ORIGINAL ARTICLE

ROLE OF INTRAVITREAL BEVACIZUMAB INJECTION FOR MANAGEMENT OF NEOVASCULAR AGE RELATED MACULAR DEGENERATION

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ABSTRACT

Background: Age related macular degeneration (ARMD) is the major cause of severe visual loss in older adults.Different treatment modalities are available such as: Laser photocoagulation,photodynamic therapy,transpupillary thermotherapy,submacular surgery & anti-vegf.

Aims & Objectives: The aim of our study was to evaluate the efficacy and safety of intravitreally administered Bevacizumab a humanized monoclonal anti –VEGF in Neovascular Age related Macular Degeneration.

Methodology: This non randomized, prospective study was carried out on 75 eyes of 75 patients attending the OPD at M & J Institute Of Ophthalmology and diagnosed as having Neovascular ARMD confirmed on FFA and SD-OCT . After taking written informed consent all patients were injected with intravitreal Bevacizumab 1.25 mg/0.05 ml. Follow up visits were scheduled one week, one month postprocedure and every monthly thereafter.

Results: 75 eyes of 75 patients were included in this non randomized prospective study. & 29.33% patients required 2 injections. Visual acuity is improved more than 3 lines from baseline in 21.33% patient, 64% patient have 2-3 lines gain & 6.66% patients showed 0-1 line gain in snellen's visual acuity. 5.33% patients have a loss of 1 line from baseline & 2.66% patients showed loss of 2-3 lines. Central foveal thickness decreased more than 200 microns from baseline in 52% patients, 28% patients have decreased of 100-200 microns & 20% patients have decreased of less than 100 microns.

Discussion: Approximately 10 % of ARMD patients manifest the neovascular form of the disease. 12 weeks). Our study showed that 80% patients had decrease in central foveal thickness more than 100 microns from baseline at the end of one year. 85% patients had gain of 2 or more lines on Snellen's visual acuity chart from baseline.No patient had any serious local or systemic adverse reactions.Limitations of our study is small number of patients,ICG not done,not compared with other anti-vegf drugs.

Conclusion: Intravitreal Bevacizumab is a safe and effective drug in treatment of neovascular age related macular degeneration without any serious systemic or local adverse effects

Key words: Age related macular degeneration, intravitreal injection, bevacizumab

INTRODUCTION

Age related macular degeneration (ARMD) is the major cause of severe visual loss in older adults. The prevalence in India varies from 0.6% to 2.7% in south India to 4.7% in north India. Most ARMD patients have dry form of disease consisting of macular drusen or RPE abnormalities or both. Approximately 10% of ARMD patients manifest the neovascular form of the disease.

Neovascular ARMD includes choroidal neovascularization & associated manifestation such as pigment epithelial detachment & retinal pigment epithelial tears, disciform scarring & vitreous hemorrhage.[1]

CNVM appears as a neovascular sprout growing under or through the RPE through breaks in bruchs membrane. These vessels proliferate between rpe & bruchs & leak fluid in all retinal layers. Choroidal neovascularization appears as a grey elevation deep to the retina with overlying neurosensory detachment. The diagnosis is confirmed by fluorescein angiography, indocyanine green angiography & optical coherence tomography.[2]

Different treatment modalities are available such as: 1). Laser photocoagulation- useful in extrafoveal or juxtafoveal cnv with well defined margins. 2). photodynamic therapy- useful in subfoveal, juxtafoveal cnv 3). transpupillary thermotherapy. 4). submacular surgery. 5). anti-vegf –pegaptanib sodium, ranibizumab, bevacizumab

Bevacizumab is a humanized monoclonal antiboby. It has been FDA approved for use in metastatic colorectal cancer. Antivegf bevacizumab is a cheaper alternative with promising results.[3] Studies are required to test its safety and efficacy of multiple injections in the long run. In our study we have evaluated safety & efficacy of intravitreal bevacizumab injection in patients of neovascular age related macular degeneration.

Current treatment options like photodynamic therapy ,pegaptanib and ranibizumab are expensive and require repeated treatments. Antivegf bevacizumab is a cheaper alternative with promising results. Studies are required to test its safety and efficacy of multiple injections in the long run.

The aim of our study was to evaluate the efficacy and safety of intravitreally administered Bevacizumab a humanized monoclonal anti –VEGF in Neovascular Age related Macular Degeneration.

METHODOLOGY

This non randomized, prospective study was carried out on 75 eyes of 75 patients attending the OPD at M & J Institute Of Ophthalmology and diagnosed as having Neovascular ARMD confirmed on FFA and SD-OCT .

Detailedinclusion and exclusion criteria were followed.

Following patients were excluded from this study –

1. Presence of NO perceptionorprojection of light.
2. Presence of any other retinal, macular or optic nerve pathology other than Neovascular ARMD likelyto affect visual outcome.
3. Presence of CNVM due to any cause other than Neovascular ARMD.
4. Uncontrolled intraocular pressureor eyes with preexisting glaucoma
5. Active inflammation in anterior segment.
6. Patients with advanced cataractous changes, complicated pseudophakia and corneal opacities making indirect ophthalmoscopy impossible.
7. Patients with advanced renal disease making fluorescein angiography impossible.
8. Patients with previoushistory of intervention in form of laser or intravitreal injections.
9. Patients with macular scarring.
10. Patients with history of cerebrovascular accidents or myocardial infarction or ECG abnormality like bundle branch blocks.

Written informed consent was taken before recruiting the patients for the study. The off-label use of the drug was explained to all patients. Baselineexamination like visual acuity, detailedanteriorsegment examination, slit lamp biomicroscopy and Fundus fluorescein angiography were done in all patients.
Routine blood investigations like RBS,Blood Urea and S.Creatinine were done before taking the patient for fluorescein angiography. Any history of adversedrug reactions was ruled out before doing angiography. Fluorescein angiography helped to confirm the diagnosis of CNVM. The membranes were classified into classic and occult depending on leakage pattern. They were classified into subfoveal, juxtafoveal and extrafoveal according to site of leakage. Sd-oct was done in all patients at baseline and on each visit. The same machine was used to make comparison easier. The following parameters were noted on OCT- central macular thickness, presence of subretinal, intraretinal or sub-RPE fluid, pigment epithelial detachment and other lesion components like blood, pigment and fibrosis.

After taking written informed consent all patients were injected with intravitreal Bevacizumab 1.25 mg/0.05 ml. The intravitreal injection was performed undertopical anesthesia with proparacaine eye drops. A lid speculum was used to keep the eyelashes awayfrom the conjunctiva. Povidone iodine 5% eye drops and antibiotic eye drops were instilled in the conjunctiva every five minutes for three times. The injection of Bevacizumab 1.25mg/0.05 ml was performed through a 26-gauge needle in the inferotemporal pars plana 4 mm posterior to the limbus.in phakic eyes and 3.5 mm posterior in pseudophakic eyes. After the injection, indirect ophthalmoscopy fundus examination was used to evaluate the perfusion of the central retinal artery.

Follow up visits were scheduled one week, one month postprocedure and every monthly thereafter.Visual acuity testing, iop monitoring, cataractassessment, slitlamp biomicroscopy , OCT were done at each visit. Fluorescein angiography was done as and when required.The main outcome measures were visual acuity and decrease in central macular thickness. The complications on follow up were also noted. Retreatment assessment was done every month and patients were treated as required. Retreatment was done if there was loss of more than one lines on Snellens visual acuity chart or there was any of the following on OCT- Increased retinal thickness without sub-retinal and/or intra-retinal fluid of more than 100µm, sub-retinal and/or intraretinal fluid, pigment epithelium detachment.

RESULTS

75 eyes of 75 patients were included in this non randomized prospective study. Out of 75 patient 42(56%) patients were male & 33(44%) patients were female. Patients have age range from 51 years to more than 70 years in this study.

All 75 patients underwent OCT & FFA. All patients undergone intravitreal bevacizumab injection 1.25mg/0.05 ml under all aseptic & antiseptic precautions. At the end of 1 year 8% patients required 4 or more injections, 62.66% required 3 injections & 29.33% patients required 2 injections.

Table 1: Characteristics of patients

Variable	No (%)
Visual acuity	
6/18 to 6/60	23 (30.66)
6/60 to 3/60	36 (48.00)
3/60 to HM	16 (21.33)
Type of membrane on FFA	
Classic	41 (54.66)
Occult	34 (45.33)
Central foveal thickness on OCT	
250-350 microns	17 (22.66)
350-450 microns	36 (48.00)
>450 microns	22 (29.33)
OCT characterisitics	
Cystoid edema	38
PED	43
Hemorrhage	50
Serous fluid	71

Table 2: Gain in visual and reduction in central foveal thickness acuity at the end of 1 year

Variable	No (%)
Gain in visual acuity at the end of 1 year	
>3 lines gain	16 (21.33)
2 to 3 lines gain	48 (64.00)
0 to 1 line gain	5 (6.66)
Loss of 1 line	4 (5.33)
2 to 3 lines loss	2 (2.66)
Reduction in central foveal thickness at the end of 1 yr	
>200 microns	39 (52.00)
100- 200microns	21 (28.00)
<100 microns	15 (20.00)

Table 3: Adverse reactions in patients

Adverse reactions	No.
Subconjunctival hemorrhage	30
Raised IOP	13
Conjunctivitis	14
Endophthalmitis	0
Retinal detachment	0
Lens injury	0

Any patient does not develop serious adverse effects such as endophthalmitis, retinal detachment & lens injury. Systemic side effects were not noted in any patients attributed to bevacizumab.

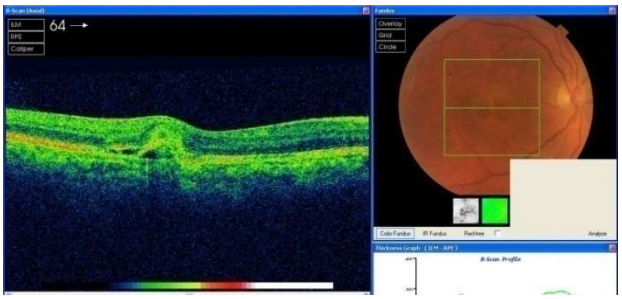

Figure 1: Pre injection OCT

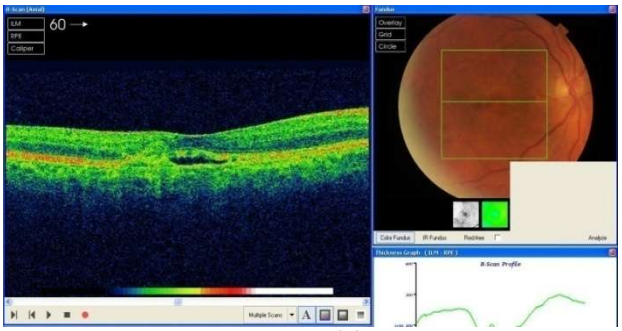

Figure 2: Post injection OCT

DISCUSSION

Age related macular degeneration (ARMD)is the major cause of severe visual loss in older adults. The prevalence in India varies from 2.7 %(dry) to 0.6 % (neovascular) in south India to 4.7 % in north India. Most ARMD patients have the dry form of the disease consisting of macular drusen or RPE abnormalities or both. Approximately 10 % of ARMD patients manifest the neovascular form of the disease. This form of the disease is accompanied by rapid loss of vision over a period of 6 to 12 months and the formation of central disciform fibrotic scar.[4]

Vision loss in the Neovascular ARMD is mainly due to two mechanisms-1) Proliferation of new capillaries is accompanied by secondary fibrosis and disorganization of the pigment epithelium and outer retina. 2)Secondary alterations in both retinal capillary and pigment epithelial permeability lead to accumulation of serous, serosanguineous fluid beneath the pigment epithelium,neurosensory retina or within the retina itself and are asscociated with acute visual dysfunction. It has now been established that vascular endothelial growth factor(VEGF) plays a principle role in the development of Neovascularization in Neovascular ARMD through its characteristics of 1) induction of angiogenesis through endothelial proliferation , migration and new capillary formation and 2) enhancement of vascular permeability.

Bevacizumab is a mouse-derived monoclonal antibody to VEGF produced by humanization of the mouse epitopes that was designed to neutralize the effects of all isoforms of VEGF in clinical disease . Preclinical studies in animal models of various tumor

cell lines as well as different forms of ocular neovascularization indicated that the fully sized antibody had excellent efficacy against the primary permeability and proliferative effects of VEGF isoforms.[5]

Ranibizumab is a humanized, murine antigen-binding fragment (Fab) with only a single affinity-matured binding site for VEGF. Ranibizumab received United States Food and Drug Administration (USFDA) approval for the treatment of neovascular AMD on June 30, 2006.

The CATT [6] (The Comparison of Age-related macular degeneration Treatment Trials) study and the IVAN[7] (The alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation randomized trial) study confirmed that both drugs might be regarded as parallel concerning visual acuity gain and safety issues.

A study by Biswas et al[8] was prospective randomized trial conducted across two centers in Kolkata, India, with 104 subjects and a total of about 302 injections in the ranibizumab group and about 216 injections in the bevacizumab group, studied results over 18 months. Parameters studied included both change in BCVA and CMT and the adverse effects of the two drugs over 18 months. They found no statistically significant difference in the efficacy and safety of ranibizumab and bevacizumab when used as intravitreal injections for treatment of CNVM due to wet AMD.

Avery RL et al[9] have shown that Bevacizumab is well tolerated and associated with improvement in vision, decreased thickness on oct and reduction in angiographic leakage. The study conducted by Avery showed that at 1, 4, 8 and 12 weeks the mean retinal thickness of central 1 mm was decreased by 61,92,89 and 67 μm, respectively ($P<0.0001$ for 1, 4 and 8 weeks and $P<0.01$ for 12 weeks).

Our study showed that 80% patients had decrease in central foveal thickness more than 100 microns from baseline at the end of one year. 85% patients had gain of 2 or more lines on Snellen's visual acuity chart from baseline.No patient had any serious local or systemic adverse reactions.

Limitations of our study is small number of patients,ICG not done,not compared with other anti-vegf drugs.

CONCLUSION

Intravitreal Bevacizumab is a safe and effective drug in treatment of neovascular age related macular degeneration in terms of improvement in best corrected visual acuity and reduction in central foveal thickness on OCT without any serious systemic or local adverse effects.

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