

16-Gy Low-Voltage X-ray Irradiation With Ranibizumab Therapy for AMD: 6-Month Safety and Functional Outcomes

Virgilio Morales Canton, MD; Hugo Quiroz-Mercado, MD; Raul Velez-Montoya, MD; Miriam J. Lopez-Miranda, MD; Andrew A. Moshfeghi, MD, MBA; Eugene M. Shusterman, MD; Peter K. Kaiser, MD; Steven R. Sanislo, MD; Michael Gertner, MD; Darius M. Moshfeghi, MD

■ **BACKGROUND AND OBJECTIVE:** To describe the 6-month safety and preliminary efficacy outcomes of the use of 16-Gy radiation with intravitreal ranibizumab for patients with neovascular age-related macular degeneration (AMD).

■ **PATIENTS AND METHODS:** A single treatment of a non-invasive, externally delivered low-voltage 16-Gy x-ray irradiation was administered in one session through three locations in the inferior pars plana. Optical coherence tomography (OCT) and Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) examinations were performed at 1 week, 1 month, and monthly thereafter, with quarterly fluorescein angiography (FA). After the two initial ranibizumab injections, subsequent injections were administered according to the following criteria: VA decline of 10 ETDRS letters compared with baseline, increase of 100- μ m central foveal thickness on OCT compared with baseline, the development of new submacular hemorrhage, and the development of a new area of classic choroidal neovascularization on FA.

■ **RESULTS:** Twenty-six patients completed a 6-month follow-up. There was no evidence of radiation retinopathy, optic neuropathy, or cataract. The mean baseline ETDRS score was 46.6 letters (range: 5 to 80; standard deviation [SD]: 21.5). At 6 months, the corresponding ETDRS score was 55.6 letters (range: 25 to 80; SD: 18.9) and the mean change in VA was 9.5 ETDRS letters (SD: 10.3). On responder analysis, 96% lost 15 or fewer ETDRS letters, 81% gained 0 or more ETDRS letters, and 50% gained 15 or more ETDRS letters. Patients received a total of 13 ranibizumab injections following two initial injections. At 6 months, patients received an average of 0.5 additional injections following the initial two mandated injections.

■ **CONCLUSION:** A single treatment of externally applied, non-invasive 16-Gy low-voltage x-ray therapy in conjunction with ranibizumab demonstrated an overall improvement of VA in patients with neovascular AMD at 6 months with no radiation-related adverse effects.

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From the Asociacion Para Evitar La Ceguera En Mexico, I.A.P. (VMC, HQ-M, RV-M, MJL-M), Mexico City, Mexico; the Department of Ophthalmology (HQ-M, RV-M), University of Colorado, Denver, Colorado; Bascom Palmer Eye Institute (AAM), University of Miami Miller School of Medicine, Department of Ophthalmology, Palm Beach Gardens, Florida; Oraya Therapeutics, Inc. (EMS, MG), Newark, California; Cole Eye Institute (PKK), Cleveland Clinic, Cleveland, Ohio; and the Department of Ophthalmology (SRS, DMM), Horngren Family Vitreoretinal Center, Byers Eye Institute at Stanford University, Stanford University School of Medicine, Palo Alto, California.

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Address correspondence to Darius M. Moshfeghi, MD, Department of Ophthalmology, Horngren Family Vitreoretinal Center, Byers Eye Institute at Stanford, Stanford University School of Medicine, 2452 Watson Court, Palo Alto, CA 94303. E-mail: dariusm@stanford.edu

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INTRODUCTION

Historically, radiation for neovascular age-related macular degeneration (AMD) has demonstrated minimal efficacy with respect to visual acuity outcomes.¹⁻¹³ However, numerous fluorescein angiography studies have shown the ability of radiation to inhibit choroidal neovascular membrane growth or to induce its regression, giving hope that some form of radiation treatment might prove useful.¹⁻¹³ With the exception of proton beam radiotherapy studies, which demonstrated high rates of radiation retinopathy^{7,13} and optic neuropathy,¹³ no cases of clinically significant radiation retinopathy have been reported following the treatment of choroidal neovascular membranes with a radiation source.^{1-6,8-12} It is believed that inaccurate targeting and/or high treatment volumes accounted for the high retinopathy^{7,13,14} and optic neuropathy^{13,14} rates associated with proton beam radiotherapy.

The targeting issue has been resolved with modern radiation techniques designed specifically for treatment of neovascular AMD.¹⁵⁻¹⁸ Recently, a non-invasive, robotically controlled, low-voltage stereotactic x-ray irradiation system has been designed for the treatment of neovascular AMD (Oraya Therapeutics Inc., Newark, CA).¹⁹ This system is intended for installation in a clinical office without additional shielding requirements and to run off standard wall power,¹⁹ thereby requiring little or no reconfiguration of the physician's facility. When the patient is seated at the device, the treated eye is held in position with a contact lens connected to an active suction apparatus (ie, small syringe).¹⁹ The eye is tracked by infrared cameras using reflective fiducials mounted on the contact lens positioning arm.¹⁹ If the patient exceeds predetermined threshold movements in the X, Y, Z planes or rotational angles, as indicated by actively tracked lens fiducials, the device will gate and will immediately interrupt the delivery of radiation.¹⁹ Additional safety measures include various interlocks designed to prevent unwanted patient interference with system movement, integrated radiation beam-stop and scatter shielding, and emergency shut-off mechanisms.¹⁹

The radiation is delivered during a single treatment session in three separate locations through the inferior pars plana; the x-ray beams overlap on the macula to give the total prescribed dose.¹⁹ We have previously demonstrated that the device delivers the full dose to

the plane of the macula within a 4-mm diameter spot size.^{18,20} The robot positions the x-ray tube so that it is precisely 150 mm from the plane of the macula. A self-tensioning speculum is applied to the lower eyelid to provide scleral exposure, and the x-ray tube is positioned to keep the lens and cornea out of the path of the radiation beams.¹⁷⁻²¹ The doses to the lens (124 to 127 mGy), optic nerve (200 to 237 mGy), and the brain (10.9 to 13.6 mGy) are well within the safety limits of these structures and demonstrate the superior targeting and tracking of this robotically controlled system.^{18,21} The treatment dose has been verified in human cadaver eyes using radiochromic film.¹⁷

The stereotactic external radiation treatment system differs from the strontium-90 (Sr-90) epiretinal brachytherapy approach in two important ways: (1) it is non-invasive^{15,16,19} and (2) it is not user dependent for dose delivery.^{15,16,20} The stereotactic external radiation treatment system is designed to deliver the full treatment dose at a distance of 150 mm from the x-ray source.²⁰ Because the plane of the macula rests exactly this predetermined distance away from the x-ray emitter, based on the eye's axial length, and because the eye is actively held and tracked in the X, Y, Z axes and angular rotation directions, there is precise knowledge of the radiation dose to macular target.¹⁷⁻²⁰ The procedure is robotically controlled, ensuring no deviation in the radiation dose.¹⁷⁻²⁰

By contrast, the Sr-90 epiretinal device is manually held by the surgeon 0.1 mm above the retina for a period of 3 to 5 minutes to deliver 24 Gy.¹⁶ The total dose with the Sr-90 device varies 10% for each 0.1 mm (ie, approximately three sheets of standard paper) increment above the retinal plane.¹⁶ The Z-distance variation associated with the Sr-90 device results in a nonlinear increase or decrease in spot size.¹⁶ The targeting and dosing with the Sr-90 epimacular brachytherapy system are further complicated by the surgical procedure itself, and the requirement for the surgeon to hold the device steadily for a prolonged period of time while the sedated patient is under monitored anesthesia care; the manufacturer of the epimacular brachytherapy system estimates a lateral deviation over an approximately 2-mm radius throughout treatment, making it more difficult to assess targeting accuracy.²²

The current study assesses the feasibility, safety, and preliminary outcomes using the non-invasive, robotically controlled, low-voltage stereotactic x-ray irra-

diation system for treatment of neovascular AMD at a 16-Gy dose, in conjunction with ranibizumab (Novartis Ophthalmics, Inc., Basel, Switzerland).

PATIENTS AND METHODS

Institutional Review Board approval for this phase I, open-label, non-randomized, uncontrolled safety trial was received from Asociacion Para Evitar La Ceguera En Mexico, I.A.P., to perform this study. Additionally, the government of Mexico approved the use of the radiation device for this trial of patients with neovascular AMD.

Study Entry Criteria

Eligible patients included individuals 50 years or older with evidence of subfoveal choroidal neovascularization (CNV) activity secondary to neovascular AMD. Pertinent exclusion criteria included previous laser or photodynamic therapy treatment for AMD and history of diabetes mellitus or elevated fasting blood glucose. Additionally, history of ipsilateral photodynamic therapy was an exclusion criterion.

Examination Protocol

Patients underwent baseline protocol Early Treatment Diabetic Retinopathy Screening (ETDRS) refraction, optical coherence tomography (OCT) testing, and fluorescein angiography (FA). OCT testing was performed monthly and FA testing was performed quarterly, unless there was an unexplained decrease in visual acuity.

Treatment Design

The treatment design consisted of two mandatory intravitreal 0.5-mg injections of ranibizumab at day 0 and day 30, with a single 16-Gy x-ray treatment between days 1 and 14. Additional ranibizumab injections were performed on a monthly basis for the following indications: (1) loss of 10 or more ETDRS letters in conjunction with persistent fluid on OCT compared with previously scheduled visit, (2) increase of 100 microns central foveal thickness on OCT compared with previously scheduled visit, (3) development of a new subretinal hemorrhage in the macula, and (4) development of an area of new classic choroidal neovascularization on FA.

Low-voltage X-ray Treatment System

Oraya Therapeutics, Inc. has developed an externally applied, non-invasive low-voltage x-ray irra-

diation system specifically for the treatment of neovascular AMD. This system consists of the following components: (1) a robotically controlled x-ray tube, (2) a patient interface, (3) an eye stabilizing device that optically couples the patient's eye to the x-ray delivery system, (4) an eye tracking system that monitors X, Y, Z and rotational movements of the eye for dose determination and safety gating, (5) graphical user interface, and (6) treatment planning software. The system is designed to deliver three overlapping 4-mm radiation beams to a specified point in space that corresponds to the patient's macula, as determined by a treatment planning algorithm using globe axial length. Actual dose over the entire macula is calculated from analysis of the ocular movements during the treatment session. Radiation therapy consisted of one fraction of 16 Gy delivered in approximately 15 minutes (approximately 3 minutes of x-ray exposure) over three equal spots in the inferior pars plana.

RESULTS

Twenty-eight patients were enrolled and treated, but one was subsequently excluded from the efficacy analysis because he was discovered to have had central retinal vein occlusion rather than CNV due to AMD. Another subject missed the 6-month follow-up visit, and is consequently not included in the aggregate 6-month visual acuity data presented in this article; however, this subject's injection history is included. Twenty-six patients completed 6 months of follow-up.

Safety

There were no cases of radiation retinopathy, optic neuropathy, cataract advancement, eyelid necrosis, or scleral injury. The only described ocular adverse outcome was an asymptomatic, self-limited superficial punctate keratopathy that resolved spontaneously. No treatment-related systemic adverse outcomes were observed.

Visual Acuity

The mean baseline ETDRS score was 46.6 letters (range: 5 to 80; standard deviation: 21.5 letters). At 6 months, the mean ETDRS score was 55.6 letters (range: 25 to 80; standard deviation: 19.3 letters). There were two subgroups: treatment naïve (n = 16) and previously treated (n = 10). Patients who were treatment naïve demonstrated a mean change from baseline of 10.1

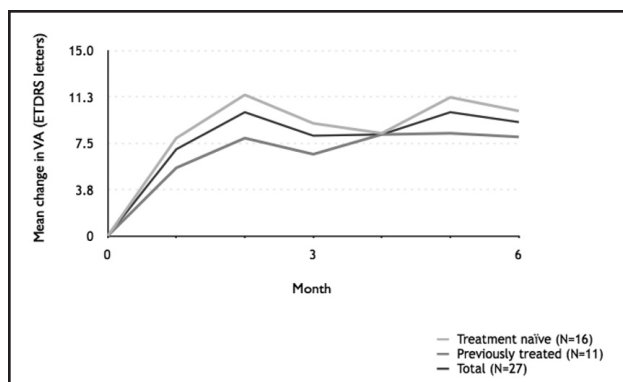


Figure 1. Mean best-corrected visual acuity. EDTRS = Early Treatment Diabetic Retinopathy Study.

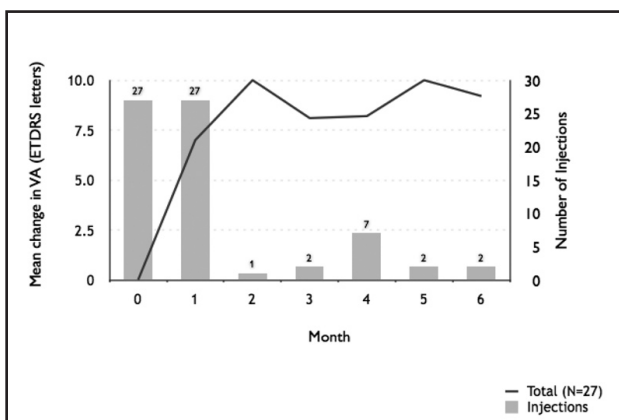


Figure 3. Mean change in visual acuity versus the number of injections. EDTRS = Early Treatment Diabetic Retinopathy Study.

ETDRS letters (standard deviation: 9.4), whereas patients previously treated demonstrated a mean change of 8.7 ETDRS letters (standard deviation: 12.0) (Fig. 1). In the responder analysis for the overall population, 96% lost 15 or fewer ETDRS letters, 81% gained 0 or more ETDRS letters, and 50% gained 15 or more ETDRS letters (Fig. 2). For patients who were treatment naïve, the responder analysis demonstrated that 100% lost 15 or fewer ETDRS letters, 81% gained 0 or more ETDRS letters, and 44% gained 15 or more ETDRS letters (Fig. 2). Similarly, in patients previously treated the responder analysis demonstrated 90% lost 15 or fewer ETDRS letters, 80% gained 0 or more ETDRS letters, and 60% gained 15 or more ETDRS letters (Fig. 2).

Injections

Each patient received two mandatory injections at days 0 and 30. An additional 13 injections were performed, for a total of 67 injections (54 mandatory and 13 as needed) in 27 patients over 6 months (Fig. 3). As a comparison, the patients previously treated had received

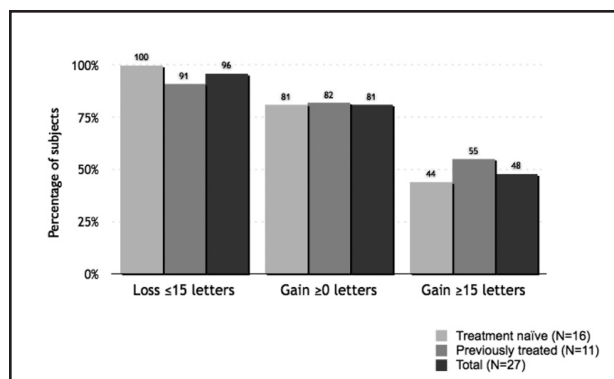


Figure 2. Responder analysis.

a total of 34 injections (mean: 3; range: 1 to 5) prior to study entry.

DISCUSSION

In this phase I, open-label, single-center, non-randomized, uncontrolled clinical trial, externally applied 16-Gy low-voltage x-ray irradiation with front-end ranibizumab load and adjunctive, as-needed injections, has demonstrated safety, a visual acuity response, and the ability to improve patients who are both treatment naïve and previously treated.

The threshold for radiation retinopathy following head and neck radiation for intracranial tumors has been reported to be 45 Gy.²³⁻³¹ These findings were further supported by studies involving radiation directly to the eye.^{7,28,32-39} The Cochrane reviews of external beam radiotherapy for neovascular AMD described no cases of radiation retinopathy or optic neuropathy in 1,154 patients.^{3,12} Similarly, there were no cases of radiation retinopathy reported with Pd-103 plaque brachytherapy⁶ and two cases of self-limited radiation retinopathy associated with Sr-90 brachytherapy for treatment of neovascular AMD.⁸ Only in proton beam therapy for neovascular AMD does there appear to be a significant rate of radiation retinopathy (14.8% to 50%) for treatment doses of 14, 16, and 24 Gy.^{7,13}

When assessing the impact of dose, treatment volume has to be taken into consideration. In the case of dose-limiting toxicity for whole-body irradiation, mortality rates are high at relatively low doses: 100% within 48 hours at 10 Gy, 50% within 2 weeks at 5 Gy, and 50% within 2 months at 2.5 Gy.⁴⁰ Similarly, the onset of radiation retinopathy in the proton beam studies was early,^{7,13} indicative of a large volume of tissue irradiated. It is evident that proton beam radiotherapy de-

livers energy to a treatment volume almost 1,000 times higher than for the stereotactic external radiation treatment system. Even for external beam radiation therapy, which is almost 100 times higher in treatment volume than that observed with stereotactic external radiation treatment system, there were no reported cases of radiation retinopathy,^{3,12} indicating that the threshold for retinal damage to radiation is relatively high.

The stereotactic external radiation treatment delivers 10% to 90% dose of 16 Gy (1.6 to 14.4 Gy isodose curves) that is constrained to an area with a 4-mm radius centered on the macula, resulting in an irradiated tissue volume of 3.14 mm³. The stereotactic external radiation treatment system therapy is robotically controlled and electronically gated for any ocular deviations or head movements that exceed a preset threshold, ensuring that the dose to the plane of the macula is reproducible and unvarying.¹⁷⁻²¹ There is more variability in the surgical Sr-90 epiretinal brachytherapy approach due to the surgeon's movement,^{16,22} yet there is still a low reported incidence of nonproliferative radiation retinopathy. Similarly, due to the lack of a vitrectomy, the highly collimated x-ray geometry, and the beam placement through the inferior pars plana, the rate of cataract progression should also be low with stereotactic external radiation treatment system, as noted in the current report.¹⁷⁻²¹ For all of the reasons stated above, it is also extremely unlikely that the stereotactic external radiation treatment system will result in an under-treatment of the macula. In other words, we have demonstrated that the stereotactic external radiation treatment system has high fidelity with respect to targeting and dose delivery to the plane of the macula with minimal deviation, ensuring a high probability that the macula will receive the intended dose, no more and no less.¹⁷⁻²¹

The visual acuity results were encouraging in the current study. In particular, the responder analysis demonstrated a strong safety profile: 96% lost 15 or fewer ETDRS letters, 81% gained 0 or more ETDRS letters, and 50% gained 15 or more ETDRS letters. The other main point is that the approach described herein was equally effective in patients who were both treatment naïve and previously treated. The MARINA and ANCHOR trials demonstrated the superiority of monthly ranibizumab injections for the treatment of neovascular AMD,^{41,42} and the PIER trial demonstrated inferiority of non-monthly dosing compared with

monthly dosing.⁴³ All three trials demonstrated the benefit of a 3-month ranibizumab loading dose,⁴¹⁻⁴³ and it has been widely assumed that no substantial visual acuity benefit was possible once a patient received this treatment load. In the current study, 11 patients received a total of 34 previous injections (bevacizumab and ranibizumab, mean of 3 injections). Patients who were previously treated in the current study demonstrated that 60% gained 15 or more ETDRS letters.

The treatment durability appears to be enhanced with the use of 16-Gy stereotactic external radiation treatment. Twenty-seven patients received a total of 67 injections (54 mandatory and 13 as needed) over a period of 6 months to achieve a mean gain of 9.5 ETDRS letters (standard deviation: 10.3). These results compare favorably to the MARINA and ANCHOR trials with respect to visual acuity, using only 41.3% of the ranibizumab injections.^{41,42}

Stereotactic, externally applied, robotically controlled 16-Gy x-ray irradiation in conjunction with a loading dose of ranibizumab, and adjunctive, as-needed ranibizumab injections for prospectively defined criteria has demonstrated no adverse effects at the 6-month follow-up in patients who were previously treated or treatment naïve. Visual acuity results in both groups are similar to those reported for monthly ranibizumab treatment regimens, but used only 41% of the injections of a monthly treatment regimen. Longer follow-up is necessary to more fully assess the safety and efficacy profile.

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