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Comparison between Avastin (Bevacizumab) and Lucentis (Ranibizumab) In the Treatment of Diabetic Retinopathy

Dr. Jitendra Kumar[1] , Dr.Amisha garg[2] , Dr. Samya singh[3]
1.Associate Professor & Head, Dept. of ophthalmology, MLB Medical College Jhansi, India. 2, 3Junior Resident, Dept. of ophthalmology,
MLB Medical College , Jhansi, India.
Corresponding author: Dr. Jitendra Kumar

Abstract:
Background*: Diabetic retinopathy (DR) is a leading cause of vision impairment, affecting 93 million people worldwide .Of these, 28 million have vision-threatening DR. Vision loss in DR is most commonly due to diabetic macular oedema (DMO), Development of drugs which target VEGF have revolutionised the management approach in DMO and have an expanding growing role in the management of DR. These anti-VEGF drugs have been reported to be safe and effective through multiple clinical trials. Since there are few studies comparing Bevacizumab and Ranibizumab, we have selected this study to evaluate the effect of intravitreal Bevacizumab compared with Ranibizumab for diabetic retinopathy.*
Materials and Methods*: In this prospective,comparative, randomised controlled study, 30 patients with diabetic retinopathy who came to Outpatident department of Department of Ophthalmology of Maharani Laxmi bai medical college,Jhansi,U.P. were randomaly divided into 2 groups. One group was given intravitreal bevacizumab and the other given intravitreal ranibizumab at monthly intervals for 6 months.Complete ophthalmic evaluation and optical coherence tomography(oct) was done at each visit along with FFA done at first visit and after 6 months. Analysis and compilation of data was done followed by compilation of results comparing the efficacy of two drugs on the basis of improvement in visual acuity,central macular thickness,side effects and cost effectiveness.*
Results*: The mean of BCVA change was 0.23+0.11(11.27+3.02 letters) in the bevacizumab group and 0.23+0.02(11.67+2.01 letters) in the ranibizumab group,which was statistically insignificant.(p=0.064).*
The mean of CSMT change demonstrated a value of 111.668 following bevacizumab injection and 112 after ranibizumab injection, which was statistically insignificant. (p=0.075).
Conclusion: *Our study indicates that both bevacizumab and ranibizumab are effective in reducing DME and increasing the BCVA in the short-term follow-up, but bevacizumab is more cost effective.*
Key Word*: Intravitreal; bevacizumab; ranibizumab; diabetic retinopathy; anti-vegf*

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I. Introduction

Diabetic retinopathy (DR) is a leading cause of vision impairment, affecting 93 million people worldwide [1] .Of these, 28 million have vision-threatening DR. Vision loss in DR is most commonly due to diabetic macular oedema (DMO), but may also be a consequence of complications of proliferative DR (PDR), such as vitreous haemorrhage from neovascularisation, tractional retinal detachment or neovascular glaucoma.

An improved understanding of the complex pathophysiology of DR has identified vascular endothelial growth factor-A (VEGF) as a key mediator of the progression to advanced disease.[2,3]Development of drugs which target VEGF have revolutionised the management approach in DMO and have an expanding growing role in the management of DR. These anti-VEGF drugs have been reported to be safe and effective through multiple clinical trials. Despite their efficacy, there are a proportion of patients who have an incomplete response to therapy. Future strategies to manage DR include alternate methods of blocking the VEGF pathway with increased efficacy and reduced number of treatments.

ANTI-VEGF DRUGS

The three most widely used anti-VEGF drugs are bevacizumab (Avastin, Genentech, San Francisco, CA, USA), ranibizumab (Lucentis, Genentech, San Francisco, CA, USA) and aflibercept (Eylea, Regeneron, Tarrytown, NY, USA).

Pegaptanib sodium (Macugen, Eyetech Pharmaceuticals, Cedar Knolls, NJ, USA) is an aptamer that selectively binds the VEGF-A 165 isoform and has some efficacy in the management of DMO and PDR. [4,5]

Use of pegaptanib in DR is not widespread due to access and availability of alternate and perhaps more effective anti-VEGF agents. These drugs are summarised in Table 1.

Bevacizumab is a 149 kDa, full-length monoclonal antibody to all isoforms of VEGF-A. This drug was developed for its anti-angiogenic effects in neoplastic disease and proved revolutionary as an adjunct to chemotherapy in prolonging survival in metastatic cancer. [6] It is not formulated for intravitreal use and consequently is most commonly prepared by compounding pharmacies.

Ranibizumab is a 48 kDa monoclonal antibody fragment that binds to all isoforms of VEGF-A. It lacks the IgG Fc segment that full-length antibodies have, and consequently, it has the lowest molecular weight of these three inhibitors. The smaller size of this drug provides a potential advantage in terms of retinal penetration. [6] The absence of an Fc segment avoids the theoretical interactionof ranibizumab with Fc receptors on immune cells, which could lead to cytotoxicity. [7]

Aflibercept is a 115 kDa fusion protein, combining the second binding domain of VEGFR-1 and the third binding domain of VEGFR-2. These are fused to the Fc segment of human IgG1 and the molecule acts as a decoy receptor, binding all isoforms of VEGF-A, VEGF-B and PlGF. [8] Aflibercept may also bind galectin-1, a protein that is physiologically expressed throughout the retina but upregulated in PDR. [9,10] It has angiogenic effects and protein levels are elevated in eyes with PDR, with no correlation to VEGF-A levels. [11,12]

Drug name	Structure	Mechanism of action	Molecular Size	Intravitreal half-life	US FDA Approved Indications
Pegaptanib (Macugen, EyeTech Pharmaceuticals)	Pegylated RNA aptamer	Binds VEGF-165 isoform of VEGF-A	50 kDa	10 days	nAMD
Bevacizumab (Avastin, Genentech)	Full length monoclonal antibody to VEGF-A	Binds all VEGF-A isoforms	149 kDa	7.0 days *	Metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer, ovarian, fallopian tube or peritoneal cancer
Ranibizumab (Lucentis, Genentech)	Monoclonal antibody fragment to VEGF-A	Binds all VEGF-A isoforms	48 kDa	2.5 days *	nAMD, RVO, DMO, mCNV, DR
Aflibercept (Eylea, Regeneron)	Fusion protein of binding domains of VEGFR-1 and -2, contains Fc portion	Decoy receptor for all isoforms of VEGF-A, VEGF-B and PlGF	115 kDa *	3.6 days	nAMD, RVO, DMO

Table 1: Summary of different anti-VEGF drugs

RANIBIZUMAB (LUCENTIS)

Ranibizumab is a 48 kDa monoclonal antibody fragment that binds to all isoforms of VEGF-A. It lacks the IgG Fc segment that full-length antibodies have, and consequently, it has the lowest molecular weight of these three inhibitors. The smaller size of this drug provides a potential advantage in terms of retinal penetration. [13] The absence of an Fc segment avoids the theoretical interaction of ranibizumab with Fc receptors on immune cells, which could lead to cytotoxicity. [14]

Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds to all isoforms of VEGF-A. Its structure is that of a monoclonal antibody FAB (fragment antigen binding) fragment, which is derived from bevacizumab, a full-length humanized monoclonal antibody against human VEGF. At present, ranibizumab is produced by Escherichia coli cells with the use of recombinant DNA technology. Ranibizumab binds with high affinity to the VEGF-A isoforms (e.g., VEGF110, VEGF121, and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Once VEGF-A is bound to its receptors it promotes endothelial cell proliferation and neovascularization, and leads to vascular leakage by affecting the tight junction proteins [15,16].Vascular leakage is the main mechanism thatcontributes to the development of DME.

Mechanism of Action

A4.6.1 antibody is one of the four antibodies of the IgG1 isotope that most effectively binds to and neutralizes VEGF121, VEGF165, and VEGF189. Ranibizumab is a **48-kD** Fab fragment of the A4.6.1 antibody [17]

Ranibizumab lacks an Fc region, allowing it to avoid Fc recycling and making it significantly smaller than the full-size antibody. The smaller size is thought to facilitate easier penetration into the the retina and faster clearance systemically; however, this may also expedite clearance from the vitreous [18].
Ranibizumab binds to the receptor-binding site on VEGF-A, which inhibits the binding of VEGF molecules to their receptors on the surface of endothelial cells.[19] Ranibizumab blocks all isoforms of VEGF-A[20]. Each molecule of ranibizumab has only one binding site for VEGF, which implies that two molecules of ranibizumab are necessary to bind a VEGF dimer [21].

Indications

Intravitreal ranibizumab injection (LUCENTIS®; Genentech, Inc) was first approved by the FDA in 2006 for wet age-related macular degeneration. Since then it has been approved for the treatment of macular edema following retinal vein occlusion and diabetic macular edema. Most recently, it was was approved in 2015 for patients with diabetic retinopathy

Dosing

The approved dose of intravitreal ranibizumab injection is either 0.3 or 0.5 mg in 0.05 mL. Dosing recommendations vary according to indications.

Neovascular (Wet) Age-Related Macular Degeneration (AMD): The recommended dose for Ranibizumab is 0.5 mg (0.05 mL) administered once a month by an intravitreal injection.

Macular Edema Following Retinal Vein Occlusion: The recommended dose for Ranibizumab is 0.5 mg (0.05 mL) administered once a month by an intravitreal injection.

Diabetic Macular Edema (DME): The recommended dose for Ranibizumab is 0.3 mg (0.05 mL) administered once a month by an intravitreal injection.

Diabetic Retinopathy (DR) with or without DME: The recommended dose for Ranibizumab is 0.3 mg (0.05 mL) administered once a month by an intravitreal injection.

Myopic choroidal neovascularization (mCNV): The recommended dose for Ranibizumab is 0.5 mg (0.05 mL) administered once a month (28 days) by an intravitreal injection for up to 3 months. Retreatment may be needed as per treatment response.

Actual treatment protocols vary, but may include strict monthly administrations (fixed schedule), "as needed" (imaging and symptom guided) treatment (pro re nata or PRN), or variable prescribed injection intervals including treat and extend regimen. These changes are dependent on disease, patient, and physician.

Preparation and Administration

Ranibizumab is supplied as a preservative-free, colorless to pale yellow, sterile solution placed in a single-use glass vial. The vial comes in two forms: 0.5 mg dose vial (delivers 0.05 mL of 10 mg/mL Ranibizumab) and 0.3 mg dose vial (delivers 0.05 mL of 6 mg/mL Ranibizumab).

Before injection, the eye should be cleaned aseptically with betadine. The contents of a vial of ranibizumab should be drawn using a 19-gauge filter needle. A sterile small gauge x ½ inch-needle should replace the filter needle for the injection. After giving the patient topical or local anaesthesia, the injection may be administered under controlled aseptic conditions. A new vial should be used for each eye. Patients should be monitored for endophthalmitis .

Safety and Precautions

Several major warnings have been noted for the use of ranibizumab and other intraocular drugs. Endophthalmitis and retinal detachments can occur on rare occasions after any intravitreal injection, including the intravitreal ranibizumab injection. On average, about 0.02% of patients using ranibizumab developed infectious endophthalmitis. Patients must self-monitor after the injection for signs of infection, such as diffuse redness, decreasing vision, or worsening pain 24 hours after the injection. The ranibizumab clinical trials report a low risk for arterial thromboembolic events after the use of VEGF inhibitors, including intravitreal ranibizumab injection.

The most commonly reported adverse reactions (>10%) included conjunctival hemorrhage, vitreous floaters, cataract, vitreous detachment, increased intraocular pressure, and eye pain. These occasionally occur with any intravitreal injection. Other adverse reactions included foreign body sensation, ocular irritation, increased lacrimation, nasopharyngitis, anemia, nausea, cough, and constipation.

BEVACIZUMAB (AVASTIN®, Genentech, Inc)

Bevacizumab is a full length, humanized monoclonal antibody directed against all the biologically active isoforms of VEGF (VEGF-A). The antibody was initially designed and studied as an anti angiogenic strategy to treat a variety of solid tumor. It received its first approval in 2004 for combination use with standard

chemotherapy for metastatic colon cancer and non-small cell lung cancer where the recommended dosage is 5mg/kg once daily every two weeks as an intravenous infusion.

Bevacizumab is a recombinant IgG1 antibody with a molecular weight of about 149kD that is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing antibiotic gentamycin.

Bevacizumab, though not formally studied or approved for any intraocular disease, Rosenfeld's pioneering work in use of intravitreal Bevacizumab for macular edema in CRVO showed significant resolution of edema documented by OCT with a corresponding improvement in vision, led to rapid and wide use of Bevacizumab all over the world. After initial studies were done with intravenous injections, this route of administration was not generally accepted due to higher costs and due to more conceivable risk of side effects .This led to its off label use intravitreally and also an impressive research effort to exclude local and systemic side effects. In clinical practice, the local side effects did not seem to differ compared to other intraocular drugs. Experimental studies have excluded short term negative effects on ocular cells and histology. The electrophysiological studies appear unaltered. This suggests that potential side effects on the cellular level cannot be detected with the present diagnostic tools in clinical practice.

Avastin® is a clear to slightly opalescent, colourless to pale brown, sterile solution with a pH 6.2.It was originally designed for intravenous infusion and is supplied in 100mg and 400mg preservative free, single use vials to deliver 4ml or 16ml of Avastin® (25mg/ml).The product is formulated in a alpha trehalose dehydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate and water for injection.

Bevacizumab binds to receptor binding domain of all VEGF-A isoforms. Consequently, it prevents the interaction between VEGF-A and its receptors (Flt-1 and KDR) on the surface of endothelial cells which starts the intercellular signaling pathway leading to endothelial cell proliferation and new blood vessel formation. After the intravitreal injection it is known to leave the ocular compartment and gain access into the systemic circulation which explains the biologic effects observed in the contralateral eye.

In addition, the retina is thinned at the foveola and lacks an inner plexiform layer, a layer which has recently been shown to be a potential diffusion barrier to molecules of greater than 76 kD. The attenuation of the ILM and the absence of an inner plexiform layer at the foveola may allow increased diffusion of bevacizumab in this region where it would be of greatest benefit in the treatment of macular diseases involving the fovea.

Pharmacokinetics of intravitreal Bevacizumab

In a study done by Bakri S et al 54 ; Vitreous concentrations of bevacizumab was seen to decline in a monoexponential fashion with a half-life of 4.32 days with concentrations of >10μg/ml bevacizumab maintained in the vitreous humor for 30 days.

Bevacizumab concentrations in the aqueous humor of the injected eye reach a peak concentration of 37.7 μg/ml 3 days after drug administration. A maximum serum concentration of 3.3 μg/ml is achieved 8 days after intravitreal injection and the concentration falls below 1 μg/ml 29 days after injection. Elimination of bevacizumab from the aqueous humor and serum parallels that found in the vitreous humor, with very low concentrations of bevacizumab detected in the fellow uninjected eye. Concentrations of bevacizumab in the vitreous of the fellow eye vary incrementally, from 0.35 ng/ml at 1 day to 11.17 ng/ml at 4 weeks. Concentrations of bevacizumab in the aqueous humor of the fellow eye reached its peak at 1 week, at 29.4 ng/ml, and declined to 4.56 ng/ml at 4 weeks.

The adverse events that have been reported following intravitreal injection of bevacizumab are

1. Corneal abrasion
2. Lens injury
3. Endophthalmitis
4. Retinal detachment
5. Inflammation or uveitis
6. Cataract progression
7. Central retinal artery occlusion
8. Subretinal haemorrhage
9. Retinal pigment epithelial tears
10. Blood pressure elevation
11. Transient ischaemic attack
12. Cerebrovascular accident

None of the adverse event rates exceed 0.21%. Intravitreal bevacizumab did not show increased potential drug related ocular or systemic side effects and has been considered safe for intravitreal use.

Uses of intravitreal Bevacizumab

1. Wet ARMD
2. Refractory macular edema in CRVO
3. Refractory macular edema in BRVO
4. CNVM
5. Diabetic macular edema
6. Post PRP refractory PDR
7. Vitreous Haemorrhage(to prevent further recurrent bleeding)
8. Pre operative adjuvant prior to vitrectomy in diabetic macular tractional Retinal Detachment
9. PDR

- Neovascular glaucoma
- Retinopathy of prematurity

II. Material And Methods

The proposed study was carried out in the department of ophthalmology, **MAHARANI LAXMI BAI MEDICAL COLLEGE, JHANSI, UTTAR PRADESH.** This study was conducted as per Declaration of Helsinki 2000 and Institutional Ethical Committee as needed

Study Design: Comparative, double masked, randomized control trial

Study Location: This was a tertiary care teaching hospital based study done in Department of Ophthalmology, at Mahrani laxmi bai medical college,Jhansi, Uttar Pradesh. (10)

Study Duration: We included the patients who were admitted in the In-Patient Department (IPD) of ophthalmology department between June 2019 to October 2020 (17 months),who fulfilled the eligibility criteria .

Sample size: 15 patients.

Subjects & selection method: Patients were included in the study under following inclusion and exclusion criteria:

Inclusion criteria: (10 Bold)

1. 1. Patients > 18 years of age who have signed an informed consent.
2. 2. Type 1 or Type 2 diabetes mellitus with glycosylated haemoglobin (HbA1c) less than 12.0 % at screening. Treatment for diabetes must have been stable for at least 2 months.
3. 3. Patients with visual impairment due to DME with a central area thickness >325 μm, who are eligible for anti-VEGF treatment according to the investigator. If both eyes are eligible, the one with the worse visual acuity, as assessed at first visit, is selected by the investigator as the study eyes.
4. 4. BCVA equal or more than 24 and less or equal to 78 letters in the study eye at screening using ETDRS-like visual acuity testing chart at a testing distance of 4 meters.

Exclusion criteria: (10 Bold)

i. Women of child-bearing potential, unless they are using two birth control methods.
ii. Pregnant or nursing (lactating) women.
iii. Inability to comply with study procedures.
iv. Active intraocular inflammation (grade + or above) in either eye at enrolment.
v. Any active infection in either eye at the time of enrolment.
vi. History of Uveitis in either eye at any time.
vii. Structural damage within 600 μm of the centre of the macula in the study eye likely to preclude improvement in visual acuity following in the resolution of macular edema, including atrophy of the retinal pigment epithelium, sub retinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques.
viii. Uncontrolled glaucoma in the study eye at screening (IOP > 24 mmHg on medication or according to investigator's judgment).
ix. Neovascularisation of the iris in the study eye.
x. Evidence of vitreomacular traction in the study eye.
xi. Active untreated proliferative diabetic retinopathy in the study eye.
xii. Any intraocular surgery in the study eye within 3 months prior to randomization.
xiii. History of vitrectomy in study eye regardless of time prior to randomization.
xiv. Planned medical or surgical intervention during the 6 months study period.
xv. Panretinal laser photocoagulation in the study eye within 3 months prior to or during the study.
xvi. Focal/grid laser photocoagulation in the study eye 3 months prior to study entry.

xvii. Treatment with anti-angiogenic drugs in the study eye within 3 months prior to randomization.
xviii. Use of other investigational drugs at the time of enrolment, or within 3 month or 5 half-lives from enrolment, whichever is longer.
xix. History of intravitreal corticosteroids in phakic eye within 18 months prior to randomization or in post-cataract surgery study eye within 4 months prior to randomization.
xx. Ocular conditions in the study eye that require chronic concomitant therapy with topical ocular or systemically administered corticosteroids.
xxi. History of stroke or transient ischemic attack (TIA) within 6 months prior to enrolment.
xxii. Renal failure requiring dialysis or renal transplant or renal insufficiency with creatinine levels > 2.0 mg/dl at screening.
xxiii. Blood pressure systolic > 165 mm Hg or diastolic > 105 mmHg at screening and randomization.
xxiv. Hypertension or change in antihypertensive treatment within 1 month preceding randomization.
xxv. Current use of or likely need for systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines and ethambutol.
xxvi. Known hypersensitivity to fluorescein, ranibizumab or bevacizumab or any component thereof or drugs of similar chemical classes.
xxvii. Any type of advanced, severe or unstable disease or its treatment, that may interfere with primary and/or secondary variable evaluations including any medical condition that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
xxviii. Concomitant conditions in the study eye which would, in the opinion of the investigator, prevent the improvement of visual acuity on study treatment.
xxix. Ocular disorders in the study eye that may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the 6-month study period, including cataract, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause(e. g., AMD, ocular histoplasmosis, or pathologic myopia)

Procedure methodology

HISTORY AND COMPLETE OCULAR EXAMINATION

⬇

PATIENTS SATISFYING THE INCLUSION CRITERIA

⬇

INFORMED CONSENT

⬇

PATIENTS RANDOMLY DIVIDED INTO 2 GROUPS

⬇

ONE GROUP GIVEN INTRAVITREAL BEVACIZUMAB AND THE OTHER GIVEN INTRVITREAL RANIBIZUMAB AT MONTHLY INTERVALS FOR 6 MONTHS

⬇

COMPLETE OPHTHALMIC EVALUATION AND OPTICAL COHERENCE TOMOGRAPHY(OCT) DONE AT EACH VISIT ALONG WITH FFA DONE AT FIRST VISIT AND AFTER 6 MONTHS

⬇

ANALYSIS AND COMPILATION OF DATA

⬇

COMPILATION OF RESULTS

Statistical analysis

Patient's protocol was recorded in data collection form. Data will be analyzed by the statistical package for the social sciences (SSPS for windows, version 24.0),quantitative data was expressed as the mean±SD (standard deviation) and qualitative variables were expressed using percentages. We applied Student's paired t-test for equal or unequal variances, the p-value of <0.05 for 1-tailed hypothesis was considered statistically significant to reject the "null hypothesis".

III. Result

From June 2019 to October 2020 , a total of 30 participants were randomized to receive intravitreal bevacizumab (n=15) or ranibizumab(n=15).The extensive inclusion and exclusion criteria of the study protocol caused the prolonged study period.

In general, ocular and demographic characteristics did not differ between treatment groups.(Table 1).Only a difference in gender distribution was noted with 4 males and 11 females in the bevacizumab group and 7 males and 8 females in the ranibizumab group.(Table 3;graph 3a)

In addition,2 participants in the ranibizumab group and 1 in bevacizumab group dropped out of study before the final 6-monthly assessment but they were replaced by the another 3 participants in the respective groups. No difference was found in the mean number of injections between treatment groups for participants who completed the entire study protocol.

Patients in the bevacizumab group and ranibizumab group both received 6 injections each .The mean follow up time between visits was 29.7+1.4 days in the bevacizumab group and 29.5+1.1 days in the ranibizumab group.

The mean age of patients in the bevacizumab group was 54.47+4.7 yrs and the mean duration of diabetes mellitus was 9.13+6.17 yrs. In the ranibizumab group ,the mean age of patients was 61.07+8.89 yrs and the mean duration of diabetes mellitus was 10.13± 6.15 yrs.(Table 2;graph 2a;table 4;graph 4a).

In the bevacizumab group diabetic retinopathy was in the pre-proliferative stage in 12 (80%) of the enrolled patients and in the proliferative stage in the remaining 3(20%).In the ranibizumab group diabetic retinopathy was in the preproliferative stage in 11 (73.33%) of the enrolled patients and in the proliferative stage in the remaining 4(26.67%).(Table 5;graph 5a).

Table no 1: Baseline characteristics

BASELINE CHARACTERISTICS	BEVACIZUMAB(n=15)	RANIBIZUMAB(n=15)
1.Mean age (SD)yrs	54.46 ± 9.022yrs	61.06+8.89yrs
2.Gender,no.(%)		
MALE	4(26.67%)	7(47.67%)
FEMALE	11(73.37%)	8(53.33%)
3.Mean visual acuity of the study eye	0.85 ± 0.17	0.71+0.21
4.Mean central macular thickness(μm)	521 ± 138.486 μm	484.2+129.534 μm
5.Mean IOP(SD)mmHg	17.2 ± 4.45 mmHg	16.4+9.11 mmHg
6.Mean duration of diagnosis of diabetes(SD)yrs	9.133 ± 6.17yrs	10.133+6.151yrs
7.Diabetic retinopathy severity,no.(%)		
MILD NPDR	2(13.3%)	1(6.67%)
MODERATE NPDR	7((46.6%)	4(26.67%)
SEVERE NPDR	3(20%)	6(40%)
PDR	3(20%)	4(26.67%)

The control visits after the injection revealed no complications or side effects considered to be caused by the anti-VEGF agent itself. Intraocular pressure changed minimally over the course of 6 months in both the bevacizumab and ranibizumab group. The mean IOP post bevacizumab injection was 17.3+2.37mmHg compared to the pretreatment mean IOP of 17.2+4.45mmHg. The mean IOP post ranibizumab injection was 16.67+2.94mmHg compared to the pretreatment mean IOP of 16.4+9.11mmHg.

The mean BCVA was 0.85+0.176(42.4+8.83 letters) preceding the bevacizumab injection and increased to 0.62+0.11(53.67+5.81 letters) at the control visit. The mean CSMT of 521+138.46 before bevacizumab injection decreased to 409+111.06 after the treatment. The change in BCVA and CSMT both was found to be statistically significant.(*p value=0.001)* **.(**Table 6)

In the patients given ranibizumab, pretreatment mean BCVA of 0.71+0.21(49+9.69 letters) increased to 0.48+0.19(60.67+9.611letters) after the treatment and the pretreatment mean CSMT of 484+129.53 declined to a level of 372+111.32 after the treatment. Statistical analysis revealed a significant change both in BCVA and CSMT(*p value=0.0017)(*Table 7).

The mean of BCVA change was 0.23+0.11(11.27+3.02 letters) in the bevacizumab group and 0.23+0.02(11.67+2.01 letters) in the ranibizumab group,which was statistically insignificant.(*p=0.064).*

The mean of CSMT change demonstrated a value of 111.668 following bevacizumab injection and 112 after ranibizumab injection, which was statistically insignificant. (*p=0.075).*

Table 6. Visual Acuity and Central Subregional Macular Thickness Values of Subjects Before and After Intravitreal Bevacizumab Injection for Clinically Significant Diabetic Macular Edema

			Pretreatment	Post treatment	P-value
Visual acuity	LogMar	M+SD	0.85+0.176	0.62±0.11	0.001
		Range	0.6-1.2	**0.5-0.8**	
	Letter score	M+SD	42.34+8.83	53.67+5.81	
		Range	25-55	45-60	
Macular thickness(μ***m***)		M+SD	521±138.46	409.332±111.06	
		Range	310-731	278-589	

Table 7. Visual Acuity and Central Subregional Macular Thickness Values of Subjects Before and After Intravitreal Ranibizumab Injection for Clinically Significant Diabetic Macular Edema

			Pretreatment	Post treatment	P-value
Visual acuity	LogMar	M ±SD	0.71±0.21	0.48±0.19	0.0017
		Range	0.3-1.0	0.2-0.8	
	Letter score	M±SD	49±9.69	60.67±9.611	
		Range	35-70	45-75	
Macular thickness(μ***m***)		M ±SD	484±129.53	372±111.32	
		Range	310-742	267-635	

Table 8: Primary outcomes after 6 months

	Bevacizumab(n=15)	**Ranibizumab(n=15)**
Visual acuity at baseline,letters	42.3 ± 8.83	49 ± 9.69
Mean change in visual acuity of study eye,letters		
Month 1	2.33 ± 0.2	3.33 ± 0.28
Month 2	8.7 ± 1.71	8 ± 1.29
Month 3	13.37 ± 1.31	10 ± 0.34
Month 4	16.03 ± 1.85	16 ± 2.38
Month 5	15.03 ± 0.2	14.67 ± 1.14
Month 6	11.27 ± 3.02	11.67 ± 2.01
Visual acuity at 6 months,letters	53.67 ± 5.81	60.67 ± 9.61
Central area thickness at baseline, μm	521 ± 138.486	484.2 ± 129.534
Mean change in central area thickness,μm		
Month 1	41 ± 2.80	56.067 ± 5.69
Month 2	68 ± 2.80	80.14 ± 4.67
Month 3	131 ± 27.14	131.14 ± 43.32
Month 4	166 ± 50.42	164.87 ± 41.51
Month 5	164 ± 18.88	176.94 ± 47.36
Month 6	111.668 ± 12.36	112 ± 13.78
Central area thickness at 6 months,μm	409.33 ± 111.06	372.6 ± 111.32

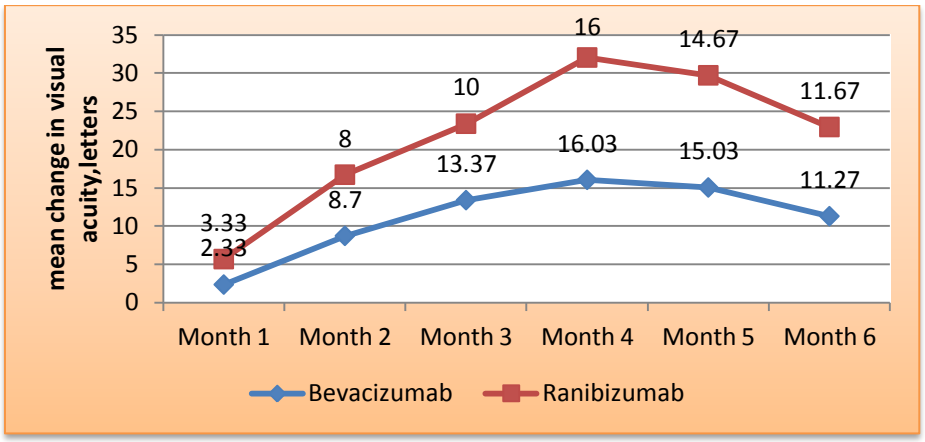

Figure 1. Graph showing mean change in visual acuity from baseline to month 6 in patients treated with bevacizumab and ranibizumab.

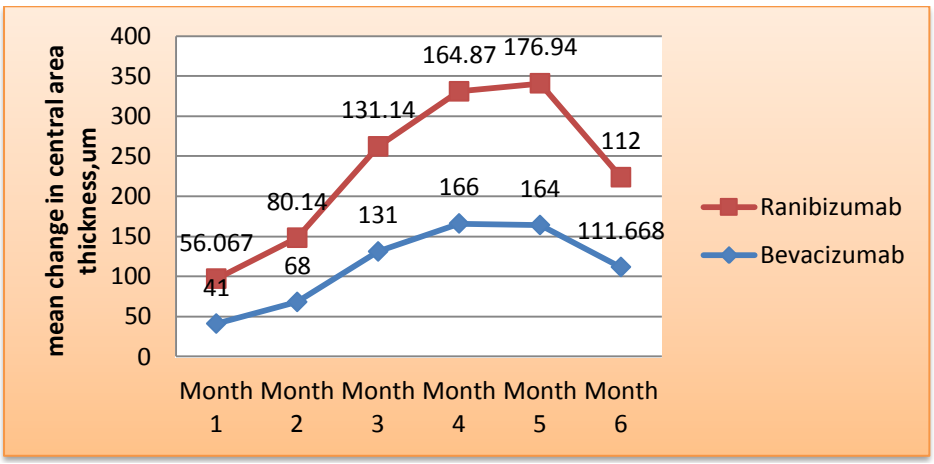

Figure 2. Graphs showing mean change in central area thickness from baseline to month 6 in patients treated with bevacizumab and ranibizumab.

Cost effectiveness

Table 8 shows the unitary and annual costs relative to diabetic retinopathy treatment. The only cost difference between the two drug groups was the drug value. The total unitary cost per injection of ranibizumab was Rs 2,206 and that of bevacizumab was Rs 950. The total annual cost (vial cost + direct costs) of the ranibizumab treatment was Rs 26,472 and Bevacizumab treatment was Rs 11,401. Our study showed that there was no significant difference in effectiveness between the two drugs. Despite the cost differences, none of the treatment strategies was better.

IV. Discussion

VEGF has been implicated as an important factor in the pathogenesis of DME. Hypoxia and hyperglycemia were shown to stimulate its secretion from the retinal pigment epithelial cells, which subsequently impaired the permeability of retinal vessels by increasing the phosphorylation of tight junction proteins. Its levels in vitreous are found to be significantly elevated in eyes with DME. Additionally, VEGF concentrations are found to be higher in eyes with extensive macular leakage compared with eyes with minimal leakage. Therefore, anti-VEGF drugs represented a great breakthrough in the treatment of DME, offering an adjunctive therapeutic option. They reduce vascular leakage and improve the function al outcomes in diabetic patients. Three VEGF inhibitors pegaptanib, ranibizumab, and bevacizumab have been recently launched.

Bevacizumab has attracted more interest than other VEGF inhibitors because of its low cost when considering the number of injections that are necessary at 4–6-week intervals. However, it is licensed for metastatic colorectal cancers, not for intraocular use. In the literature, there are many studies with different study designs and patient groups evaluating the effect of bevacizumab on DME and the majority of them have demonstrated beneficial effects. One of the largest series reported by the Pan-American Collaborative Retina Study Group19 showed a decrease of macular thickness from 466.5 to 322.2 mm at the 1st month and an

increase of visual acuity from 20/150 to 20/100 when intravitreal bevacizumab was applied as primary treatment in 139 eyes with diffuse DME. The study of Kook et al., which also included a large study group of 126 patients with chronic DME like our study, detected a mean macular thickness decrease of 72 mm and a mean change of + 5.2 ETDRS letters at the 6th week control.

In our study, 4–6 weeks after bevacizumab treatment, the Mean visual acuity change was + 2.33ETDRS letters and the mean change in macular thickness measurements was 41 mm. The results of Kook et al. are similar to our findings. The better results of Pan-American Collaborative Retina Study Group may be attributed to the application of intravitreal bevacizumab as primary treatment and shorter duration of DR, compared with our patient group.

Ranibizumab demonstrated an increase of 7.8 ETDRS letters in visual acuity and a decrease of 197.3 mm in the mean CSMT at the 3rd month control according to the preliminary study of Chun et al. Querques et al. observed a reduction of CSMT from 468 to 358.50 mm at the end of 56 days after 1 dose intravitreal ranibizumab injection. In our study, intravitreal injection of ranibizumab to the same patient group demonstrated a mean value of 131.14 mm in CSMT, despite the uncontrolled period and the longer duration of DME. The median visual acuity change was + 8 ETDRS letters at the 4–6 weeks control. These results are in accordance with the 1-month results of the ranibizumab monotherapy group in the RESTORE study. They reported an increase of 6.1 letters in median BCVA and a decrease of 103 mm in median central retinal thickness.

In this small prospective study, we detected that the median change in visual acuity was higher (11.67+2.012ETDRS letters) after ranibizumab injection compared with bevacizumab injection (11.37+3.02 ETDRS letters), which was statistically insignificant(P = 0.58). It was also of note that ranibizumab provided a similar reduction in macular edema as provided by bevacizumab, although the duration of DME was longer (Table 3) (P = 0.064).

Our study indicates that both bevacizumab and ranibizumab are effective in reducing DME and increasing the BCVA in the short-term follow-up, but bevacizumab is more cost effective.

Since the first reported use of bevacizumab in 2005, the off-label use of bevacizumab for DR treatment has increased worldwide because of its low cost. Its use has increased after the evidence of the non-inferiority of this drug in comparison with ranibizumab in the CATT and IVAN studies. As the commercially available vial is superior to the necessary intravitreal dose, the repackaging of bevacizumab becomes possible and attractive when considering the cost reduction. However, repackaging could increase the risk of contamination, besides a hypothetical reduction in the efficacy of the drug.

This economic evaluation indicated that bevacizumab is more cost-effective than ranibizumab. Other published studies found similar results. Raftery et al. evaluated the cost-effectiveness of the two drugs from a British health system (NHS – National Health System)perspective, using cost data from 2005. Their results showed that ranibizumab was not cost-effective when compared to bevacizumab. Ranibizumab would have to be 2.5 times more effective to be more cost-effective than bevacizumab. They also demonstrated that the adverse events had a minimal impact on the cost-effectiveness values.

Another cost-effectiveness study comparing the two drugs was conducted by Patel et al. from an American health system perspective . These authors demonstrated that bevacizumab use was 95% more cost-effective than ranibizumab in neovascular AMD treatment. The dominance of one drug over another occurs if one of them is less effective and has a higher cost. The lower cost strategy predominates over the higher cost when there is equivalence in effectiveness. There was no dominance of any strategy evaluated in this study.The effectiveness values included were based on the CATT study. This study showed no statistically significant differences in effectiveness of the strategies used.

Therefore, bevacizumab may be considered as more cost-effective since its cost is lower. Considering the much lower cost and repackaging, we concluded that the best strategy for Diabetic retinopathy treatment was the bevacizumab treatment.

It is known that complications may modify the treatment course, increasing costs and consequently influencing the economic evaluations. However, the procedures related to the analyzed treatments are identical, and the only difference is the type of drug being injected. Studies have demonstrated that complication rates are very similar for the two drugs.Furthermore, complication rates were very low which would not have a significant impact on outcomes.

However, our findings should be confirmed with larger, planned, randomized,long-term studies.Our study with limited number of patients indicates that both bevacizumab and ranibizumab are effective in reducing the DME and increasing the BCVA in the short-term follow-up.

V. Conclusion

This study indicates that bevacizumab is cheaper and more affordable in India. Bevacizumab is available in 100 mg and 400 mg (25mg/ml) vials (intraocular dose required is 1.25mg in 0.05ml) and thus upto

30 doses can be prepared from a single vial. Whereas ranibizumab is available as 10 mg/ml or 0.5mg dose single use vial and seems expensive to patients in India.

Bevacizumab is used as off-label drug by ophthalmologists (Drug controller general of India banned it in Jan 2016) and Ranibizumab is FDA- approved drug indicated in DME/DR (April 15, 2017).

The post cluster endophthalmitis cases in bevacizumab occur because of sub optimally compounded bevacizumab or fake bevacizumab, sterilization failure due to multiple doses prepared from same vial and deviation from asepsis during the procedure.

Numerous trials worldwide have shown Bevacizumab (CATT trial, IVAN trial) injection in the eye to be non-inferior to Ranibizumab in terms of efficacy and safety.

Limitations of this study can be emphasized as having less number of study subjects and cost of the treatment. So a long term, multicentric study with more study subjects, follow-up visits and study duration is the need of the coming future.

Our study indicates that both bevacizumab and ranibizumab are effective in reducing DME and increasing the BCVA in the short-term follow-up, but bevacizumab is more cost effective.

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