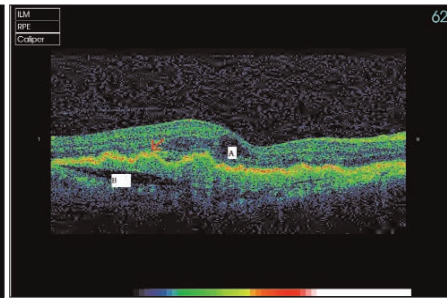


Figure 2: OCT of right eye of same patient: shows AMD and RPE bulges (arrow) and fluid in sensory layers marked A, and fluid in sub-RPE space marked B. VA is 6/60.

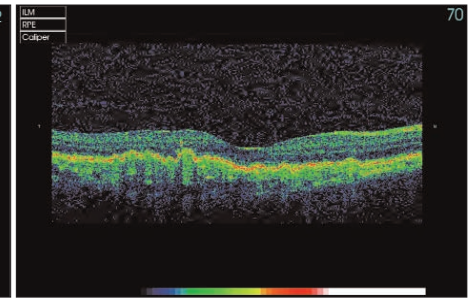


Figure 3: OCT of same patient six weeks after anti-VEGF injection shows complete resolution of retinal and sub-RPE fluid and VA improved to 6/18.

untreated hypertension, myocardial infarction (MI) and cerebrovascular accident (CVA). Patients not having a clear media in the involved eye for carrying out fundus Fluorescein angiography and OCT and those with history of any other treatment of AMD (like PDT, argon laser, intravitreal injections) were also excluded.

After the risks, benefits and alternatives were discussed with patients, informed consent was obtained for the off-label use of intravitreal Bevacizumab. The study was approved by the Ethical and Research Committee of the Hospital.

Data was collected from the patients regarding age, gender, past medical history, history of their present visual problem, number and type of previous treatments and history of diabetes, hypertension and other medical conditions. Examination included evaluation of visual acuity, intraocular pressure (IOP), and blood pressure (BP). Anterior segment examination was done for presence of anterior chamber inflammation, Iris examination, lens and fundus examination was done for lesions of AMD. Digital fundus Fluorescein angiography was performed with classification of subfoveal CNV on presentation. Optical coherence tomography (OCT), Topcon Mark 2 was performed in all patients to assess central macular thickness and macular volume.

All eyes were treated with 5% Povidone/Iodine and topical antibiotics. Using aseptic technique, 1.25 mg (0.05 ml) of Bevacizumab was injected into the Vitreous cavity via the Pars Plana. Patients were instructed to use topical antibiotics in eyes for 3 days. The patients received monthly injections of Bevacizumab for 06 months. Follow-up was done initially after 5 days to assess any infection and then monthly, follow-up was done. On each follow-up visit, patients visual acuity was recorded followed by measurements of intraocular pressure. This was followed by anterior segment examination, fundus examination and OCT every month up till 6 months. Repeat FFA was done if the decision was difficult to be established on OCT. Recurrences were noted, and defined on OCT as an increase in subretinal or intraretinal fluid or a significant increase in hemorrhage. The data was analyzed using latest

version of SPSS 17 and described as frequency percentage, mean and standard deviation. Student t-test was used to determine significance which was kept at $p < 0.05$. The initial VA noted in Snellen was converted to decimals for easy entry into SPSS data, (for example 6/60 became 0.1).

RESULTS

Fifty eyes of patients who met all inclusion criteria were included in the study. Their mean age was 50.66 ± 8.72 years. Thirty-one (62%) were female. Twenty-five patients (50%) had hypertension, 9 patients (18%) had coronary artery disease and 2 (4%) patients had prior myocardial infarction. At the time of initial diagnosis, 9 eyes (18%) had predominantly classic CNV, 9 (18%) had minimally classic CNV, and 32 (64%) had occult CNV. The pre-injection mean visual acuity was 0.21 ± 0.11 and mean visual acuity after injections at six months was 0.43 ± 0.11 . The difference between mean initial visual acuity and mean post injections visual acuity was statistically significant ($p < 0.001$, Figures 1 - 3).

Overall, the mean initial macular thickness for all eyes was 354.58 ± 14.75 microns. Macular thickness decreased at 4 weeks to 259.6 ± 10.79 microns ($p < 0.001$) and at 24 weeks to 255.8 ± 9.18 microns ($p < 0.001$). Forty eyes (80%) had reduced thickness at the last follow-up. The macular thickness before and after injections was decreased, four weeks after the injections which was maintained at 24 weeks after the injections.

In the first 24 weeks (6 months) of treatment, all eyes received a mean of 3.28 ± 0.85 injections. The initial induction dose of intravitreal Bevacizumab was given at the discretion of the doctor, and ranged from one to four monthly injections. After induction, patients were reinjected if recurrence was noted.

Eighteen eyes (36%) developed a recurrence in the first 6 months. After 6 months, 03 eyes developed a second recurrence and an additional 10 eyes developed their first recurrence. In total, 22 eyes (44%) did not experience recurrence at the last follow-up.

There were no statistically significant changes in IOP, systolic BP, or diastolic BP at each monthly and final

follow-up period. No anterior chamber inflammation, retinal detachment, or endophthalmitis was noted in any eye. No patient developed myocardial infarction or thromboembolic event.

DISCUSSION

Intravitreal anti-VEGF therapies have emerged as important modality in the treatment of neovascular AMD. Pegaptanib, an anti-VEGF aptamer, was approved by the Food and Drug Administration for the treatment of wet AMD.⁶ Preliminary data from phase III clinical trials of Ranibizumab, an anti-VEGF antibody fragment which binds all isoforms of VEGF-A, demonstrates an improvement in visual acuity in a significant proportion of treated patients.¹¹ More recently, investigators have found that intravitreal injections of Bevacizumab, the antibody similar in origin to Ranibizumab, can improve visual and anatomic outcomes in patients with neovascular AMD.^{10,12}

This study supports the growing body of evidence that Bevacizumab is an effective treatment for exudative AMD.^{10,12} It is also reported to be beneficial in the treatment of choroidal neovascular membranes due to other causes like Myopia.¹³ Eyes treated with intravitreal Bevacizumab experienced a rapid and significant sustained improvement in not only standardized visual acuity, but also macular thickness and volume through at least 24 weeks of follow-up. Finally, the number of eyes that did not experience a recurrence was 44% at the end of 6 months follow-up. In another study by Avery and co authors, mean VA improved from 20/200 to 20/125 ($p < 0.001$) at 8 weeks.¹⁰ Their results regarding improvement in visual acuity are similar to the results presented here. Intravitreal Bevacizumab at a dose of 1.25 mg (0.05 mL) appeared to be well tolerated by all patients. There is an increased risk of elevated BP and thromboembolic events following the administration of intravenous Bevacizumab (5 mg/kg) and concurrent chemotherapy in patients with metastatic colon cancer.¹⁴ However, the administered intravitreal dose of Bevacizumab is approximately 1/400th that of the intravenous dose.¹² The patient population had no reported thromboembolic events or change in BP during the study. Additionally, there were no adverse ocular events following the intravitreal injection of Bevacizumab.

This study is limited by a small number of patients. Lesion size and chronicity were not evaluated in this study. Furthermore, the large percentage of eyes (64%) presenting with occult neovascularization make comparisons with other studies difficult. Finally, the number of Bevacizumab injections per eye was not uniform in this study. At 24 weeks follow-up, patients may still require further treatment and may not have

exhibited their final visual acuity. We did not study the effects of dietary supplements which are reported to be beneficial in the treatment of AMD.¹⁵ These results support the need for a prospective, randomized long-term clinical trial of intravitreal Bevacizumab in the treatment of neovascular AMD.

CONCLUSION

These results demonstrate an overall rapid visual improvement after one intravitreal injection of Bevacizumab. This improvement may remain stable for up to a period of 24 weeks.

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