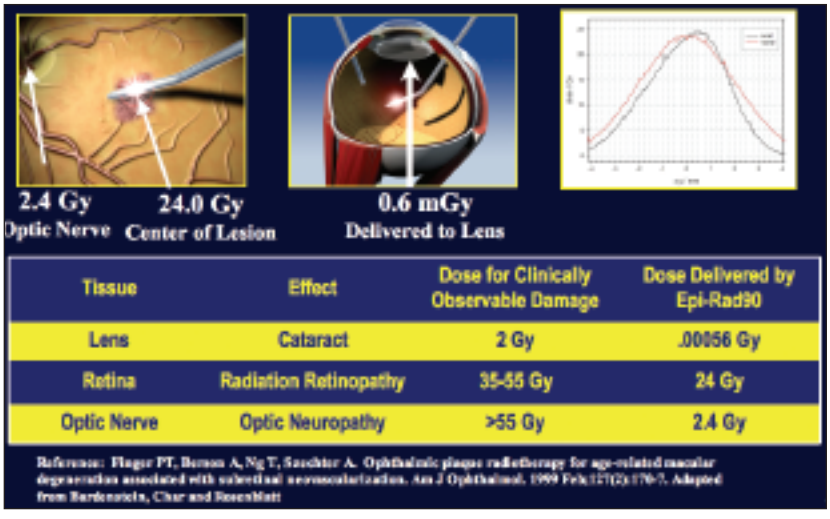
Combination Brachytherapy and VEGF Inhibition for Treatment of Neovascular AMD

Preliminary results promising; prospective controlled clinical trial is under way.

BY BARUCH D. KUPPERMANN, MD, PHD

Choroidal neovascularization (CNV) is a pathologic condition in which choroidal blood vessels grow into the retinal pigment epithelium, proliferate, and begin to cause damage in the photoreceptor layer through vessel leakage and other mechanisms. The neovascular complexes contain a network of vessels, inflammatory cells, and fibroblasts.[1] The occurrence of CNV in age-related macular degeneration (AMD) has been compared to the proliferative wound-healing process, in which inflammatory cells and proliferating cells have been shown to be sensitive to radiation.[2] Extensive studies have been done on the effects of radiation on injured vasculature, mostly in the field of cardiology.[3,4] Irradiated cells lose the ability to replicate, although they do not lose their cellular integrity or undergo necrosis.



Tissue	Effect	Dose for Clinically Observable Damage	Dose Delivered by Epi-Rad90
Lens	Cataract	2 Gy	.00056 Gy
Retina	Radiation Retinopathy	35-55 Gy	24 Gy
Optic Nerve	Optic Neuropathy	>55 Gy	2.4 Gy

Reference: Hagar PT, Berson A, Ng T, Sanchez A. Ophthalmic plaque radiotherapy for age-related macular degeneration associated with subretinal neovascularization. Am J Ophthalmol. 1999 Feb;127(2):176-7. Adapted from Bardenstein, Char and Rosenblatt

Figure 1. Radiation exposure within the ocular compartment beyond the center of the lesion treated with EpiRad.

Radiation therapy, in the form of external beam radiation and ophthalmic plaque radiation, has been previously studied for the treatment of CNV in AMD, with mixed results.[5-10] Radiation has been shown to destroy vascular tissue and to inhibit growth of new vessels (Figure 1).

In a recently introduced radiation treatment modality, epiretinal brachytherapy, the radiation source is

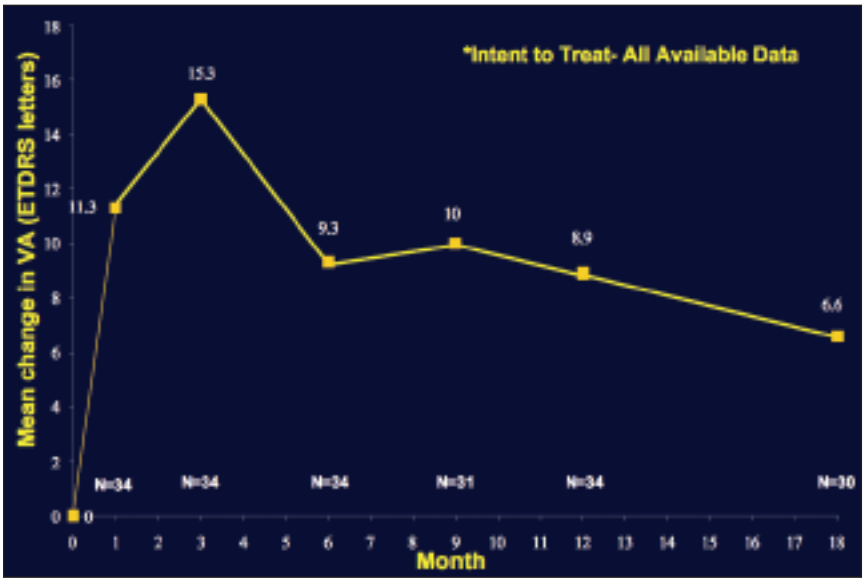


Figure 2. The mean change in visual acuity at month 12 and 18.

placed temporarily in the vitreous cavity, above the area of neovascularization, to deliver a controlled, focal dose of radiation to the target tissue. With other radiation modalities such as external beam and plaque radiation, large areas and volumes of retinal tissue were irradiated to deliver a therapeutic dose to the neovascular lesion. In contrast, with the rapid fall-off in radiation dose characteristic of the strontium-90 used in the intraocular device (EpiRad; NeoVista, Fremont, CA), radiation exposure is limited to the area immediately surrounding the lesion.

The EpiRad device has been evaluated in two prospective, nonrandomized multicenter pilot studies for neovascular AMD.[11] One study (NVI-068) examined the safety and feasibility of epiretinal brachytherapy alone, and a second study (NVI-111) evaluated epiretinal brachytherapy in combination with a vascular endothelial growth factor (VEGF) inhibitor. In NVI-068, in 34 subjects with CNV secondary to AMD who received 24 Gy radiation in a single treatment with epiretinal brachytherapy, there was a mean gain of 8.9 letters of visual acuity, 68% had no loss or improved vision, and 38% gained more than 15 letters at 12 months. The primary adverse events in the study were attributed to the vitrectomy performed to allow access of the radiation source to the CNV lesion. Cataract formation was seen in 25% of eyes by the 12-month follow-up.

RATIONALE FOR COMBINATION THERAPY

Antiangiogenic therapy for neovascular AMD with VEGF inhibitors has become common practice in the current decade, but the regimen of indefinite monthly visits for examination and intravitreal injection of anti-VEGF agents[12,13] places a significant burden on patients, caregivers, physicians, and health care systems. A complementary, synergistic response might be achieved through a combination of radiation therapy and antiangiogenic therapy. Whereas anti-VEGF agents have a rapid onset of action and require repeated injections to achieve a sustained effect, radiation has a delayed response and a more prolonged effect.

In addition, the two modes of therapy have different mechanisms of action; antiangiogenic agents inhibit vascular growth factors, and radiation therapy kills local inflammatory cells and vascular endothelial cells. The combination of these two mechanisms may allow more complete recovery of vision, perhaps with fewer treatment sessions needed.

COMBINATION THERAPY: PILOT STUDY

A prospective, nonrandomized, multicenter pilot study (NVI-111) was conducted to evaluate the combination of epiretinal brachytherapy with the anti-VEGF drug bevacizumab (Avastin, Genentech).[11] One eye in each of 34 patients with CNV secondary to AMD received 24 Gy radiation in a single treatment with epiretinal brachytherapy and two injections of 1.25 mg bevacizumab. The objective of the study was to evaluate the safety and feasibility of this combination treatment.

> Antiangiogenic agents inhibit vascular growth factors, and radiation therapy kills local inflammatory cells and vacular endothelial cells.

Patients received the first dose of bevacizumab either 1 week to 10 days before epiretinal brachytherapy or at the time of surgery, after delivery of the radiation. The second dose was given 1 month after surgery. Patients were followed monthly, and additional injections of bevacizumab could be given at the discretion of the investigator based on lesion activity.

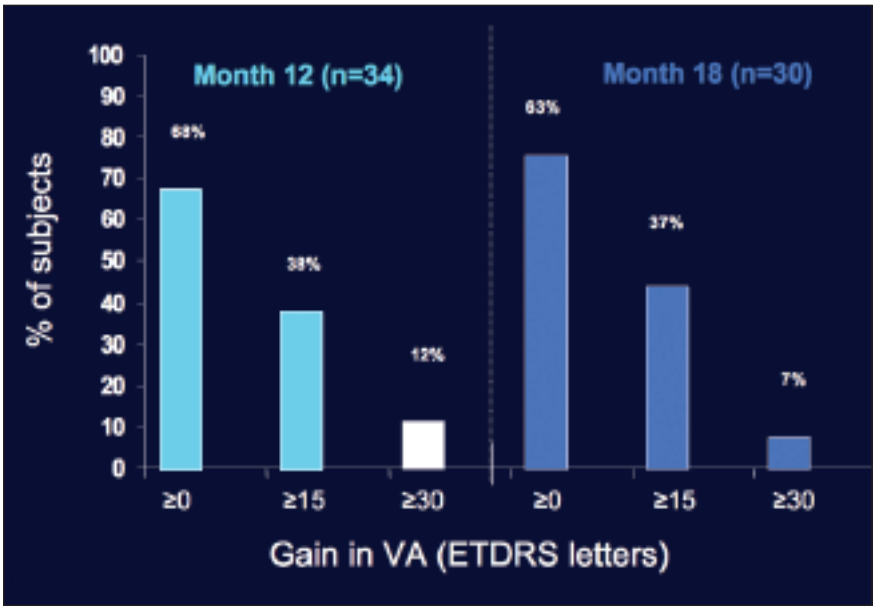


Figure 3. Vision gains at month 12 and month 18.

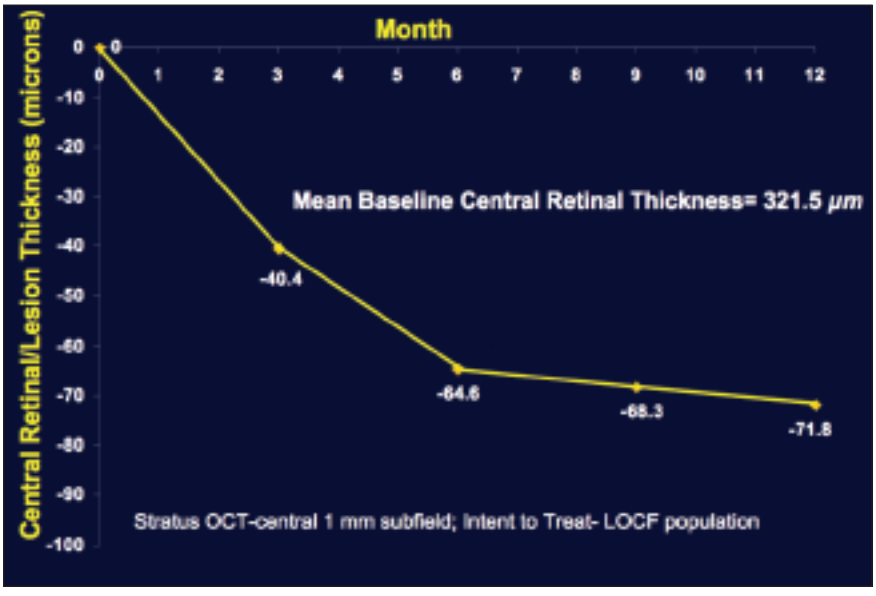


Figure 4. Mean change in central retinal thickness at month 12.

Patients in the study had not been previously treated for CNV secondary to AMD. Mean age was 71 years, ranging from 51 to 91, which is consistent with the natural course of neovascular AMD in a general population. There was a mix of lesion types, including 29% predominantly classic, 21% minimally classic, and 50% occult with no classic. Mean central retinal thickness on optical coherence tomography (OCT) was 321.5 µm. Mean baseline Snellen visual acuity was 20/160.

Visual acuity in the intent-to-treat population improved from baseline by a mean of 8.9 letters at 12 months (N=34), and by 6.6 letters at 18 months (N=30; Figure 2). The highest peak of visual acuity improvement occurred at month 3, with a mean gain of more than 15 letters, or three lines. This is consistent with results of trials of anti-VEGF monotherapy,[12,13] in which the greatest visual acuity gains occurred in the first 3 months.

At 12 months (n=34), 91% of patients treated with the combination therapy lost fewer than 15 letters of visual acuity. Also at 12 months, 68% gained zero or more letters, 38% of patients experienced an improvement of 15 or more letters—a clinically significant improvement in vision— and 12% gained 30 or more letters. At 18 months (n=30), 63% of patients gained zero or more letters, 37% gained 15 or more, and 7% gained 30 or more (Figure 3).

In four eyes that developed pigment epithelial detachment (PED), fluid resolved by 6 months in all cases, and these eyes gained a mean 22.7 letters at 12 months. Historically, PED takes multiple injections to resolve and results in loss of vision.

Mean reduction of central retinal thickness on OCT from baseline to 12 months was 71.8 µm, to a mean thickness of 249.7 µm (Figure 4). Anatomic data for 18 months is not yet available.

By 18 months follow-up, 26 of 34 subjects had received no additional bevacizumab injections. A total of 12 additional injections were administered in eight patients by 18 months.

Regarding safety, no incidence of radiation toxicity or other adverse event attributable to intraocular radiation exposure were seen by 18 months.

In addition, in the NVI-068 pilot study, in which mean follow up is now 33 months, no radiation retinopathy has been reported at 24 months in patients treated with

epiretinal brachytherapy alone.

Adverse events in NVI-111 deemed to be related to the device or the vitrectomy procedure included one subretinal hemorrhage, one retinal tear, two cases of subretinal fibrosis, one epiretinal membrane, and cataract development in six eyes of 24 phakic patients.

COMBINATION THERAPY: ONGOING CONTROLLED STUDY

A prospective, randomized, multicenter active-controlled study of epiretinal brachytherapy is currently enrolling patients. The CABERNET trial (CNV Secondary to AMD Treated with Beta Radiation Epiretinal Therapy) will compare EpiRad brachytherapy plus ranibizumab (Lucentis, Genentech) with ranibizumab alone in patients with CNV in AMD.

> The radiation component of the combined treatment appears to add durability of effect.

The goal of the trial, ongoing at approximately 45 sites worldwide, is to evaluate the safety and efficacy of focal epiretinal radiation delivery for the treatment of CNV associated with AMD. The trial will enroll 450 patients with all CNV lesion types, randomized 2:1 to the combination therapy or ranibizumab monotherapy. Primary endpoints will be percentage of subjects gaining more than 15 letters of visual acuity and percentage of patients losing more than 15 letters. Secondary endpoints will include mean change in visual acuity, mean change in lesion size from baseline, and number of ranibizumab retreatments.

Patients in one arm of the trial will undergo vitrectomy with epiretinal brachytherapy and two injections of ranibizumab 0.5 mg, one at the time of surgery and 1 month later. Patients in the other arm will receive three monthly injections of ranibizumab 0.5 mg followed by quarterly injections for 2 years. Additional injections of ranibizumab will be given at monthly visits per retreatment criteria. All subjects will be followed for 3 years.

In preliminary safety data submitted to the Food and Drug Administration to allow expansion of the CABERNET study to its full cohort, in 20 patients followed for a mean of 3 months, there has been one case of ocular hypertension, one sterile presumed endophthalmitis, one intraretinal hemorrhage, one subconjunctival hemorrhage, and one case of worsening geographic atrophy.[14]

CONCLUSIONS

Intraocular administration of 24 Gy radiation via epiretinal brachytherapy appears to be safe in studies to date. Concomitant delivery of brachytherapy plus an anti-VEGF agent has shown more promising results than brachytherapy alone. The radiation component of the combined treatment appears to add durability of effect, as evidenced by reduced need for retreatment with anti-VEGF therapy. A prospective randomized trial comparing the combination treatment with ranibizumab alone is under way and actively recruiting. The potentially synergistic effect of ionizing radiation with epiretinal application of strontium-90 plus anti-VEGF therapy may prove to be a valuable and durable treatment for neovascular AMD. ■

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