Proton Beam Irradiation with Anti-Vascular Endothelial Growth Factor for Exudative Age-Related Macular Degeneration: 2 Year Results

Lekha Mukkamala, MD,¹ Kabita Mishra, MD, MPH,² Inder Daftari, PhD,² Ala Moshiri, MD, PhD,¹ Susanna S Park, MD, PhD¹

¹Dept of Ophthalmology & Vision Science, University of California Davis Eye Center, Sacramento, CA; ²Department of Radiation Oncology, University of California San Francisco, San Francisco, CA

Purpose

To determine if the combination of low dose proton beam irradiation with anti-vascular endothelial growth factor (anti-VEGF) therapy results in a safe and effective therapy long-term for exudative age-related macular degeneration (eAMD) compared to intravitreal anti-VEGF therapy alone.

Methodology

- **Baseline Characteristics**
  - Of 34 patients initially enrolled, 16 maintained follow up for 2 years and were included in the analysis. Baseline characteristics are shown in Table 1.

- **2 Year Results**
  - Visual acuity (VA) changed minimally over the 2 year study period (Table 2).
  - The number of anti-VEGF injections needed was significantly less in the 24GyE radiation group compared to sham at 1 and 2 years (Figure 1).
  - The proportion of eyes without intra- or sub-retinal fluid was higher in the radiation groups than sham, but was not significant (p=0.17) (Figure 2).

- **Imaging Analysis Results**
  - The size of the CNVM lesion on FA was not significantly different compared to 2 years for the whole cohort (p=0.79) or each group (p=0.68 0.16, 0.10 for sham, 16GyE, and 24GyE, respectively), but the severity of leakage tended to decrease, especially in the radiation groups (Figure 3).
  - There was a trend of increasing size of geographic atrophy (GA) measured on FA at baseline and 2 years (Table 3, especially in the radiation groups. However, the radiation groups had more GA at baseline compared to the other cohorts, but the difference was not significant (p=0.43). GA occurred in areas of previously active lesions (Figure 4 A and B).

- **Baseline Characteristics of Eyes in the 2 Year Analysis by Treatment Group**
  - Table 1. Baseline characteristics of eyes in the 2 year analysis by treatment group

- **Mean Number of Injections Required by Each Treatment Group at Year 1**
  - Table 2. Mean number of injections required by each treatment group at year 1

- **Prevalence and Mean Area in Disc Diameters (DD) of Geographic Atrophy (GA)**
  - Table 3. Prevalence and mean area in disc diameters (DD) of geographic atrophy (GA) at baseline and 2 years, with rate of growth.

- **Extended Follow Up**
  - Most patients (15 of 16) maintained follow up for several years after study exit (Table 4).
  - The number of injections needed averaged over the duration of follow up continued to be significantly lower in the 24GyE radiation group compared to sham (p<0.02, Figure 6).
  - Visual acuity was lower in the 24GyE group (logMAR 1.03) compared to sham (logMAR 0.30) at last follow up, attributed mostly to the presence of GA (p=0.008).

- **Safety Considerations**
  - There were no eyes with severe vision loss (>15 letters), or with vision loss from radiation retinopathy or papillopathy.
  - No cases of radiation-induced cataract progression.
  - 3 patients developed mild retinal vascular changes that may have been due to early radiation retinopathy vs branch retinal vein occlusion, but none were visually significant.

- **Limitations**
  - Small sample size.
  - No standard anti-VEGF agent used.
  - Variable treatment protocol after study exit may influence extended follow up outcomes.

- **Conclusions**
  - Low dose PBT reduced the number of intravitreal anti-VEGF injections in eyes with newly diagnosed eAMD for at least 2 years, without significant safety concerns.
  - Greater progression of GA was noted in radiation groups but this may be due to natural progression of AMD since more GA was noted baseline in the radiation group.
  - A larger multicenter study would be beneficial to determine the role of proton beam therapy for eAMD.

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The authors have no relevant financial disclosures related to this study.

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*Note: The text has been anonymized and modified for clarity and conciseness.*
Methods

- Phase I/II, interventional, prospective, randomized sham-controlled, double-masked study (Clinical Trials ID #NCT01213082)

- Inclusion criteria: Eyes with newly diagnosed active eAMD and best corrected visual acuity (BCVA) of 20/40-20/400 in worse-seeing study eye

- Exclusion criteria: Macular/optic nerve comorbidities, history of head/neck radiation or diabetes

- Each study eye was randomized 1:1:1 to 24GyE, 16GyE, or sham radiation

- Three initial monthly anti-VEGF (ranibizumab 0.5mg or bevacizumab 1.25mg in 0.05ml) injections were given, with PBT administered within 6 weeks of enrollment

- Monthly exams with optical coherence tomography (OCT) were performed, with anti-VEGF treatment given PRN new fluid or hemorrhage by a masked retina specialist for two years.

- Fluorescein angiography (FA) was performed at baseline, 1 and 2 years. The lesion size and area of geographic atrophy (GA) were measured. OCT angiography (OCTA) was performed when available during extended follow up.
Results

- Of 34 patients initially enrolled, 16 maintained follow up for 2 years and were included in the analysis. Baseline characteristics are in Table 1.
- Visual acuity (VA) changed minimally over the 2 year study period (Table 2).
- The number of anti-VEGF injections needed was **significantly less** in the 24GyE radiation group compared to sham at 1 and 2 years (Figure 1).
- The proportion of eyes without intra- or sub-retinal fluid was higher in the radiation groups than sham, but was not significant (p=0.17) (Figure 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham (n=6)</th>
<th>16 GyE (n=4)</th>
<th>24 GyE (n=6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79.1±9.5</td>
<td>74.4±4.1</td>
<td>79.4±6.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Classic CNVM</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mean visual acuity (logMAR)</td>
<td>0.55±0.24</td>
<td>0.59±0.14</td>
<td>0.72±0.37</td>
<td>0.59</td>
</tr>
<tr>
<td>Central macular thickness (µm)</td>
<td>321.8±52</td>
<td>350.0±111</td>
<td>366.4±225</td>
<td>0.88</td>
</tr>
<tr>
<td>Phakic</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
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</table>

Table 1. Baseline characteristics of eyes in the 2 year analysis by treatment group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Change in VA at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=6)</td>
<td>0.55±0.24</td>
<td>0.37±0.18</td>
<td>0.53±0.53</td>
<td>-0.02</td>
</tr>
<tr>
<td>16GyE (n=4)</td>
<td>0.59±0.14</td>
<td>0.49±0.36</td>
<td>0.40±0.42</td>
<td>-0.19</td>
</tr>
<tr>
<td>24GyE (n=6)</td>
<td>0.72±0.37</td>
<td>0.59±0.43</td>
<td>0.74±0.36</td>
<td>+0.02</td>
</tr>
<tr>
<td>TOTAL (n=16)</td>
<td>0.62±0.27</td>
<td>0.49±0.33</td>
<td>0.58±0.44</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

Table 2. Mean visual acuity at baseline, 1 and 2 years. P-values shown are compared to baseline.

Figure 1. Mean number of injections required by each treatment group at year 1 and 2 of study.

Figure 2. Number of eyes in each cohort with (blue) and without (yellow) intra- or sub-retinal fluid on OCT at 2 years.
Results (con’t)

- The size of the CNVM lesion on FA was not significantly different at baseline compared to 2 years for the whole cohort (p=0.79) or each group (p=0.68, 0.16, 0.10 for sham, 16GyE, and 24GyE, respectively), but the severity of leakage tended to decrease, especially in the radiation groups (Figure 3).

- There was a trend of increasing size of geographic atrophy (GA) measured on FA at baseline and 2 years (Table 3), especially in the radiation groups. However, the radiation groups had more GA at baseline compared to the other cohorts, but the difference was not significant (p=0.43). GA occurred in areas of previously active lesions (Figure 4 A and B).

- The volume of subretinal hyperreflective material (SRHM) on OCT was measured at baseline and 2 years. Almost all patients had SRHM at baseline, which resolved in all patients who received radiation. Two of 5 patients had residual SRHM in the sham group.

- OCT angiography (OCTA) performed on a subset of eyes (n=7) identified areas of possible flow on the “CNVM” map (n=3 in sham, 1 in 16GyE, 1 in 24GyE; Figure 5 A and D) and “avascular” map (n=3 in sham; Figure 5 B and E). However, treatment was given only for the presence or absence of subretinal fluid on OCT (n=1 in sham; Figure 5 C and F).

Table 3. Prevalence and mean area in disc diameters (DD) of geographic atrophy (GA) at baseline and 2 years, with rate of growth.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Prevalence</th>
<th>Mean Area (DD)</th>
<th>2 Years Prevalence</th>
<th>Mean Area (DD)</th>
<th>New GA</th>
<th>Prevalence compared to baseline</th>
<th>Rate of Growth (DD/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>5/6 (83%)</td>
<td>0.17±0.1</td>
<td>5/6 (83%)</td>
<td>0.33±0.1</td>
<td>0</td>
<td>0.27</td>
<td>0.04±0.05</td>
</tr>
<tr>
<td>16GyE</td>
<td>1/6 (17%)</td>
<td>0.07±0.0</td>
<td>1/6 (17%)</td>
<td>0.12±0.0</td>
<td>0</td>
<td>0.42</td>
<td>0.42±0.0</td>
</tr>
<tr>
<td>24GyE</td>
<td>4/6 (67%)</td>
<td>0.33±0.1</td>
<td>5/6 (83%)</td>
<td>2.41±2.2</td>
<td>1</td>
<td>0.16</td>
<td>0.39±0.4</td>
</tr>
</tbody>
</table>

Figure 3. Severity of leakage on fluorescein angiogram at baseline and 2 years in each cohort.

Figure 4. Fluorescein angiogram at baseline (A) and 2 years (B) of an eye that underwent 24GyE. The large classic lesion progressed to geographic atrophy.

Figure 5. En face OCTA images of “CNVM” (A, D) and “avascular” (B, E) maps demonstrating areas of possible flow (arrow), with corresponding OCTs (C, F) in patient 1 (A-C) and patient 2 (D-F) in the sham cohort.
Most patients (15 of 16) maintained follow up for several years after study exit (Table 4).

The number of injections needed averaged over the duration of follow up continued to be **significantly lower** in the 24GyE radiation group compared to sham (p=0.02, Figure 6).

Visual acuity was lower in the 24GyE group (logMAR 1.03) compared to sham (logMAR 0.30) at last follow up, attributed mostly to the presence of GA (p=0.008).

**Safety considerations:**

- There were no eyes with severe vision loss (>15 letters), or with vision loss from radiation retinopathy or papillopathy
- No cases of radiation-induced cataract progression
- 3 patients developed mild retinal vascular changes that may have been due to early radiation retinopathy vs branch retinal vein occlusion, but none were visually significant

### Table 4. Characteristics of patients with extended follow up in each cohort.

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=5)</th>
<th>16GyE (n=4)</th>
<th>24GyE (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Follow Up Time</td>
<td>47.7±20.0</td>
<td>48 (p=0.98)</td>
<td>54.2 ± 21.4 (p=0.60)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Study Follow up</td>
<td>23.5±19.1</td>
<td>23.3 (p=0.98)</td>
<td>30.2±21.6 (p=0.59)</td>
</tr>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Acuity</td>
<td>0.30</td>
<td>0.55 (p=0.84)</td>
<td>1.03 (p=0.008)</td>
</tr>
<tr>
<td>Mean Number of</td>
<td>12.2±25.6</td>
<td>3.8±0.5 (p=0.32)</td>
<td>2.5±4.3 (p=0.17)</td>
</tr>
<tr>
<td>Injections Post-Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Number of</td>
<td>20±17.0</td>
<td>11±2.2 (p=0.71)</td>
<td>7±5.7 (p=0.20)</td>
</tr>
<tr>
<td>Total Injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Additional Injections</td>
<td>1</td>
<td>0 (p=0.9)</td>
<td>3 (p=0.55)</td>
</tr>
<tr>
<td>Needed</td>
<td></td>
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</tr>
</tbody>
</table>

![Figure 6. Mean number of injections averaged over the follow up period after study exit (yellow) and the entire duration of follow up (blue).](image)
Conclusions

- Low dose PBT reduced the number of intravitreal anti-VEGF injections in eyes with newly diagnosed eAMD for at least 2 years, without significant safety concerns.

- Greater progression of GA was noted in radiation groups but this may be due to natural progression of AMD since more GA was noted baseline in the radiation group.

- Limitations of the study included small sample size, use of different anti-VEGF agents, and a variable treatment protocol after study exit that may have influenced extended follow up outcomes.

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