TWELVE-MONTH SAFETY AND VISUAL ACUITY RESULTS FROM A FEASIBILITY STUDY OF INTRAOCULAR, EPIRETINAL RADIATION THERAPY FOR THE TREATMENT OF SUBFOVEAL CNV SECONDARY TO AMD

MARCOS P. ÁVILA, MD,* MICHEL EID FARAH, MD,†
ARTURO SANTOS, MD,‡ ZIYA KAPRAN, MD,§
JOÃO PAULO DUPRAT, MD,† BENJAMIN W. WOODWARD, PHD,¶
JEFFREY NAU, MMS¶

Purpose: The purpose of this study was to evaluate the short-term safety and feasibility of intraocular, epiretinal delivery of beta radiation for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration for 12 months. A 3-year follow-up period is planned to assess the long-term safety of the procedure.

Methods: In this nonrandomized, multicenter feasibility study, 34 treatment-naïve patients with predominantly classic, minimally classic, or occult lesions due to subfoveal choroidal neovascularization secondary to age-related macular degeneration received a single treatment with either 15 Gray (Gy) (8 patients) or 24 Gy (26 patients) beta radiation (strontium-90) using a novel intraocular delivery device. Adverse events and safety endpoints were observed and recorded. Visual acuity was measured preoperatively and postoperatively using standard Early Treatment Diabetic Retinopathy Study vision charts.

Results: Twelve months after treatment, no adverse events associated with exposure to radiation were observed. All patients in both 15 Gy (n = 4) and 24 Gy cohorts (n = 17) who met inclusion criteria and were treated according to protocol lost fewer than three lines of vision. Fifty percent (2/4) of the 15 Gy-treated patients and 76% (13/17) of the 24 Gy-treated patients improved or maintained their visual acuity at 12 months. In the 24 Gy group, 29% (5/17) gained three lines or more in visual acuity. The mean change in visual acuity observed at month 12 was +10.3 letters in the 24 Gy study cohort and −1.0 letters in the 15 Gy cohort.

Conclusion: The short-term safety and efficacy of intraocular, epiretinal delivery of beta radiation for the treatment of subfoveal choroidal neovascularization was promising in this small study group and should be studied in a larger cohort of patients.

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Therapies that have been proven to be effective in treating choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) in randomized clinical trials include laser treatment,[1] photodynamic therapy,[2] and anti-vascular endothelial growth factor (anti-VEGF) therapy.[3,4] Treatment with newer anti-VEGF compounds such as ranibizumab (Lucentis) has proven highly effective, although a majority of patients require multiple treatments over an indefinite period of time, and may be dependent on

the drug for the rest of their lives. This indefinite length of treatment will have a significant impact on healthcare system costs as well as quality of life and may represent a financial burden for the patient. Additional studies of combination therapies and emerging treatments are ongoing.

Radiation therapy has been studied as a possible alternative to current treatments for AMD. Ionizing radiation acts by causing double strand breaks in the DNA double helix thus impairing replication of vascular endothelial cells within the rapidly dividing CNV complex. After low-dose radiation, vascular endothelial cells demonstrate morphologic and genetic changes,[5,6] inhibition of replication,[7,8] increased cell permeability,[9] and apoptosis.[10]

The first report of radiotherapy for the treatment of AMD was a pilot study utilizing external photon beam therapy [10 or 15 Gray (Gy) in 5 fractions of 2 or 3 Gy of 6 MV photons] that suggested that low-dose radiation can maintain central vision and induce regression of CNV.[11] Subsequent studies of external proton and photon beam therapy have reported mixed efficacy results with doses ranging from 7.5 to 40 Gy (most using fractions of 2 Gy, but some using fractions ranging from 6 to 14 Gy).[12–31] Randomized, controlled studies with doses from 20 to 24 Gy using larger fractions have reported the most promising results.[15,32]

Most studies of external proton and photon beam therapy have demonstrated a favorable safety profile with no radiation retinopathy observed. However, Flaxel et al reported the development of radiation retinopathy in 11 of 27 eyes receiving proton beam (a proton dose equivalent to 14 Gy delivered by cobalt-60 teletherapy) over a range of 3 to 30 months.[18]

In contrast to external beam radiotherapy, plaque brachytherapy allows a larger dose to be delivered to the macula with less irradiation of normal ocular structures. Several studies have evaluated plaque brachytherapy in CNV secondary to AMD. Finger et al evaluated palladium-103 plaque brachytherapy in doses from 12.5 Gy to 24 Gy in patients with CNV with favorable results.[33,34] Jaakkola et al evaluated episcleral strontium-90 plaque brachytherapy in single doses of 12.6,[35] 29,[36] or 32.4 Gy[35] in patients with CNV (doses differ from those published, based on recent recalibration measurements; A. Jaakkola, personal communication, 2007). To deliver the radiation, an applicator was surgically introduced in the episcleral surface under the macula and held in place manually for the treatment period of up to 54 minutes. Favorable efficacy results were reported with the higher doses (29 Gy and 32.4 Gy), but not with the 12.6 Gy dose.

After up to 7 years of follow up, only one incidence of radiation retinopathy-like symptoms has been reported in patients with AMD treated with beta radiation.[33–36,37] One eye treated with 32.4 Gy radiation developed nonsight threatening localized changes.[35] In a retrospective study of 1,300 patients treated with plaque brachytherapy for posterior uveal melanoma over a 16-year period, the median foveal dose for those patients free of radiation retinopathy was 44.5 Gy, whereas the median foveal dose for those with radiation retinopathy was 70.3 Gy.[38] The authors concluded that a dose of 50 Gy or less in plaque brachytherapy can be safely tolerated by the fovea.

Much of the literature for radiation therapy in AMD describes modalities that treat from outside into the interior of the eye and involve delivering a "supertherapeutic" dose to the underlying choroid and sclera to accomplish a therapeutic dose at the lesion. An investigational medical device (intraocular strontium-90 applicator) has been developed to allow focal delivery of beta radiation to the CNV while minimizing the amount of radiation received by surrounding structures and the healthy retina. The device can deliver a dose of 24 Gy in as little as 3 to 5 minutes. Because beta radiation has a very limited range in the vitreous humor (comprised primarily of water), the lens and optic nerve receive doses of radiation ranging from 0.56 mGy to 6.3 Gy, respectively.

This investigational device has been evaluated in two preclinical studies described below (data on file NeoVista, Inc.). The feasibility of the subretinal intervention technique was evaluated in 10 rabbit eyes using a dummy device (i.e., with no radiation source), demonstrating that the surgical intervention as proposed was feasible and safe, with no complications observed in the intraoperative and postoperative period (follow up of 1 month). A second preclinical study evaluated and quantified the acute effects of beta radiation on retinal and subretinal tissue over a prescribed dose range in 120 rabbit eyes using the epiretinal approach. No clinically significant acute changes were observed in the retinal or subretinal tissues at dosages up to 103 Gy at up to a 6 month follow up. There were progressive clinical changes in the sub-

From the *Centro de Referência em Oftalmologia, Universidade Federal de Goiás, Goiânia; †Departamento de Oftalmologia, Universidade Federal de São Paulo, São Paulo, Brazil; ‡Centro de Retina Médica y Quirúrgica, S.C., Centro Medico Puerta de Hierro, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico; §Eye Department, Beyoglu Eye Research and Training Hospital, Istanbul, Turkey; and ¶NeoVista, Inc., Fremont, California.

Dr. Woodward and Mr. Nau are employed by NeoVista, Inc., and have a proprietary interest in the investigational device.

Reprint requests: Marcos P. Ávila, MD, Centro Brasileiro de Cirurgia de Olhos, CEP 74210-010 Goiânia, Goiás, Brazil; e-mail: retina@cbco.com.br

groups receiving a single maximum dose of 123, 164, or 246 Gy between the follow-up time periods of 4 and 24 weeks.

The purpose of this study was to evaluate the feasibility of intraocular, epiretinal delivery of beta radiation (strontium-90) for the treatment of subfoveal CNV secondary to AMD. Based on the safety and efficacy data summarized above, doses of 15 or 24 Gy were selected. The following is a review of the short-term safety outcomes and a discussion of the efficacy measures used to evaluate feasibility for the first 12 months of this study. The long-term safety of the device will be assessed for 3 years.

Methods

Study Design

This was a nonrandomized, multicenter feasibility study of a single intraocular treatment with either 15 or 24 Gy beta radiation (strontium-90) in patients with predominantly classic, minimally classic, or occult (with no classic) CNV secondary to AMD. Patients were evaluated at the Screening visit, treated at Baseline, and brought in for follow-up visits at Month 3, 6, 9, 12, 18, 24, 30, and 36.

Patient Selection and Eligibility Criteria

Only patients who provided informed consent and signed an ethics-committee–approved Informed Consent form were eligible for screening. Only one eye per patient received the investigational treatment. To be enrolled into the study, patients had to be at least 55 years of age; have a best corrected visual acuity of 20/70 to 20/400 in the study eye [Snellen equivalent determined with the use of an Early Treatment Diabetic Retinopathy Study (ETDRS) chart]; have evidence of lesion activity defined as a decrease in visual acuity of two lines on the visual acuity chart (Snellen) in the last 2 months or new onset ($\leq$1 month) of blood and/or lipid in the macular region; have subfoveal CNV secondary to AMD; have predominantly classic, minimally classic, or occult lesion subtype; have lesions composed of at least 50% CNV; and have a maximum lesion size of 12 Macular Photocoagulation Study disk areas. The eligibility of lesions was confirmed by an independent central reading center with the use of standardized criteria and trained graders. A complete list of eligibility criteria is included in the Appendix.

Treatment

The active source of beta radiation is strontium-90 (29-year half life) in equilibrium with yttrium-90 (64-minute half life), the latter being the daughter product of strontium-90 after beta decay. Yttrium-90 is also a beta emitter, and thus the radiation emitted by this source is from both isotopes. Yttrium-90, however, emits more energetic beta particles, and therefore the therapeutic effect occurs primarily from the yttrium-90 component. The radiation source is housed within a sealed canister and laser welded to a positioning wire which is stored within the handpiece. The position of the radioactive source is controlled by a slide mechanism attached to the positioning wire. When the mechanism is in the retracted (storage) position, the source is shielded by a Densimet (tungsten alloy) and aluminum Thoraeus filter. In the engaged (treatment) position, the radioactive source is deployed to the tip of the stainless steel cannula where there is minimal shielding (0.1 mm stainless steel), allowing the radiation to treat the CNV. The cannula is plugged at the tip, creating a sealed system and preventing the sealed canister from coming into direct contact with intraocular tissues. The radioactive material is always fully enclosed within the device and remains within the patient's eye for less than 5 minutes. The device is visually positioned by the surgeon, following a vitrectomy, by centering a laser-etched cross visible on the cannula tip over the CNV (Figure 1).

Vitrectomy Procedure. Patients received treatment at the baseline visit. They were brought to the operating suite under local anesthesia and prepped in the standard sterile fashion for vitrectomy. A partial "core" vitrectomy was performed to remove the vitreous and create an access channel over the CNV. Removal of the vitreous allowed for ease of placement of the delivery device and minimized mechanical traction on the peripheral retina. Both 20- and 25-gauge instrument systems were used. When 25-gauge instruments

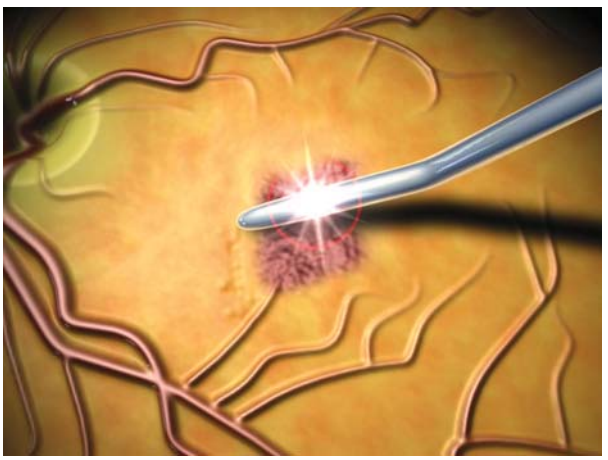

Fig. 1. An illustration of the intraocular, epiretinal beta radiation (strontium-90) delivery device placed in proximity to the CNV complex.

were employed, the superotemporal sclerotomy was enlarged to 20 gauge to accommodate the delivery device. If the posterior hyaloid membrane was detached it was removed; intact membranes, in most cases, were not removed.

Dosage. The characterization in terms of absorbed dose rate in water (assumption is that tissue is composed primarily of water) has been performed using radiochromic film dosimetry developed in conjunction with the National Institute of Standards and Technology. A Dosimetry Standard Source has been developed by developing an 11 mCi source, calibrated by National Institute of Standards and Technology, utilizing an extrapolation chamber and radiochromic film HD-810. The strontium-90 dose rate in water at 2.6 mm is determined by the manufacturer utilizing a National Institute of Standards and Technology-traceable Dosimetry Standard Source for each radiation delivery device and the dose rate is recorded on each device calibration certificate. The specified dose rate is then used to calculate the treatment time based on a predefined dose of 24 Gy, the dose at the peak of the dose rate profile for the irradiated area, as shown in Figure 2A. Figure 2B illustrates the isodose curves at the treatment site. Figure 3 illustrates the dose distribution of a single 24 Gy treatment. Each surgeon is trained and certified utilizing a feedback eye model that measures device position and stability to assure minimal amount of movement during the treatment time.

A previous trial evaluating the subretinal delivery of beta radiation used a 29 Gy dose—a dose thought to be below the threshold for retinal radiation toxicity[38] and allowing for an optimal delivery window of 3 to 5 minutes. Due to poor visual acuity outcomes and complications related to subretinal surgery, a dose of 15 Gy—roughly half the dose of the previous trial—was selected in the current study. Initial results with this dose showed a loss of biologic effect, suggesting that the limited improvement in visual acuity observed in the previous trial was likely attributable to the novel delivery approach and not a toxic effect. The dose was increased to 24 Gy, based upon available safety data (no apparent toxicity had been observed at either the 15 or 29 Gy dose) and the widespread use of strontium-90 at this dose by the cardiovascular community for treatment of endovascular plaques.

Radiation Procedure. Each delivery device was calibrated to deliver either 15 or 24 Gy over a prespecified time that ranged from 3 to 5 minutes. As strontium-90 has a half life of 29 years, the devices were recalibrated after 1 year or 10 uses, whichever came first. Appropriate precautions for dealing with radioactive sources were maintained throughout the procedure, including personal monitoring devices and radiation surveys before and after surgery. The delivery device was steam sterilized before each use.

After removing the delivery device from the sterilization tray and inserting the cannula into the midvitreous cavity, the surgeon oriented the device in the desired position and lowered it to the point where the "cross" engraved on the cannula was centered over the fovea and the cannula tip was hovering at or just above the

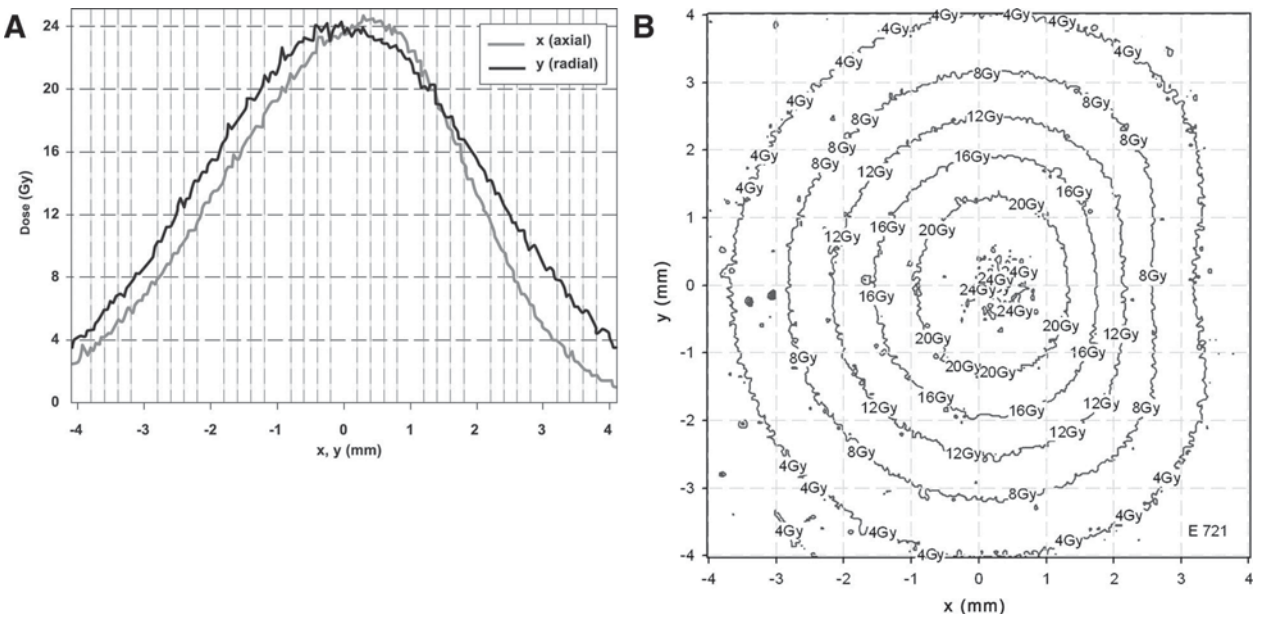

Fig. 2. The treatment time needed to supply a dose of 24 Gy was determined by measuring the dose rate profile. **A**, Dose profile and (**B**) isodose curves at treatment site.

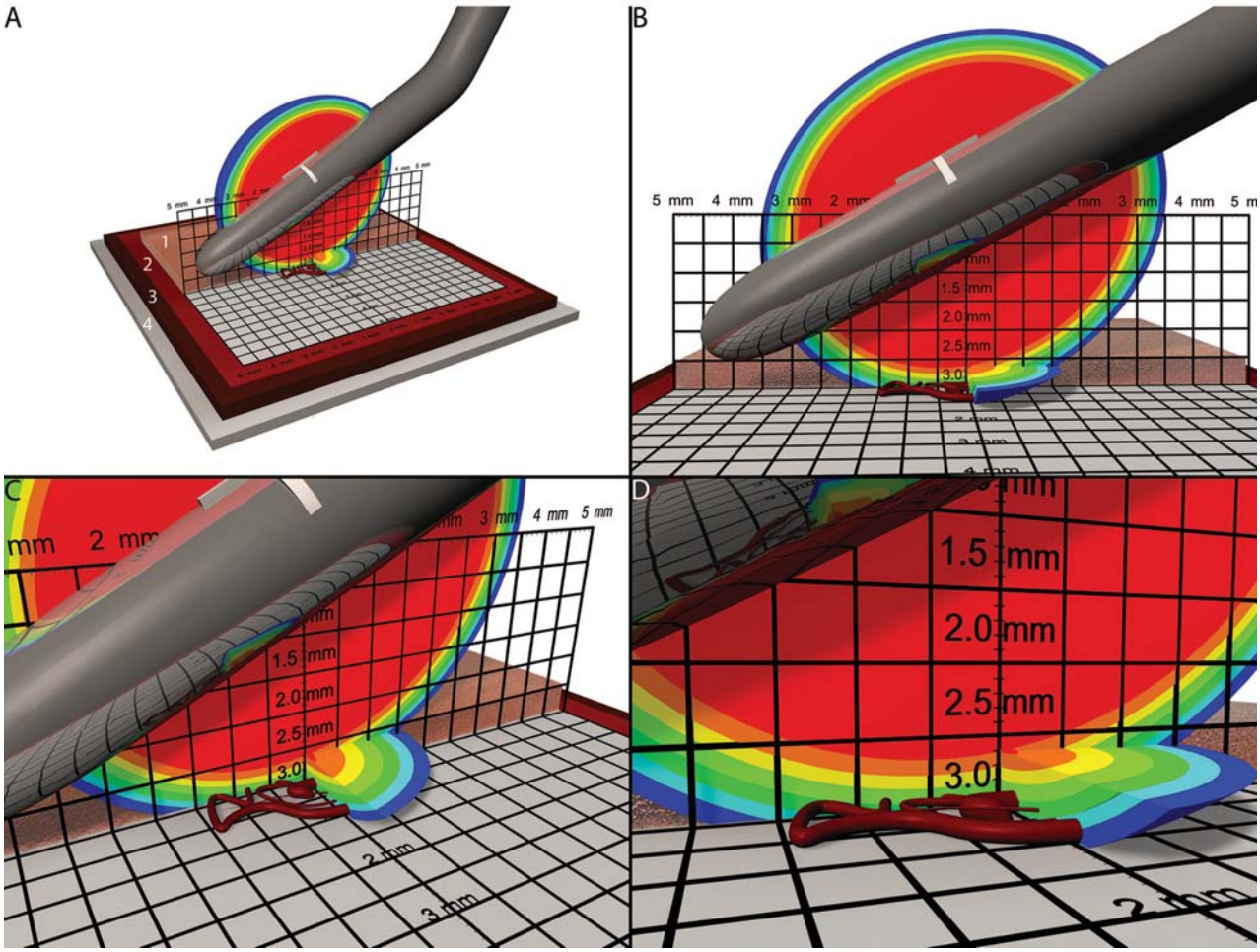

Fig. 3. Dosimetry representation showing dose distribution at surface of lesion (red = 24 Gy) and in 0.1 mm increments (orange = 20 Gy, yellow = 17 Gy, light green = 14 Gy, dark green = 11 Gy, light blue = 10 Gy, and dark blue = 9 Gy). **A**, Image showing key anatomical layers of the retina[1]: photoreceptor layer,[2] choriocapillaris,[3] choroid, and[4] sclera. **B–D**, Images showing orientation of cannula and dosimetry in retina.

retinal surface (within 0.1 mm). This preliminary procedure allowed the surgeon to locate the various landmarks that were used in the subsequent delivery of radiation. After this phase, the surgeon moved the cannula tip back to the midvitreous cavity, where the radiation source was moved down to the engaged or "treatment" position. The surgeon then moved the cannula tip back to the intended treatment position, and the timer was started. The device was held by hand in the intended position for the full period of the treatment, which is specifically determined by the calibration of the device. Treatment time varied from approximately 3 minutes to approximately 5 minutes, depending on the source activity, but was specified to the nearest second. As soon as the treatment was completed, the cannula tip was pulled back to the midvitreous cavity and the source was retracted to the locked position. The delivery device was removed from the eye with the source fully shielded in the handpiece.

Closure and Postoperative Procedures. Standard closure techniques for sclerotomies were utilized. A subconjunctival injection of an appropriate prophylactic antibiotic and steroid was administered, 20-gauge sclerotomies were sutured, and the eye was patched. Patients were treated postoperatively with topical antibiotics and a tapering topical steroid regimen.

Study Endpoints

Preliminary efficacy endpoints included changes in visual acuity as assessed by the ETDRS chart at 2 m, as well as the proportion of patients who lost fewer than 15 letters, demonstrated stabilized or improved vision (lost fewer than 0 letters), and gained 15 letters or more from baseline. Loss of more than 3 lines (15 ETDRS letters) of visual acuity results in a decrease in the quality of life[39] and represents a doubling of the visual angle.

Safety parameters evaluated included incidence and severity of adverse events, and ocular adverse events identified by eye examination. Adverse events prospectively identified at the outset of the study included those related to the effects of radiation (damage to the optic nerve/retina/choroid, cataract, glaucoma, radiation retinopathy, or vision loss) and surgery (retinal detachment/tear, bleeding, edema, or infection). Other adverse events prospectively identified include changes in intraocular pressure, lens changes, presence of large cotton wool spots, hypopyon, hyphema, or retinal vascular occlusion.

Statistical Analyses

Data were collected on case report forms, and all analyses performed using SAS version 9.1. Missing data were addressed by analyzing available data alone and by applying last observation carried forward (LOCF) methodology.

Results

Demographics and Study Population

A total of 34 patients were enrolled at four sites in Turkey, Mexico, and Brazil (two sites) from February 2005 through February 2006. Patient demographics are summarized in Table 1. The mean age for the study participants was 73.1 year, consistent with the natural occurrence of wet AMD in the general population. Sixty-two percent of the patients were male and 65% were white. Angiographic lesion classification was distributed among predominantly classic, minimally classic, and occult subtypes.

Table 1. Study Patient Demographics and Baseline Characteristics

Number of patients	34
Age, years	
Mean (SD)	73.1 (7.64)
Median	73
(Minimum, maximum)	(55, 84)
Gender, n (%)	
Male	21 (61.8)
Female	13 (38.2)
Race, n (%)	
Caucasian	22 (64.7)
Hispanic	9 (26.5)
Other	3 (8.8)
Lesion type, n (%)	
Predominantly classic	14 (41.2)
Minimally classic	12 (35.3)
Occult	8 (23.5)
Mean ETDRS BCVA	
Mean (SD)	37.7 (13.17)
Median	36
(Minimum, maximum)	(15, 69)

SD, standard deviation; BCVA, best corrected visual acuity.

The intent-to-treat (ITT) population was defined as all patients treated with epiretinal beta radiation therapy who returned for at least one follow-up visit. All 34 patients enrolled in the study were included in the ITT population. The per-protocol-analysis (PPA) population was defined as all patients who were treated with epiretinal beta radiation therapy, returned for at least one follow-up visit, and had no major protocol deviations. During the course of the study, the primary investigators established the eligibility requirements and refined the treatment protocol after a review of the results from the initial study participants. The dose change from 15 to 24 Gy also occurred at this time. Ten of the patients enrolled in the study before the investigators' review did not meet these eligibility requirements: 5 were diabetic, 2 had a lesion size larger than 5.4 mm, 2 had baseline visual acuity outside the inclusion criteria parameters, and 1 displayed Alzheimerlike symptoms and was ineligible for the study. One additional patient was treated outside of the established treatment protocol. This patient received an initial dose of 24 Gy and an additional dose of 24 Gy after the 6-month visit. These patients were monitored for adverse events and included in the safety analysis, but are excluded from the PPA population.

Of the 34 patients in the ITT population, 8 received treatment with 15 Gy and 26 received treatment with 24 Gy radiation. Of the 23 patients included in the PPA population, 5 received treatment with 15 Gy and 18 received treatment with 24 Gy radiation.

At month 6, 1 patient who received treatment with 24 Gy radiation was lost to follow up. At his last exam, his visual acuity had decreased by 6 letters. One patient who received a dose of 15 Gy was absent during the required 12-month visit, but returned at month 18 for continued follow up.

Safety

In the safety analysis, we considered all 34 treated patients, regardless of whether they met the protocol-specified eligibility criteria or were treated according to protocol. There were no reports of radiation-induced toxicity or adverse events that could be attributed to radiation exposure after epiretinal beta radiation therapy, either during the first 12 months of this study, or at following visits (some patients had follow-up visits as late as 24 months). Radiation-related toxicity may become evident several years after treatment; therefore, the long-term safety of the device will be evaluated over an extended 3-year follow-up period.

The primary adverse events observed in the study were attributed to the partial vitrectomy required to gain access to the patients' intraocular cavity. There was one retinal tear that occurred while the surgeon was performing a separation of the posterior hyaloid membrane (during vitrectomy and before introduction of the device). There was one peripheral retinal tear at the site where the device tip came in contact with the retina, which was treated with laser photocoagulation and resolved with no sequelae. This event occurred during the first case performed by this surgeon and was not repeated in later surgeries. Eleven patients (42% of phakic eyes) developed cataracts in the study eye. There were no visually significant cataracts reported preoperatively, and 9 of the 11 cataracts were removed by the 12-month report.

Five out of 34 enrolled patients (15%) experienced a visual loss of more than three lines during the course of the study. Two of the five patients who manifested 3-line vision loss were diabetic at baseline and were suspected to have had compromised vasculature before radiation delivery; another two had vision loss due to cataract formation, and vision was subsequently improved to fewer than three lines lost with phacoemulsification and intraocular lens implantation. The fifth patient had subretinal fibrosis at baseline.

Additional adverse events that occurred in single patients with mild severity were intraretinal blood, pigment on the lens, submacular hemorrhage, and cotton wool spots. The investigators concluded that the cotton wool spots were not consistent with radiation toxicity as they were observed at the month 1 follow-up visit, located superior to the optic nerve (received <2.4 Gy), and disappeared by month 2 most likely representing a historical process.

Visual Acuity

The ITT population responded well to the single dose of radiotherapy. As illustrated in Figure 4A, the mean change in visual acuity from baseline to month 12 in the ITT population was a loss of a single letter of vision in patients who received 15 Gy radiation ($n = 6$) and a gain of 4.4 letters in patients who received 24 Gy radiation ($n = 24$; all available data). Using LOCF to account for missing data, the mean change in visual acuity from baseline to month 12 was a loss of 10.4 letters in patients who received 15 Gy radiation ($n = 8$) and a gain of 2.8 letters in patients who received 24 Gy radiation ($n = 26$; Figure 4B). When all available data were analyzed, 100% of patients treated with 15 Gy radiation and 83% treated with 24 Gy lost fewer than 15 letters at month 12, 50% and 63% gained 1 or more letters, and 0% and 21% gained 15 or more letters, respectively. Using LOCF to account for missing data, 88% of patients treated with 15 Gy and 81% treated with 24 Gy radiation lost fewer than 15 letters, 38% and 58% gained 1 or more letters, and 0% and 19% gained 15 or more letters.

In the PPA population, when all available data were analyzed, the mean change in visual acuity from the baseline visit to month 12 was a loss of a single letter of vision in patients who received 15 Gy ($n = 4$) and a gain of 10.3 letters (+2 lines) in patients who received 24 Gy radiation ($n = 17$; Figure 5A). Using LOCF to account for missing data, the mean change in visual acuity was a loss of 2.4 letters in patients who received a 15 Gy dose ($n = 5$) and a gain of 9.4 letters in patients who received a 24 Gy dose ($n = 18$; Figure 5B).

When all available data were analyzed, all patients in the PPA population in both the 15 Gy ($n = 4$) and 24 Gy ($n = 17$) study cohorts lost fewer than 15 letters or 3 lines of vision at 12 months (Figure 6, A and B). In addition, of those in the PPA population treated with 15 Gy radiation, 50% had no loss or improved vision at month 12 (Figure 6A). Among those treated with 24 Gy radiation, 76% had no loss or improved vision at month 12 and 29% experienced gains of over 15 letters (Figure 6B). When LOCF was used to account for missing data, all patients in both the 15 Gy ($n = 5$) and 24 Gy ($n = 18$) study cohorts lost fewer than 15 letters at 12 months. Forty percent of patients treated with 15 Gy radiation had no loss or improved vision at month 12. Among patients treated with 24 Gy radiation, 72% had no loss or improved vision at month 12 and 28% experienced gains over 15 letters.

Representative Case Report

A 72-year-old man with neovascular AMD was diagnosed with predominantly classic CNV in his right eye. Visual acuity was 20/200 in the right (study) eye and 20/25 in the left (fellow) eye. Dilated fundus examination and fluorescein angiography in the study eye revealed drusen, a small area of hyperpigmentation, and that the patient was phakic with a clear lens (Figure 7). After informed consent was obtained, the subject was treated with a single dose of 24 Gy beta radiation with the intraocular delivery device with no sequelae. The subject had stable vision of 20/200 at the Month 3 visit with a reduction in the area of early CNV leakage. At the Month 6 visit the subject's vision remained stable. At the Month 9 visit the subject had a decrease in visual acuity to 20/500 due to the formation of a nuclear cataract, although leakage continued to decrease and involution of the lesion was observed. Phacoemulsification with intraocular lens implantation was performed. At the Month 12 visit the

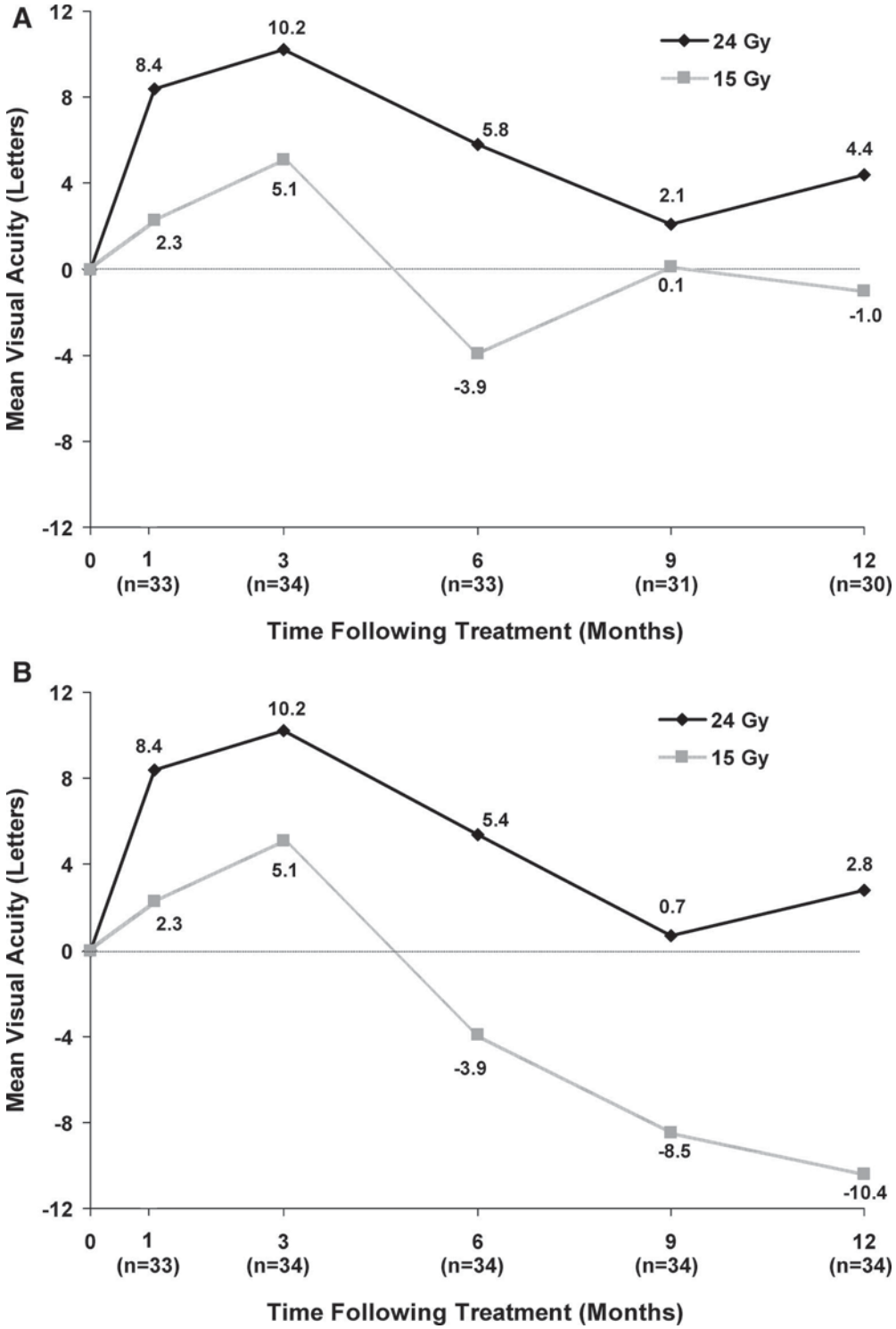

Fig. 4. Mean change in visual acuity for the ITT population who received 15 Gy or 24 Gy radiation, according to an analysis of (**A**) all available data or (**B**) LOCF.

subject's vision improved to 20/160 and there was no classic component evident on fluorescein angiography.

Discussion

The two most common concerns associated with radiation therapy for exudative AMD have been 1) the appropriate dose and delivery modality to maximize visual acuity benefit while minimizing radiation-induced adverse events; and 2) the long-term viability of radiation as a solution to preventing vision loss.

Over the 12 months during which the patients were observed for this study, no adverse events were re-

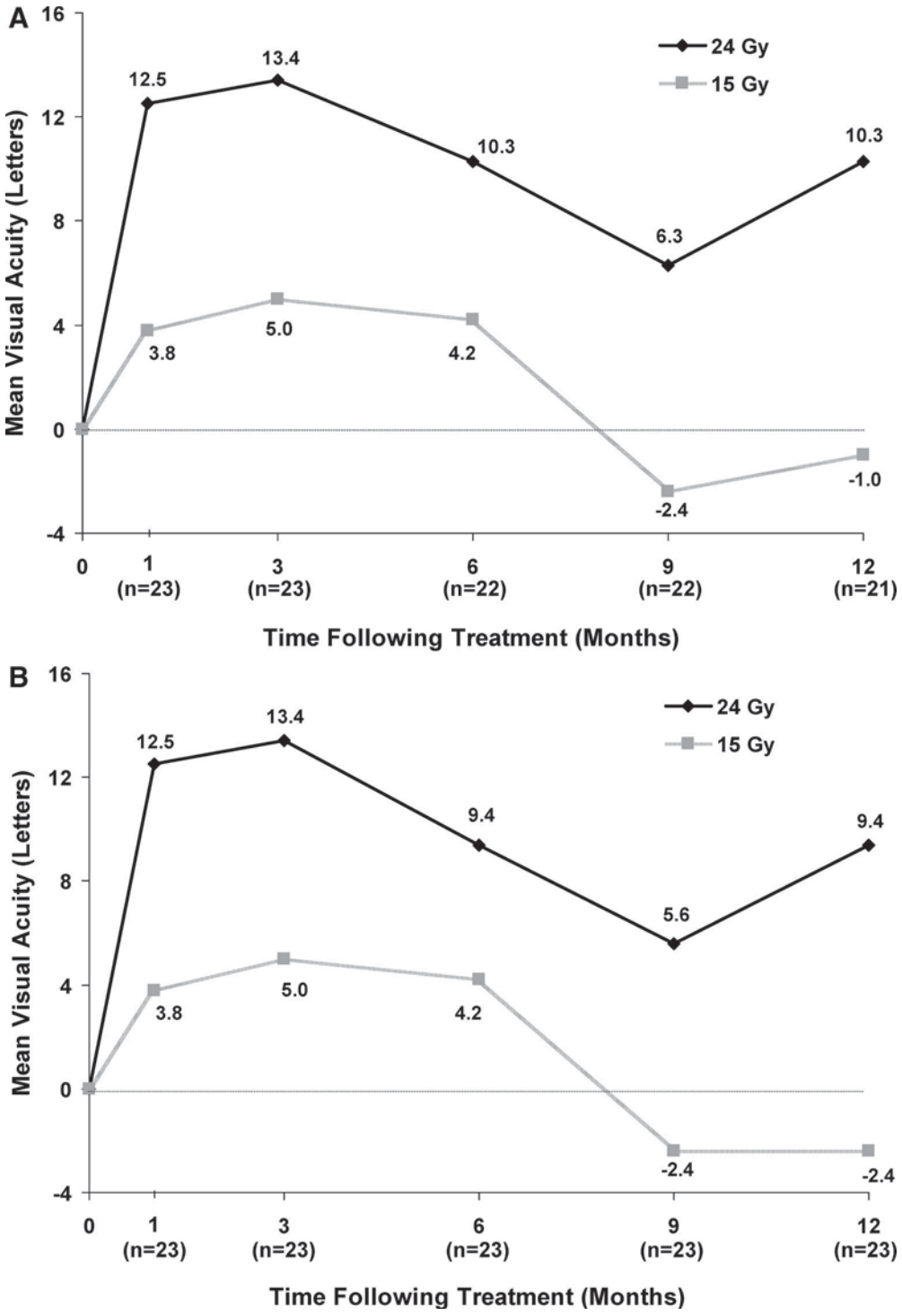

Fig. 5. Mean change in visual acuity for PPA population who received 15 Gy or 24 Gy radiation, according to an analysis of (**A**) all available data or (**B**) LOCF.

ported that could be attributed to radiation toxicity. This may be explained by the limited range and energy of strontium-90/yttrium-90 beta particles administered using this investigational delivery method. The system was designed to deliver radiation to a small volume of retinal tissue thus minimizing the risk of damage to adjacent tissues. Radiation toxicity to the retina is well documented and may manifest over many years after treatment. All 34 patients enrolled in this study will be followed for 3 years to assess the long-term safety of treatment. The surgical procedure for the intraocular, epiretinal delivery of beta radiation was well tolerated and complications were similar to those seen in standard vitrectomy procedures (e.g.,

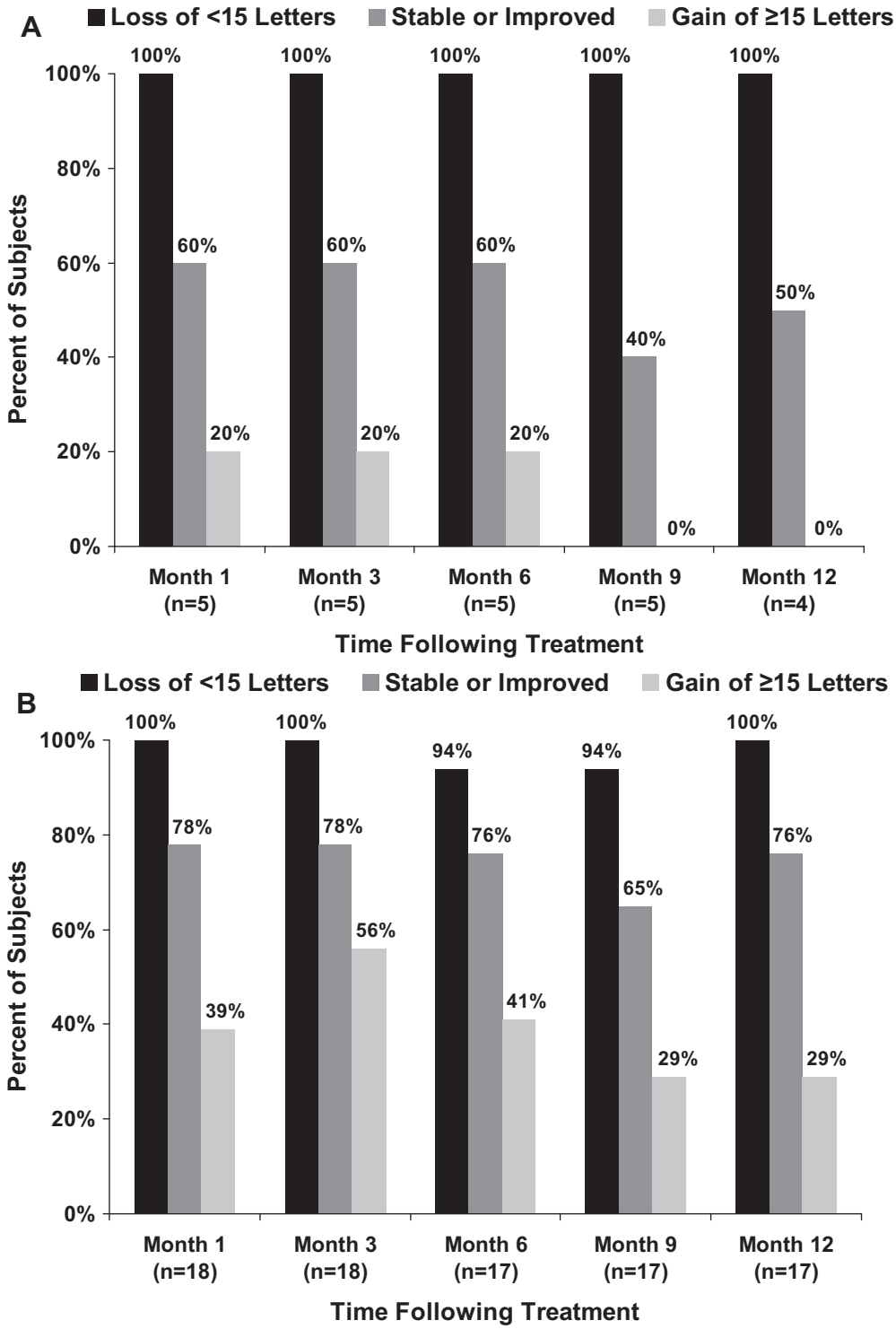

Fig. 6. Proportion of PPA population with a loss of visual acuity (<15 letters), unchanged or improved visual acuity (≥0 letters), or a gain of visual acuity (≥15 letters) after treatment with (**A**) 15 Gy or (**B**) 24 Gy radiation. All available data were analyzed for both doses.

submacular hemorrhage, increased incidence of cataract formation/progression, retinal tear). However, the cataract rate is below that expected in a study utilizing pars plana vitrectomy procedures.[40–42]

The patients enrolled in this study also responded positively to treatment. Over the 12 months after treatment, all PPA population patients in both cohorts lost fewer than three lines of vision (Figure 6, A and B). The results are more encouraging when we examine the patients who received a single dose of 24 Gy radiation with roughly 75% of the patients losing no letters and 25% of the patients gaining three lines of

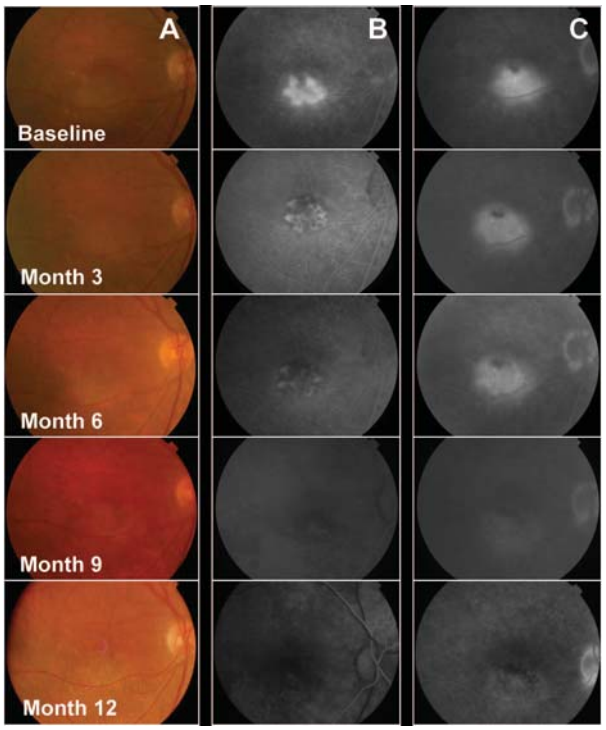

Fig. 7. (**A**) Color fundus, (**B**) early/midphase fluorescein angiography, and (**C**) late-phase fluorescein angiography images for a patient receiving intraocular, epiretinal beta radiation therapy. Images were captured at baseline, at month 3, month 6, month 9, and month 12 following treatment.

vision or more (considering both all available data and LOCF analyses). Historically, patients with exudative AMD who go untreated do not fare as well. In the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study, the TAP study group reported that 39.3% and 55.3% of untreated patients with CNV lesions classified as predominantly classic and minimally classic, respectively, lost fewer than 3 lines of vision after 12 months.[43] Outcomes for untreated patients with occult CNV lesions are similar. The investigators for the Verteporfin in Photodynamic Therapy trial reported only 44.6% of untreated patients with occult lesions lost fewer than three lines of vision a year following enrollment.[44] As reported in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration study, untreated patients with minimally classic or occult CNV lesions lost, on average, 10.4 letters at 12 months, with 62% losing fewer than 15 letters.[4] In a more recent study (PIER), the mean change in visual acuity among untreated patients with occult, minimally classic, and predominantly classic lesions was a loss of 16.3 ETDRS letters by month 12 for all groups[45]; 49% of these patients lost fewer than 15 ETDRS letters.[46]

Given the initial short-term safety and efficacy results of patients enrolled in this study, localized delivery of beta radiation may be an effective alternative to current treatment for exudative AMD. The long-term safety of the procedure will be assessed for 3 years. It has been postulated that radiation combined with antiangiogenic therapy may be another potential treatment for the disease.[47] Recent findings in cancer therapy lend support to this theory. One study showed that whereas anti-VEGF therapy alone may not increase median survival, combined with cytotoxic agents it could increase overall survival.[48] These findings suggest that radiation and anti-VEGF pharmaceuticals also may have a beneficial synergistic effect in the treatment of exudative AMD. Further studies should be performed on a larger patient population and in combination with other treatments to determine the best use of intraocular, epiretinal beta radiation therapy.

Key words: age-related macular degeneration, retina, beta radiation, brachytherapy, medical device, intraocular, strontium, subfoveal choroidal neovascularization.

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APPENDIX: Study Eligibility Requirements

Patients underwent pretreatment screening examinations for eligibility; all patients presented with subfoveal CNV secondary to AMD, and informed consent was obtained from those eligible and participating in the study. Only one eye per patient received the investigational treatment.

Inclusion Criteria

1. Subfoveal, choroidal neovascularization (CNV) secondary to AMD in the study eye; lesion composition must be at least 50% CNV.
2. Evidence of activity of CNV as documented by fluorescein angiography in the study eye.
3. Decrease in visual acuity of 2 or more lines within the last 2 months in the study eye, or evidence of new onset ($\leq$1 month) blood and/or lipid in the macular region with or without evidence of visual acuity deterioration in the study eye.
4. Lesion size (greatest linear dimension of entire lesion, not only CNV component) $\leq$5.4 mm and $\leq$12 Macular Photocoagulation Study disk areas in the study eye.
5. Best-corrected visual acuity no better than 20/70 (Snellen Equivalent) but no worse than 20/400 in the study eye.
6. Age 55 years or older.

Exclusion Criteria

1. Prior or concurrent subfoveal CNV therapy including thermal laser photocoagulation (with or without photographic evidence), photodynamic therapy, intravitreal or subretinal steroids, transpupillary thermotherapy (TTT), and systemic or intravitreal antiangiogenic agents in the study eye. (Note: This includes patients with no known history, but with photographic evidence of prior therapy).
2. Patients on chronic systemic corticosteroid or other immunosuppressive therapy that may affect wound healing (e.g., patients who have undergone chemotherapy within the last 6 months), and any immunocompromised patients (e.g., positive for human immunodeficiency virus).
3. History of optic neuritis.
4. Evidence of significant subretinal fibrosis in the study eye.
5. CNV not secondary to AMD in the study eye.
6. Presence of media opacities that prevent adequate visualization of the posterior pole.
7. Presence of other ocular diseases that could cause a decrease in vision (e.g., glaucoma, ocular histoplasmosis, or degenerative myopia) in the study eye.
8. Presence of Type 1 or Type 2 diabetes mellitus.
9. Visual acuity improvement ($\geq$10 letters on the ETDRS chart) with the presence of the CNV lesion in the study eye in the past 2 months.
10. Best-corrected visual acuity 20/800 or worse in the fellow eye.
11. Previous intraocular surgery, excluding cataract surgery; if the patient has had cataract surgery, it must have been $>$3 months before entry into the study.
12. Previous head or neck radiation treatment.
13. Women who are pregnant, lactating, or of childbearing potential.
14. Known sensitivity or allergy to fluorescein.
15. Current participation in another drug or device clinical trial, or participation in such a clinical trial within the last year.
16. History of use of drugs with known macular toxicity, including:
    - chloroquine (Aralen, an antimalarial drug)
    - hydroxychloriquine (Plaquenil)
    - phenothiazines, e.g.,
    - chlorpromazine (Thorazine)
    - thioridazine (Mellaril)
    - fluphenazine (Prolixin)
    - perphenazine (Trilafon)
    - trifluoperazine (Stelazine)
17. Requiring current anticoagulation therapy at the time of surgery.
18. Unwilling or unable to give informed consent or to comply with required follow-up.