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# Comparative Evaluation of Pan Anti-VEGF with Selective Anti-VEGF with Laser for Diabetic Macular Edema in Indian Eyes: A Randomized Prospective Study

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### Abstract

**Background**: To evaluate intravitreal 0.5 mg ranibizumab plus laser with 0.3 mg pegaptanib plus laser with focal/ grid laser alone for treatment of diabetic macular edema (DME)

**Methods:** A total of 45 study eyes with DME involving the fovea and visual acuity (VA) of 20/32 or worse were randomized into three groups, ranibizumab 0.5 mg + prompt laser (Group 1), pegaptanib sodium 0.3 mg + prompt laser (Group 2) and laser alone (Group 3) with 15 eyes in each study arm. Retreatment was based on optical coherence tomography measurements and VA changes.

**Results:** The mean VA change ( $\pm$  standard deviation) at 1 year in Groups 1, 2 and 3 were 10.4 $\pm$ 2.1, 7.6 $\pm$ 2.3 and 2 $\pm$ 2.7 letters (p<0.001) respectively on a standardized ETDRS chart. There was no significant difference between the VA gain between Group 1 and 2 at 1 year (p=0.189) however significant difference existed between Groups 1 and 2 when compared to Group 3 (p=0.0001).

**Conclusions:** Ranibizumab and Pegaptanib with prompt focal/grid laser proved to be more effective than prompt focal/grid laser alone in treatment of center involved DME. There was no statistical difference in the visual gain achieved in the two intravitreal groups.

**Keywords:** Diabetic macular edema; Ranibizumab; Pegaptanib; Laser photocoagulation

# Introduction

Diabetic mellitus (DM) is a common metabolic disorder characterized by sustained hyperglycemia of variable severity, secondary to lack, diminished efficacy, or both of endogenous insulin. Diabetic retinopathy is commoner in type 1(40%) than in type 2 DM (20%) and is the most common cause of legal blindness between ages of 20 and 65 years. Involvement of fovea by edema and hard exudates or ischemia is the most common cause of visual impairment in diabetic patients particularly those with type 2 DM [1,2]. The exact cause of diabetic micro vascular disease is unknown. It is believed that exposure to hyperglycemia over extended period results in number of biochemical and physiologic changes that ultimately cause vascular endothelial damage. Specific retinal vascular changes include the loss of pericytes and basement membrane thickening, which compromises the capillary lumen, as well as decompensation of the endothelial barrier function. Focal/grid photocoagulation, the current standard care for diabetic macular edema (DME), has been the mainstay of treatment since its benefit was demonstrated in the Early Treatment Diabetic Retinopathy Study (ETDRS) in 1985 [1]. Other treatment modalities, including anti-vascular endothelial growth factor (VEGF) therapy and steroids, alone or in combination with laser, are under investigation [3, 4]. Recent trials involving anti vascular endothelial growth factor (VEGF) alone or in combination with laser have demonstrated the possibility of better visual gain in DME patients as compared to laser alone [5-7]. The rationale for anti-VEGF therapy for DME is based on the finding that VEGF levels are increased in the retina and vitreous of eyes with diabetic retinopathy [8]. We observed however most studies had fixed regimens of administration and hence a need for a trial with injections being administered on an 'as needed' basis was felt. There also was no study comparing a pan anti- VEGF like bevacizumab and ranibizumab with a selective anti-VEGF like pegaptanib sodium in patients of center involved DME.

Ranibizumab (LUCENTIS, Genentech, South San Francisco, CA) is a humanized antibody fragment that binds to VEGF-A isoforms of VEGF, thereby preventing binding of VEGF-A to the receptors. Ranibizumab for centre-involving DME is administered as an intravitreal injection (IVT) with optimum dosing intervals still to be determined from ongoing trials3.

Pegaptanib sodium (MACUGEN, Eyetech Pharmaceuticals, Inc. and Pfizer Inc, New York, NY) is a ribonucleic acid aptamer that selectively targets the VEGF165 isoform that is currently approved in a number of countries worldwide for the treatment of neovascular age-related macular degeneration (AMD). Phase II trial results of pegaptanib in subjects with DME have been reported, and it is currently being evaluated in phase III trials for treatment of DME [9]. The administration of anti- VEGF drugs rapidly reduces the macular edema and leads to a more rapid visual acuity improvement, whereas slower benefit accrues over time as a result of laser treatment. In addition, the lessening of edema due to the anti- VEGF drug will also make applying laser more effective. Also, laser treatment theoretically should reduce the number of required injections by permanently 'sealing' the leaking aneurysms. Hence the need for conducting this study where we

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evaluated the combination therapy of anti-VEGF injections and laser with only laser photocoagulation in DME.

# Materials and Methods

We conducted a prospective study on patients being examined and treated at our vitreo-retinal facility at Dr. Rajendra Prasad Centre of Ophthalmic Sciences, AIIMS, New Delhi between August 2008 to March 2010.

# **Study population**

All patients enrolled were 30 years or older, either type 1 or 2 diabetics willing to give written informed consent. The inclusion criteria for the study eye was any grade of Non Proliferative Diabetic Retinopathy with center involving non fractional DME with best corrected visual acuity on ETDRS chart as 20/32 or worse and the central subfield thickness (CSFT) being equal to or more than 250 micron measured on time domain optical coherence tomography (OCT).

The main exclusion criteria were the following

# Study subject

- 1. Unstable control over blood pressure, cardiovascular disease and blood glucose
- 2. Significant renal disease
- 3. Blood pressure > 180/110 (systolic above 180 or diastolic above 110)
- 4. Major surgery within 28 days prior to randomization.
- Patients with major cardiovascular disorders, on treatment, previous history of myocardial infarction, Stroke, transient ischemic attack, or Congestive heart failure patient on treatment.
- 6. Women of childbearing age: Pregnant or lactating.
- 7. Allergy to the investigational drug

# Study eye

- 1. Non diabetic macular edema
- 2. Possibility of another ocular pathology impeding improvement of visual acuity despite improvement of macular edema.
- 3. Significant cataract decreasing visual acuity by more than 3 lines.
- 4. DME treated 3months prior to randomization
- 5. Glaucoma
- 6. History of YAG capsulotomy performed within 2 months prior to randomization.

After enrollment the patients were orally explained about the treatment protocol and a written informed consent was taken. Institutional review board/ethics committee approval and patients' informed consent were obtained for this study. The patients were randomized into one of the following three groups:

- 1. Intravitreal 0.5 mg Ranibizumab plus focal/ grid photocoagulation (Group 1)
- 2.Intravitreal 0.3mg Pegaptanib sodium plus focal/ grid photocoagulation (Group 2)
- 3. Focal/grid photocoagulation alone (Group 3)

The enrolled patients were followed up to 1 yr from baseline every

1 month plus every 7 days post intravitreal injection to monitor adverse reaction. The patients were also asked to report immediately in case of marked redness, pain, sudden drop in vision and any eye discharge.

# **Examination and investigations**

At all follow ups best corrected visual acuity was measured by a masked examiner at 4 meters on an ETDRS chart. Fast macular scans comprising of 6 radial scans 6 mm in length were performed to quantify the edema using the Zeiss Stratus OCT (OCT3) machine (Carl Zeiss Meditec, Inc.,Dublin, CA). At baseline other investigations performed were slit lamp examination combined with stereoscopic viewing of the fundus with a 90D Volk Lens, intraocular pressure (IOP) measurements, clinical picture of fundus and fluoroscein angiography, blood pressure (systolic and diastolic), fasting blood sugar, post prandial sugar, HbA1c and lipid profile.

# Treatment protocol

In Group 1 and Group 2 intravitreal drug (ranibizumab and pegaptanib) was given at baseline and at the first two 1 monthly follow ups. Focal/ grid laser was done 7 days after the baseline injections in Group 1 and 2

Retreatment with injections was considered in Group 1 and 2 after 3 months at every monthly visit. Retreatment with injections was done if either the following criteria were fulfilled

- 1. Visual acuity ETDRS score 12 letters or worse than baseline.
- 2. OCT central subfield thickness  $\geq$  300 micron.
- 3. Macular oedema present clinically.

Follow up laser 7-10 days after intravitreal injections in groups 1 and 2 were done if laser was not done in the previous 3 months and the following two criteria was fulfilled

- 1. OCT central subfield thickness was  $\geq$  300 micron.
- 2. Complete laser (direct treatment to all microaneurysms within areas of oedema and grid treatment to all other areas of macular oedema) was not done previously.

In the Group 3 focal and grid laser was done at the baseline. Retreatment after 3 months was considered if the above criteria fulfilled.

Statement of Ethics: We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

# Results

Between August 2008 to March 2010, 45 eyes belonging to a 34 patients with a mean age of  $53.8 \pm 7.13$  yrs with 53 percent male preponderance with respect to the eyes were recruited. The mean baseline letter score of all the eyes recruited was  $24.6 \pm 4.6$  on standard ETDRS chart read at 4 meters with a mean CSFT of  $387.24 \pm 56.42$  microns. The 45 eyes were randomized into 3 groups of 15 eyes each. Statistical analysis for descriptive statistics was performed using Strata V9.1 statistical software.

# Effect of treatment on visual acuity

The mean visual acuity in letters ETDRS Group 1, Group 2 and Group 3 at baseline were  $24.33\pm4.76$ ,  $24.6\pm4.33$  and  $25\pm4.87$  respectively.

## Intra group analysis

**Six month outcome**: The mean visual acuity in Group 1, Group 2 and Group 3 at 6 month were  $33.53\pm4.67$ ,  $31.26\pm5.16$  and  $27.66\pm4.88$ ETDRS letters with p values of < 0.001 when compared to baseline values with paired't' test. (Figure 1). The mean gain in vision of Groups 1, 2 and 3 were  $9.2\pm2.00$ ,  $6.66\pm2.09$  and  $2.66\pm1.49$  ETDRS letters respectively at end of 6 months

**One year outcome:** The mean visual acuity in Group 1, Group 2 and Group 3 at 1 yr were  $34.73\pm4.56$ ,  $32.2\pm6.13$  and  $27\pm5.14$  ETDRS letters with p values of <0.001 when compared to baseline values with paired- t test. (Figure 1a). The mean gain in vision in Groups 1, 2 and 3 were  $10.4\pm2.1$ ,  $7.6\pm2.3$  and  $2\pm2.27$  ETDRS letters respectively at the end of one year of follow up.

### Intergroup analysis

At end of one year the mean letter gain in Groups 1, 2 and 3 were  $10.4\pm2.09$ ,  $7.6\pm2.26$  and  $2\pm1.25$  ETDRS letters respectively. Intergroup analysis did not reveal statistically significant difference between Group 1 and 2 at end of 1 year (p=0.189). There was however statistically significant difference in the visual acuity gain between both Group 1 and 2 when compared with Group 3 at the end of 1 year (p=0.0001). Hence the injection groups fared better than the laser only group at the end of 1 year of follow up.

# Effect of treatment on Central Subfield Thickness

### Intra group analysis

**Six month outcome:** The CSFT values of Groups 1, 2 and 3 decreased from  $396.2\pm 55.26$ ,  $388.26\pm 50.92$  and  $387.24\pm 56.42$  microns to  $301.33\pm 20.02$ ,  $303.27\pm 9.15$  and  $326.93\pm 44.65$  microns respectively at the end of 6months. (p values <0.001). The mean decrease in CSFT in Groups 1, 2 and 3 were  $94.86\pm 50.09$ ,  $85\pm 52.27$  and  $50.33\pm 38.29$  microns respectively at end of six months.

**One year outcome**: The final CSFT values of Groups 1, 2 and 3 at end of last follow up were 264.8±14.58, 273.47±19.9 and 303.6±48.16 microns respectively which were all statistically significant compared to baseline values. (p value <0.001) (Figure. 1b) The mean decrease in CSFT in Groups 1, 2 and 3 were 131.4±44.30, 114.8±35.51 and 73.66±26.38 microns respectively at end of one year of follow up.

### Intergroup analysis

At end of one year the decrease in retinal thickness was similar in Group 1 and 2 with p value of 0.164. The intergroup analysis of Group 1 vs Group 3 showed a statistically significant difference in the decrease in retinal thickness with p value=0.002. The other injection group that is the pegaptanib arm also showed a significantly more decrease in retinal thickness when compared with Group 3 (p=0.022). Hence both the injection groups were more effective in decreasing the retinal thickness than laser only in our study patients.



Figure 1: a) Bar diagram showing the mean visual acuities of group1, 2 and 3 at baseline, 6 months and 1 year. b) Line plot showing the central subfield thickness trends of groups 1, 2 and 3 through 1 year of follow up. c) Graph showing frequency distribution of intravitreal injections in group 1. d) Graph showing frequency distribution of intravitreal injections in group 2. e) Graph showing frequency of complications in intravitreal groups.

### Number of injections and laser

The frequency of the number of intravitreal injections given in Groups 1 and 2 (Figure 1c and 1d) on statistical analysis showed no significant difference (p=0.6317). The number of sittings of laser given in Groups 1, 2 and 3 were analyzed, however no statistically significant difference was revealed in our study (p=0.063).

## Complications

Adverse events were minimal with minor conjunctival congestion, subconjunctival hemorrhages and occasional floaters being observed in few eyes only. No cases of endophthalmitis occurred during the study. None of the eyes injected had significantly elevated IOP post injection. No occurrence of retinal detachment was reported during the study period. The frequency of complaints were analyzed in between the intravitreal groups for conjunctival congestion (p=0.4963), pain (p=0.4506), subconjunctival haemorrhage (p=0.6205), floaters (p=0.4083) and tearing (p=0.6935) (Figure. 1e). Thus there was no difference in the frequency of complaints noted in the two intravitreal groups.

### Discussion

In this study both ranibizumab and pegaptanib when combined with focal/ grid laser produced greater gain in visual acuity than laser alone at 1 year of follow up. 8 out of the 15 patients receiving ranibizumab and 4/15 of the patients receiving pegaptanib gained at least two lines on the ETDRS chart at 1 year of follow up. The analysis of the patients recruited in our study led us to the following conclusions:

- 1. Visual acuity improvement was statistically significant in both ranibizumab and pegaptanib groups at end of one year.
- 2. Ranibizumab and Pegaptanib groups fared better in the number of letters gained at the end of one year when compared to the laser only group and the difference was statistically significant. In between the two injection groups the difference was not statistically significant.
- 3. There was a statistically significant drop in CSFT in all three groups at the end of one year. However the injection arms were more effective than the plain laser arm in our study eyes.

Our study although limited by the small sample size showed the beneficial effect of anti- VEGF drugs in improving the visual outcome of patients of DME. The effectiveness of ranibizumab is supported by primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2). This study showed that during a span of 6 months, multiple ranibizumab injections by had a significantly better visual outcome than focal/grid laser treatment in patients with DME [10].

Similarly the safety and efficacy of pegaptanib were assessed in a randomized, sham controlled, double-masked, Phase 2 trial enrolling 172 diabetic subjects with DME affecting the center of the fovea by Cunningham E T Jr et al. and they concluded that 0.3 mg pegaptanib was significantly superior to sham injection. It also suggested that a selective anti- VEGF may be better suited to a diabetic eye than a pan anti- VEGF especially in eyes having ischemic changes in the macula 5. There are also other studies that have evaluated pegaptanib as monotherapy or in combination with laser in DME [9,11,12].

A recent study by the DRCR, net evaluated intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME) in a multicenter, randomized clinical trial

involving a total of 854 study eyes of 691 participants with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320 and DME involving the fovea [3]. The 1-year mean change (±standard deviation) in the visual acuity letter score from baseline was significantly greater in the ranibizumab +prompt laser group (9±11, P=0.001) and ranibizumab + deferred laser group (9±12, P=0.001) but not in the triamcinolone plus prompt laser group (4±13, P=0.31) compared with the sham +prompt laser group (3±13). Reduction in mean central subfield thickness in the triamcinolone+ prompt laser group was similar to both ranibizumab groups and greater than in the sham +prompt laser group. Two-year visual acuity outcomes were similar to 1-year outcomes.

There are isolated reports of macular ischemia being initiated or aggravated by the use of bevacizumab which is a pan VEGF inhibitor [13]. Ranibizumab also being a pan VEGF inhibitor theoretically may have similar side effect though there being no such reports. Pegaptanib being a selective anti VEGF may offer this advantage especially when multiple intravitreal injections were being needed for this chronic disorder. Till date no study have compared pan with selective anti VEGF in DME. Our study showed that combination therapy of intravitreal anti-VEGF and laser was more effective than laser alone at the end of 1 year both in terms of visual acuity and central sub field thickness changes. However no difference could be established between ranibizumab and pegaptanib. Also the combination therapy resulted in decrease of requirement of intravitreal injections. A recent trial (BOLT study) has quoted the median number of intravitreal bevacizumab injections to be 9 in a 1 year study in patients with DME [14].

Newer trials are also exploring the higher dosage regimens of intravitreal anti- VEGF drugs. The changes in capillary perfusion may also need to be explored in the coming trials. The use of anti-VEGF drugs is becoming increasingly more common and some unresolved issues such as the ideal regimen, total duration of treatment, role of combination therapy, and safety concerns with long-term VEGF inhibition deserve further investigations. Multicenter randomized trials with large sample sizes carried over extended periods of time need to confirm and establish the role of anti- VEGF drugs in the near future. Ongoing trials like the RESTORE, RISE and RIDE will further establish the role of anti- VEGF drugs in DME in the near future [15,16,17].

All patients were properly monitored throughout the entire study duration and all tolerated the therapy uneventfully. Strict aseptic precautions were maintained while administering intravitreal injections and no case of endophthalmitis occurred during the study. There were no eyes with significantly raised intraocular pressures. Common complaints/ signs reported/noted in decreasing order of frequency were reddening of eyes, mild ocular pain, sub conjunctival hemorrhage and floaters. None of the eyes showed signs suggestive of increased intraocular inflammation on follow up. In conclusion, the results of our study confirm that anti- VEGF drugs when combined with focal/ grid laser within 7 to 10 days hold promise in ensuring a better visual outcome in patients of DME without causing significant ocular or systemic toxicities.

Our study shows that intravitreal anti- VEGF injection when combined with laser fared better than laser photocoagulation alone in the treatment of DME. Ranibizumab and pegaptanib both showed similar results. However retreatment protocol followed in our study needs to be further refined for which a study with a larger sample size and longer follow up needs to be carried out. Studies in Age related Macular Degeneration have proven the efficacy of combination therapy and with VEGF playing a central role in both the pathologies, we believe combination therapy is here to stay and holds promise in

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the management of DME. We thus recommend a treatment regimen combining the two modalities with retreatment being guided by the visual acuity gain, OCT changes in the macular thickness and clinical assessment of the macular edema.

The limitations of our study include the small number of patients and relatively short follow-up. Further larger multicenter studies are required with longer follow-up (up to 2 years) that also compare laser with laser plus various anti-VEGF drugs. Because of the chronic nature of the underlying disease process and the mechanism of action of anti VEGF agents, monotherapy with anti-VEGF drugs is likely to be non effective.

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