

Preliminary Results With Noninvasive Radiation Therapy for Wet AMD

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Recently, interest in the use of radiotherapy for treatment of age-related macular degeneration (AMD) has been rekindled. The radiation oncology literature amply demonstrates that radiation has antiangiogenic, antiinflammatory, and antifibrotic qualities. It is also known that radiation is a long-term treatment, producing its effects over the course of weeks to years. This suggests that radiation treatment may be complementary to treatment with antiangiogenic drugs such as vascular endothelial growth factor (VEGF) inhibitors, which work quickly. The combination of the early effect of anti-VEGF drugs and the late effect of radiation may improve the treatment of AMD.

Recently, an intraocular probe that delivers radiation to the retina via epimacular brachytherapy has been evaluated in clinical trials.¹ Although this intraocular radiation delivery system shows promise, it requires a trip to the operating room for treatment.

Another device, the IRay (Ora Therapeutics Inc., Newark, CA) stereotactic radiotherapy system, delivers treatment in-office. The IRay received the European CE Mark earlier this year, but it does not yet have regulatory clearance in the United States.

This robotically controlled x-ray device adjusts delivery in response to both eye and patient movement. The patient's treatment parameters are input by the operator, the eye is stabilized and any movement is tracked throughout the procedure, and sequential beams deliver low-voltage x-rays through the sclera to a single treatment spot on the macula. For the 16 and 24 Gy doses currently being evaluated in clinical trials, the treatment duration is approximately 3 minutes, and a patient encounter typically requires less than 15 minutes start to finish.

The energy used by this device is similar in strength to that used for dental or chest x-rays, or even the x-ray scanners we pass through in security at the airport. The doses delivered to surrounding tissues are low; the optic nerve receives about 0.24 Gy and the lens about 0.48 Gy,

well below toxicity levels.²

This office-based procedure can be performed with minimal personnel, does not require room shielding modifications, and poses negligible radiation exposure risk to the staff during normal use.

CLINICAL RESULTS

An open-label phase 1 clinical study has evaluated the safety and preliminary efficacy of the IRay in combination with ranibizumab (Lucentis, Genentech) for treatment of choroidal neovascularization (CNV) secondary to AMD.^{3,4} In this trial, patients received a radiation dose of either 16 or 24 Gy.

Patients included in each dose group were 50 years of age or older with subfoveal CNV due to AMD and with baseline visual acuity between 20/40 and 20/320 Snellen equivalent on the Early Treatment Diabetic Retinopathy Study chart. Two cohorts were included in each group: one with treatment-naïve patients, and a second with patients who had been previously treated with anti-VEGF therapy but who needed ongoing treatment as demonstrated by leakage on fluorescein angiography or by increased retinal thickness or persistent fluid on optical coherence tomography (OCT).

All patients in the study were treated in Mexico City according to the following design: patients received one mandated ranibizumab injection at day 0, followed by IRay treatment (either 16 or 24 Gy) within 14 days, followed by an additional mandated injection at 30 days. After that, retreatment with ranibizumab was on an as-needed (PRN) basis as determined by OCT, clinical, and fluorescein criteria.

The group receiving 16 Gy numbered 27 patients, 15 of whom were treatment-naïve. All have completed at least 18 months of follow-up. Phase 1 trials are designed to demonstrate safety, and no device-related serious adverse events were seen. The only noted device-related adverse event was asymptomatic superficial punctate keratopathy related to the vacuum-coupled contact lens placed on the eye during the procedure; this was seen in most patients

on routine post-procedure exam and resolved without treatment in all cases by the time of the next follow-up visit.

The group receiving 24 Gy numbered 19 patients, eight of whom were treatment-naïve. All have completed at least 9 months of follow-up. As in the 16-Gy group, the only device-related adverse event seen was asymptomatic corneal irritation related to contact lens placement, which also spontaneously resolved without treatment.

Although this feasibility study was intended only to assess safety, a number of encouraging efficacy signals emerged. Visual acuity was stabilized or improved in 96% of patients in the 16-Gy group and 100% in the 24-Gy group at the 18- and 9-month time points respectively. In both groups, the number of required ranibizumab injections was low during the PRN treatment phase, with a mean of two per patient for 18 months in the 16 Gy group, and 0.7 per patient for 9 months in the 24 Gy group. In the 16 Gy group, 20% of patients have needed no additional injections through at least 18 months of follow-up, and 68% of patients in the 24 Gy group have not required retreatment through 9 months (Figure 1). Mean retinal thickness decreased from baseline in both groups, providing anatomic correlation of the visual acuity data.

CONCLUSIONS

The IRay, an in-office stereotactic robotically delivered x-ray treatment system, combined with ranibizumab, appears to be safe and well-tolerated and shows early evidence of efficacy. Treatment with the IRay provides an apparently promising biologic effect in both treatment-naïve and previously treated patients with AMD of all lesion types, and seems to decrease the need for additional anti-VEGF injections. Visual results appear to be at least equal to those seen with monthly ranibizumab treatment. No radiation retinopathy or cataract formation as a result of treatment has so far been noted with up to 18 months' follow-up in the 16 Gy group.

Further clinical trials with the IRay device have begun. A double-masked, randomized, sham-controlled study (INTREPID: IRay plus anti-VEGF treatment for patients with wet AMD) is now recruiting in Europe with an enrollment goal of at least 150 patients with a randomization scheme

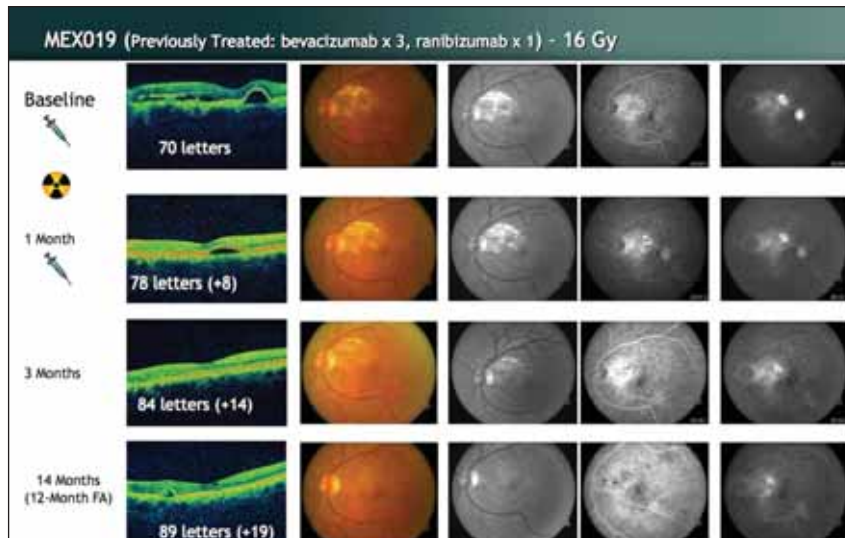


Figure 1. Outcomes observed for a subject enrolled in Oraya's clinical pilot study. This patient, treated with anti-VEGF injections prior to study entry, received 16 Gy of radiation to the macula, in conjunction with two mandatory on-study injections of ranibizumab bracketing radiotherapy. The patient has demonstrated significant anatomic and visual acuity improvement up to 14 months' follow-up and has required no additional anti-VEGF treatments.

of 2:1:2 (16 Gy:24 Gy:sham radiation). Another multicenter trial is expected to begin soon in the United States and elsewhere, recruiting at least 300 patients. We look forward to assessing the results of these clinical studies. ■

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