To Compare Photodynamic Therapy with Ranibizumab vs Photodynamic Therapy with Pegaptanib for Subfoveal Choroidal Neovascularization in Age-related Macular Degeneration

Rajvardhan Azad, Neelam Runda, Atul Kumar, Yograj Sharma, Parijat Chandra

ABSTRACT

Purpose: Comparison of efficacy and safety of combination therapy of photodynamic therapy (PDT) with Ranibizumab and Pegaptanib sodium respectively for subfoveal choroidal neovascularization in age-related macular degeneration.

Design: Prospective, comparative, interventional case series.

Materials and methods: Twenty patients received either PDT with 0.5 mg Ranibizumab (group 1; n = 10) or PDT with 0.3 mg Pegaptanib sodium (group 2; n = 10). Three doses of anti-VEGF injections were given monthly followed by reinjections pro re nata basis in both groups. Data recorded included visual acuity (VA), central macular thickness (CMT) by optical coherence tomography and greatest linear dimension (GLD) by angiography at 1 week, 1, 2, 3 and 6 months follow-up.

Results: At 6 months follow-up, groups 1 and 2 showed 13.7 ± 10.25 and 2.8 ± 6.87 letters gain (p = 0.020), CMT decreased to 78.2 ± 61.28 μm and 13 ± 23.83 μm (p = 0.011) and decrease in GLD from baseline was 640 ± 687.6 μm and 584.0 ± 565.15 μm respectively (p = 0.971).

Conclusion: PDT with Ranibizumab demonstrated superior VA and anatomical outcome than PDT with Pegaptanib. Both the modalities were equally safe for patients.

Keywords: Photodynamic therapy, Ranibizumab, Pegaptanib, Age-related macular degeneration.

INTRODUCTION

Treatment of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) has been an area of active research. Earlier TAP study established photodynamic therapy (PDT) as a standard treatment for subfoveal CNV due to AMD.1,2 With the advent of anti-vascular endothelial growth factor (anti-VEGF) drugs there has been a paradigm shift in the favored standard of care treatment of AMD.3 Despite the clinical advantage from anti-VEGF, multiple intravitreal injections are required every 4 to 6 weeks to maintain its efficacy.4,6 Therefore, surfaced the rationale to investigate the efficacy of combination therapeutic approach (PDT and anti-VEGF) that would target different components of CNV, maintain visual acuity (VA), provide anatomic benefits and reduce the number of reinjections, improve compliance and decrease treatment burden in aged population. Combination of PDT with anti-VEGF has been studied in the past, as in FOCUS study (Ranibizumab + PDT)7 and VIA trial (Bevacizumab + PDT).8 Studies comparing Ranibizumab and Bevacizumab are CATT (US)9 and IVAN (UK) trials.10 However, no comparative trials have been done till date between the two FDA-approved anti-VEGFs (Ranibizumab and Pegaptanib). Our objective was to compare the safety and efficacy of the two combination therapies-Ranibizumab with PDT and Pegaptanib with PDT in the treatment of subfoveal CNV due to AMD.

MATERIALS AND METHODS

We conducted a prospective interventional comparative case series to evaluate the safety and efficacy of verteporfin PDT and Ranibizumab vs verteporfin PDT and Pegaptanib in the treatment of subfoveal CNV due to AMD. Twenty patients were enrolled and randomly assigned to study treatment with PDT + Ranibizumab injections (group 1; n = 10) or PDT + Pegaptanib injections (group 2; n = 10). Informed consent was taken from all the study participants.

Key eligibility criteria included age ≥50 years with subfoveal CNV due to AMD, best corrected VA of 20/40-20/200 in the study eye using a standardized protocol refraction with Early Treatment Diabetic Retinopathy Study (ETDRS) charts at a starting distance of 4 m and total lesion size not exceeding 5,400 μm. Fluorescein fundus angiography (FFA) was done in all cases to confirm the diagnosis. All angiographic subtypes of AMD (predominantly classic, minimally classic and occult) were enrolled. Optical coherence tomography (OCT) was done as a baseline investigation and the efficacy of treatment regimen was analyzed during follow-up visits. Patients with uncontrolled diabetes, chronic renal failure and stroke were excluded.
At baseline, eligible patients were randomized in a 1:1 ratio to receive verteporfin PDT and 0.5 mg Ranibizumab injections or verteporfin PDT and 0.3 mg Pegaptanib injections.

**PDT AND INJECTION PROTOCOL**

Patients were treated with standard PDT with verteporfin (Visudyne; Novartis AG, Basel, Switzerland) as follows: Verteporfin (6 mg/m² body surface area) was infused for 10 minutes followed by activation 5 minutes later by a 689 nm diode laser delivering 50 J/cm² at an intensity of 600 mW/cm² for 83 seconds using a spot size of diameter 1,000 μm larger than the greatest linear dimension (GLD) of the lesion. After the procedure, patients were asked to wear protective sunglasses and avoid exposure to sunlight for 48 hours.

Intravitreal anti-VEGF injection was given after 48 hours of PDT. Maintaining strict asepsis protocol, we injected 0.05 ml of 0.5 mg Ranibizumab loaded in tuberculin syringe or 0.3 mg of 90 μl of prefilled syringe of Pegaptanib, 3.5 to 4 mm posterior to the limbus at inferior 6 o’clock position through pars plana route. Patients were observed closely for any adverse events and if intraocular pressure (IOP) was >21 mm Hg then pressure lowering agents were prescribed.

Total of three injections of intravitreal anti-VEGF (Ranibizumab or Pegaptanib) was given as a loading dose every 4 to 6 weeks in both the groups. Further reinjections were administered on pro re nata (as needed) basis. Subjects were followed up at 1 week, 1, 2, 3 and 6 months. At every follow-up, distance VA measurement using ETDRS charts, central foveal thickness (CFT) with OCT (Stratus-OCT, Carl Zeiss Meditec, Dublin, California, USA version 4) and GLD calculated using fluorescein fundus angiography (Zeiss camera) was done. A detailed slit-lamp examination for assessment of inflammation, IOP and blood pressure measurement was also done.

After three loading doses of anti-VEGF, decision to reinject was based on: Loss of five letters with fluid under the macula as detected by OCT, an increase in OCT central macular thickness of at least 100 μm, new onset classic CNV, new macular hemorrhage, or persistent submacular fluid detected by OCT at least 1 month after the previous injection of anti-VEGF.

The primary efficacy outcome was the proportion of eyes that were prevented from loss of less than 15 letters from baseline VA. The secondary outcome measure was the gain in greater than 15 letters from the baseline VA at the end of 6 months. Other outcome measures were mean change in letters from baseline, CFT, and greatest linear dimension, requirement of reinjection and assessment of rise in blood pressure and IOP and occurrence of endophthalmitis.

Descriptive statistical analyses to determine mean and standard deviation were performed using SPSS version 15. VA measurement done by ETDRS charts were converted to corresponding logMAR values. In the case of unrelated samples, the Mann-Whitney test was used. To determine a significant trend within the variables in each group Wilcoxon signed rank test and Friedman test was used. Fischer’s exact test was used for analyzing categorical variables. p < 0.05 was considered statistically significant.

**RESULTS**

All 20 patients completed 6 months of follow-up. Number of injections administered was 3.1 ± 0.32 in both the groups. Baseline study eye characteristics are shown in Table 1.

VA outcomes: Both the combination groups prevented the loss of 15 letters or more from baseline at the end of 6 months in all the 20 patients. The proportion of patients who at 6 months gained greater than 15 letters from baseline VA score favored PDT + Ranibizumab group over PDT + Pegaptanib group (Table 2). For mean change in the baseline VA, the clinical benefit achieved in PDT + Ranibizumab group when compared with PDT + Pegaptanib group was evident in the second month of treatment (15.5 ± 12.57 letters vs 2.50 ± 9.20 letters respectively, p = 0.005). At 6 months the difference between the two groups had reached 10.9 letters (a mean gain from baseline of 13.7 letters in PDT + Ranibizumab group vs a gain of 2.8 letters in PDT + Pegaptanib group; p < 0.020) (Fig. 1).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PDT + ranibizumab (n = 10)</th>
<th>PDT + pegaptanib (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity (no. of letters)</td>
<td>45 ± 15.84</td>
<td>51 ± 19.32</td>
</tr>
<tr>
<td>CNV lesion subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly classic</td>
<td>8 (80%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Minimally classic</td>
<td>1 (10%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Occult with no classic</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Greatest linear dimension (microns)</td>
<td>3198.0 ± 1199.53</td>
<td>4100 ± 1132.55</td>
</tr>
<tr>
<td>Central foveal thickness (microns)</td>
<td>304.9 ± 50.45</td>
<td>303 ± 52.32</td>
</tr>
</tbody>
</table>

**Abbreviations:** PDT: Photodynamic therapy; CNV: Choroidal neovascularization
To Compare Photodynamic Therapy with Ranibizumab vs Photodynamic Therapy with Pegaptanib

OCT outcomes: Difference between treatment groups for the VA outcomes were reflected in the difference in the change in the CFT from baseline. OCT measurements were taken at 1 week, 1, 2, 3 and 6 months. At 6 months significant decrease of 78.2 ± 61.28 μm in the CFT from baseline was noted in the PDT + Ranibizumab combination compared to a decrease of 13.0 ± 23.83 μm in the PDT + Pegaptanib group (p < 0.014). This difference in the decrease in CFT was first noted at the third month after the third anti-VEGF injection (80.8 ± 58.83 μm in group 1 compared to 14.9 ± 25.96 μm in group 2 (p < 0.005) (Fig. 2).

Angiographic outcomes: Patients underwent angiographic evaluation at baseline and 1, 2, 3 and 6 months. The treatment groups were well-balanced for patients’ anatomic characteristics of the choroidal neovascularization lesion (angiographic type and greatest linear dimension) in the study eye. At 6 months the decrease in the greatest linear dimension from baseline was 640.0 ± 687.6 μm in Ranibizumab combination compared to 584.0 ± 565.15 μm in Pegaptanib combination (p = 0.971) (Fig. 3).

Adverse events outcomes: There were no notable differences among treatment groups in the occurrence of adverse events. At 6 months the mean systolic and diastolic blood pressure was 135.2 ± 19.5 and 82.2 ± 6.69 mm Hg in group 1 compared to 136.2 ± 4.56 and 81.4 ± 6.11 mm Hg in group 2 (p = 0.85 for systolic and p = 0.783 for diastolic blood pressure). No serious systemic adverse events were observed.

There was no evidence of endophthalmitis or uveitis in either group. The mean IOP at 6 months follow-up was 15.2 ± 1.68 mm Hg in group 1 compared to 15.2 ± 1.93 mm Hg in group 2 (p = 1.00).

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Table 2: Visual acuity changes from baseline after 6 months

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>PDT + ranibizumab (n = 10)</th>
<th>PDT + pegaptanib (n = 10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of letters change from baseline</td>
<td>13.7 ± 10.25</td>
<td>2.8 ± 6.87</td>
<td>0.020</td>
</tr>
<tr>
<td>≥15 letter increase</td>
<td>6 (60%)</td>
<td>0 (0%)</td>
<td>0.0108</td>
</tr>
<tr>
<td>≥30 letter increase</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>≥15 letter decrease</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

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Fig. 1: Mean VA change from baseline across time. PDT + ranibizumab group showed significant improvement in VA (p = 0.006 at month 2, p = 0.016 at month 3 and p = 0.020 at month 6) over PDT + pegaptanib group.

Fig. 2: Mean change from baseline in central macular thickness. PDT + ranibizumab showed significant decrease in macular thickness (p = 0.005 at month 2, p = 0.011 at month 6) over PDT + pegaptanib combination

Fig. 3: Mean change in greatest linear dimension across time. No significant difference in the decrease in greatest linear dimension was noted between two combination therapies (p = 0.089 at month 1, p = 0.971 at month 6)
Only one patient needed third injection in each treatment group.

DISCUSSION

The results of our study showed that both the combination therapies prevented moderate visual loss of 15 letters or more and were safe. However the VA benefits observed with Ranibizumab + PDT was superior to Pegaptanib + PDT. At 6 months, the most notable VA benefits of Ranibizumab combination included a greater proportion of patients gaining 15 letters or more and a greater improvement in the mean number of letters from baseline. In our study the Ranibizumab combination group achieved gain in 15 letters or more from baseline in larger proportion of patients in comparison to FOCUS study (60 vs 23.8%).7 Also the mean improvement in the number of letters from baseline were more in our study (13.7 ± 10.25 vs 4.9 ± 14.7 letters). The VA benefits observed with Ranibizumab combination were accompanied by corresponding benefits of decrease in CFT with OCT. These functional and anatomic benefits were noted first after the third anti-VEGF injection at third month and persisted throughout the 6 months period. In comparison to MARINA study11 where decrease in the CFT was 123 μm at 12 months, our study had a comparable 80 μm decrease at 6 months in Ranibizumab combination. We found no statistically significant difference in the reinjection rate between the two groups. Most patients showed stabilization of VA, CFT and greatest linear dimension after the third injection. In the recent report by MONT BLANC (Ranibizumab + PDT) study,12 4.8 injections were required in 12-month duration.

Due to lack of studies in literature pertaining to Pegaptanib + PDT combination in treatment of subfoveal CNV, outcomes could not be comparatively analyzed with other studies. Calvo-Gonzalez et al13 studied Pegaptanib + PDT combination in predominantly classic juxtafoveal CNV which showed poor visual and anatomic outcomes due to aggressive behavior of juxtafoveal lesions.

No adverse ocular or systemic events were observed in our study. Heier et al showed endophthalmitis in 1.9%, intraocular inflammation in 38%, hypertension in 12.4% and stroke in 3.8% of the patients in FOCUS study.7 In VISION trial14 0.10% of the patients had endophthalmitis, 25% had eye pain and 24% had rise in IOP.

The results of our study demonstrate Ranibizumab + PDT combination superior to Pegaptanib + PDT combination. However, we recommend a controlled clinical trial with larger sample size and longer duration to prove the superiority of Ranibizumab + PDT over Pegaptanib + PDT.

REFERENCES

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