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Phase I/II Randomized Study of Proton Beam with Anti–Vascular Endothelial Growth Factor for Exudative Age-Related Macular Degeneration

One-Year Results

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Objective: To assess the safety and efficacy of proton beam therapy (PBT) as an adjunct to intravitreal anti–vascular endothelial growth factor (VEGF) for the treatment of exudative age-related macular degeneration.

Design: Phase I/II, interventional, prospective, randomized, sham-controlled double-blinded study.

Participants: Eyes with newly diagnosed exudative age-related macular degeneration with vision between 20/40 and 20/400 were included. Exclusion criteria included diabetes or other ocular comorbidities affecting vision.

Methods: Eyes were randomized to receive either 16 GyE, 24 GyE, or sham PBT. All eyes had 3 monthly intravitreal anti-VEGF treatments, followed by monthly visits with treatments as needed.

Main Outcome Measures: Mean change in best-corrected visual acuity (BCVA), mean number of anti-VEGF injections, proportion of eyes with >15 letters BCVA decrease, proportion of eyes developing radiation retinopathy or papillopathy, proportion of eyes with cataract progression, and mean changes central retinal thickness on optical coherence tomography and lesion size on angiography at 1 year.

Results: Of 30 enrolled eyes, 22 completed follow-up monthly for 12 months for analysis. The BCVA improved by a mean of 8 letters (0.48±0.36 logarithm of the minimum angle of resolution) overall from baseline. Overall, central retinal thickness decreased from 340±155 to 246±48 ($P = 0.008$) at 12 months. The mean change in BCVA and central retinal thickness was not different among the 3 study groups. The mean number of anti-VEGF injections at 12 months was 6.13 for sham irradiation arm, 5.52 in the 16 GyE arm, and 3.83 for the 24 GyE arm ($P = 0.004$ between sham and 24 GyE). No eye had severe visual loss, radiation retinopathy, or papillopathy.

Conclusions: No safety issue was noted associated with combining 16 GyE or 24 GyE PBT with intravitreal anti-VEGF therapy in eyes with exudative age-related macular degeneration. Overall improvements in BCVA and imaging parameters were not affected by the addition of PBT, but the number of anti-VEGF treatments needed was significantly lower with the addition of 24 GyE PBT. *Ophthalmology Retina 2016;■:1–10 © 2016 by the American Academy of Ophthalmology*

Exudative age-related macular degeneration (eAMD) remains a leading cause of blindness among the elderly in the developed world, and its prevalence will only continue to increase in the coming decades with an aging populace.[1,2] Great strides have indeed been made with the advent of intravitreal anti–vascular endothelial growth factor (VEGF) therapies for eAMD, and visual prognosis of eyes with eAMD has greatly improved. Vision loss can be minimized in a majority of treated eyes with eAMD.[3] Although these intravitreal anti-VEGF treatments are effective and have a relatively favorable safety profile, the current standard of care necessitates frequent monitoring and retreatment with intravitreal injections.[4] This results in a significant burden for patients and for the health care system as a whole. Thus, an unmet need remains in the current era of intravitreal anti-VEGF monotherapy to develop an effective therapy for eAMD that is more sustained without compromising visual benefit. A noninvasive treatment modality to augment the current armamentarium for treating this disorder would be highly desirable if shown to be safe and effective.

The notion of using radiation as treatment for eAMD has existed for some time, based primarily on the principle that radiation targets proliferating cells within the fibrovascular membrane. Several previous trials and case series demonstrated that low-dose radiotherapy was relatively well-tolerated

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in eyes with eAMD but ineffective as a monotherapy in preventing vision loss associated with eAMD.[5,6] Nonetheless, because synergy has been demonstrated between radiation and anti-VEGF therapy in certain tumors,[7,8] a possible synergism between radiation and anti-VEGF therapy in management of eAMD has been explored. The underlying rationale for exploring this combination therapy is that radiation potentially treats both the vascular and avascular components of the choroidal neovascular membrane (CNVM), and VEGF suppression addresses mainly the vascular component of CNVM. Several clinical studies using intravitreal epimacular brachytherapy with vitrectomy combined with intravitreal anti-VEGF for the treatment of eAMD have demonstrated a potential synergism of this combination therapy in terms of a decrease in the number of intravitreal anti-VEGF treatments needed.[9] However, a large multicenter randomized prospective study (CABERNET Study [A Randomized, Prospective, Active Controlled, Study of the Epi-Rad90 Ophthalmic System for the Treatment of Subfoveal Choroidal Neovascularization Associated With Wet Age-Related Macular Degeneration]) showed that the mean visual outcome of eyes with this combination therapy was inferior to eyes treated with intravitreal anti-VEGF monotherapy after 2 years of treatment for eAMD.[10] Whether this negative effect on vision was due to progression of cataract from vitrectomy in eyes with combination therapy or from a direct negative effect of this combination therapy on macular function is unclear.

Proton beam therapy (PBT) is an attractive option for delivering radiation to the macula without surgical intervention. Based on a favorable dose distribution, with a rapid fall-off of outside-the-intended treatment target area, PBT allows a precise localized delivery of radiation to the macula with minimal risk to the surrounding normal retina and optic nerve.[11,12] This feature, of course, is crucial with regard to limiting the occurrence of radiation retinopathy and papillopathy in otherwise healthy eyes with eAMD. Proton beam has been used extensively to treat intraocular tumors, most notably uveal melanoma, with local success rates of $\geq$95%.[13]

Proton beam radiation up to 24 GyE divided in 2 fractions has been used safely as monotherapy to treat eAMD.[14] The authors have completed a small pilot study demonstrating that proton beam irradiation (24 GyE divided in 2 fractions) combined with intravitreal ranibizumab is tolerated in eyes with eAMD with no incidence of radiation retinopathy when followed for $\geq$3 years after treatment.[15] A possible synergism resulting in a more sustained intravitreal anti-VEGF treatment effect was noted among eyes with newly diagnosed eAMD. The current phase I/II randomized, prospective, sham-controlled, double-blinded study was undertaken to test the hypothesis that combining low-dose PBT with intravitreal anti-VEGF therapies is safe and more effective than intravitreal anti-VEGF monotherapy in treating eyes with eAMD. This 1-year interim analysis of this ongoing study was conducted to determine whether the current phase I/II study was large enough to detect efficacy of this combination therapy and to determine whether there are any associated safety concerns.

Methods

This is a phase I/II, interventional, prospective, randomized, sham-controlled, double-blind study. The study enrollment and follow-up examinations were conducted at the University of California Davis Eye Center. The PBT was conducted at the Crocker Nuclear Laboratory at the University of California Davis by the radiation oncology team from the University of California San Francisco (KKM, ID). The study was conducted according to a protocol approved by the Food and Drug Administration (IND 108,360), the Office of Human Research Protection (Institutional Review Board) at the University of California, Davis School of Medicine, and the Office of Radiation Safety at the University of California Davis. The study was registered with www.clincaltrials.gov (Clinical Trials ID # NCT01213082) before enrollment and was conducted in adherence with the Declaration of Helsinki. The study was complaint with the Health Insurance Portability and Accountability Act of 1996.

All study subjects were screened and enrolled among patients seen at the Vitreo-retinal Service at the University of California Davis Eye Center between September 2010 and January 2015. Individuals were considered for study enrollment if the eye had either newly diagnosed eAMD or evidence of recurrent active eAMD. Only eyes with subfoveal or juxtafoveal choroidal neovascularization identified by fundus fluorescein angiography (FA), and with a best-corrected visual acuity (BCVA) of 20/40 to 20/400 were considered for enrollment. The BCVA of the study eye was worse than the contralateral eye at enrollment. Subjects were excluded if they had additional macular or optic nerve comorbidities, a history of diabetes mellitus, or a history of prior head and neck radiation. Subjects who have received intravitreal anti-VEGF treatment in the study eye within the 6 weeks before enrollment were excluded. Eyes with newly diagnosed eAMD eyes were preferred for study enrollment, but eyes with $<$3 prior intravitreal anti-VEGF therapies and with recurrent active eAMD were considered for study enrollment.

All subjects signed a written informed consent at the time of enrollment. All subjects underwent a baseline complete eye examination including BCVA and tonometry. The subjects were randomized 1:1:1 to 1 of 3 arms at enrollment: sham radiation, 16 GyE PBT, or 24 GyE PBT (Fig 1). The randomization was conducted by the unmasked study coordinator using a sequential coin toss, first to determine sham versus PBT, then 1 of 2 doses of PBT if subject was randomized to PBT. Because this is a small study, the total enrollment of each study group was roughly equal throughout the study with variations in enrollment number limited to within 2 subjects relative to the other study groups during the study after accounting for any subjects who were excluded from the study after study enrollment. The first anti-VEGF injection was administered at enrollment. Sham or PBT was administered within 6 weeks of enrollment and delivered in 2 separate fractionated doses 24 hours apart. Radiation was administered at the Crocker Nuclear Laboratory at the University of California Davis. All subjects were seen monthly at the University of California Davis Eye Clinic for a total of 3 monthly intravitreal anti-VEGF treatments (ranibizumab 0.5 mg or bevacizumab 1.25 mg in 0.05 mL). After these 3 monthly intravitreal anti-VEGF treatments, subjects were examined monthly with dilated fundus examination and spectral domain optical coherence