Neovascular age-related macular degeneration (AMD) has a substantial negative impact on the quality of life and activities of daily living of many older adults in developed countries, and its prevalence is projected to increase over the coming decade. Treatment with anti-VEGF agents may now be considered the standard of care for most patients with neovascular AMD, providing visual acuity gains or stabilization in a large percentage of patients. However, experience has shown that frequent anti-VEGF treatment is required over an extended period to maintain these benefits, and that as many as a third of patients lose their initial visual gains. Perhaps as a result, many patients drop out of treatment over time. A treatment that could reduce the burden of anti-VEGF therapy for patients and health care systems would be a welcome addition to our armamentarium against neovascular AMD.

Radiation has a history of use in ophthalmology, with well-known antifibrotic, antiangiogenic, and antiinflammatory effects, all of which are important factors in the pathophysiology of wet AMD (Figure 1).

Early experience with external beam radiotherapy (EBRT) in AMD suggested visual benefits, but minimal functional benefits were seen in randomized clinical trials. Devices in use at that time could not deliver precise collimated doses of ionizing radiation to small targets; the entire posterior of the globe had to be included in the field of radiotherapy, which precluded use of sufficient doses because of the risk of inducing radiation optic neuropathy or retinopathy. In addition, accurate placement of the radiation beam could not easily be confirmed.

Recently, 2 newer radiation treatments for neovascular AMD have been investigated: epimacular brachytherapy and stereotactic radiotherapy. In epimacular brachytherapy with the Vidion system (NeoVista Inc.), beta radiation is delivered to the lesion with a handheld device inserted into the posterior segment after pars plana vitrectomy. The device is held over the AMD lesion for approximately 4 minutes. The total surgical time, including vitrectomy, takes about 30 to 80 minutes. Correct positioning of the probe is critical. A phase 3, randomized prospective multicenter study, CABERNET, evaluating epimacular brachytherapy in treatment-naïve eyes with neovascular AMD, failed to meet its primary endpoint. A study in previously treated eyes (MERLOT) has yet to report.

In stereotactic radiotherapy with the IRay device (Oraya), 3 overlapping beams of low voltage x-rays from an external device are directed onto the AMD lesion. Each beam delivered by the IRay device measures 4.0 mm in diameter and is centered at the fovea, with a much attenuated dose beyond this treatment zone. The eye is stabilized by the device, and an eye tracking system ensures accurate delivery of highly collimated radiation. A minimal dose of radiation is delivered to nontargeted areas such as the optic disc and crystalline lens. Residual radiation is absorbed by the bones of the skull. The minimal effective dose is given, equivalent to about 0.1 tenth the dose from a computed tomography scan of the head. The noninvasive procedure takes about 20 minutes in an office setting.
INTREPID STUDY

The results of a 1-year study, dubbed INTREPID, evaluating the safety and efficacy of IRay therapy for neovascular AMD, were recently presented at an international retina meeting.\textsuperscript{12} The primary outcome of the study was the number of as-needed (prn) 0.5 mg ranibizumab (Lucentis, Genentech) injections over 52 weeks. Secondary outcomes included ETDRS visual acuity; loss of fewer than 15 letters, gain of 15 letters or more, and gain of 0 letters or more; and change in total lesion size and choroidal neovascular (CNV) lesion size on fluorescein angiography (FA). Safety measures included adverse events.

Patients included in the study had been diagnosed with CNV (of any lesion composition) within the past 3 years, had received 3 or more injections of an anti-VEGF agent within the past year, and needed additional anti-VEGF therapy at the time of enrollment due to increased fluid or persistent cysts on FA or optical coherence tomography (OCT).

Retreatment was given if 1 or more of these criteria were met: a 100 µm increase in OCT central subfield thickness from best previous OCT; new or increased macular hemorrhage; or a greater than 5 ETDRS letter decrease in visual acuity since the last visit or baseline with disease activity (eg, persistent or increased fluid on OCT or increased leakage on FA).

RESULTS

A total of 230 subjects were randomly assigned to 1 of 3 arms: group 1 (n=75) received 16 Gy radiotherapy; group 2 (n=75) received 24 Gy radiotherapy; group 3 (n=80) received sham radiotherapy. All groups received an injection of ranibizumab at baseline, and prn ranibizumab at each month thereafter, with the primary endpoint at 12 months and ongoing safety assessment.

Patient demographics in the 3 groups were well-matched for age, mean duration of neovascular AMD, baseline visual acuity, and lesion subtypes.

The primary outcome of the study was met; prn ranibizumab injections were significantly reduced by a third with the 2 radiotherapy treatments compared with sham. Patients who received either dose of radiation were more than twice as likely to need no more injections as those who received sham, and half as likely to need 4 or more injections.

There was no mean loss of visual acuity in either treatment group at 1 year. Visual acuity gains were seen, especially in the 24 Gy group, in the early weeks of the study, but vision returned to at or near baseline by 52 weeks. There was twice as much reduction in central subfield thickness on OCT in the 2 treatment groups (–26% and –23% in the 24 Gy and 16 Gy groups, respectively) as in the sham group (11%).

Adverse events were generally equally distributed among the groups, and no radiation retinopathy or other serious adverse events were seen in any study eye.

A post-hoc analysis looked for the best responders to stereotactic radiotherapy and found that they had significant fluid at baseline and a lesion size of 4 mm or less in greatest linear dimension. This dimension corre-
sponds to the size of the spot beam diameter (90% isodose) projected onto the retina by the IRay device. The 26% of patients with both of these characteristics had a 55% reduction in number of prn injections ($P = .0001$) and an improvement of a mean of 6.8 ETDRS letters, significantly better than equivalent patients in the control group ($P = .0037$).

**CONCLUSIONS**

In the INTREPID study, stereotactic radiotherapy with the IRay device resulted in a significant reduction in the number of prn ranibizumab injections given over the course of 1 year, equivalent or better visual acuity, and twice the reduction in thickness on OCT, compared with sham irradiation. A post-hoc responder analysis was also encouraging.

The 1-year results of the INTREPID study are encouraging for clinicians and for individuals with neovascular AMD. The prospect of needing fewer eye injections will appeal to any patient receiving anti-VEGF therapy, and for certain subsets there is the added advantage of an improved visual outcome. The study showed a favorable safety profile for the procedure, but ongoing safety review is important, as radiation retinopathy can occur beyond 1 year.

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