Radiation Therapy for Age-Related Macular Degeneration

Investigational devices are designed to provide targeted delivery of radiation.

BY DARIUS M. MOSHFEGHI, MD; ANDREW A. MOSHFEGHI, MD, MBA; AND PETER K. KAISER, MD

Radiation therapy has been evaluated extensively as a treatment for choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) because of its antiangiogenic, antifibrotic, and anti-inflammatory properties.1-3 Historically, radiation for AMD has been delivered with two broad approaches: (1) radiotherapy with external beam (megavoltage X-rays, proton beam) and (2) brachytherapy with radioactive isotopes (strontium-90, palladium-103).4-11 Radiation therapy was never widely adopted by the retinal community because it did not demonstrate a reproducible positive effect on the visual acuity in patients with AMD.7,8 Radiation therapy also had inconclusive, beneficial anatomic findings8,11 and was associated with complications in a small number of patients.6 To date, the results of radiation therapy in AMD have been disappointing, and its use has been supplanted by vascular endothelial growth factor (VEGF) inhibitors.12-14

DELAYED ONSET
The effects of radiation on neovascularization are usually delayed, sometimes by several months. During this period, the choroidal neovascular membrane can continue to grow and cause retinal damage, leading to a reduction in visual acuity.

Epimacular Brachytherapy—a Promising Treatment Option for Patients With Neovascular AMD

BY PRAVIN U. DUGEL, MD

The direct health care cost associated with age-related macular degeneration (AMD) is estimated to be $255 billion.1 Health care systems cannot continue to afford this cost, and retinal services do not have the time or the personnel to adequately treat the growing number of patients who need monthly intravitreal injections of antivascular endothelial growth factor (anti-VEGF). Combination radiation and anti-VEGF therapy may significantly decrease the treatment burden of patients with neovascular AMD. When used together, anti-VEGF agents and radiation produce better outcomes in oncology patients than either therapy does on its own.2

The antiangiogenic properties of radiation treatments are also associated with radiation therapy.6 Clinical studies of external beam radiation in neovascular AMD have produced mixed results, leaving retinal specialists undecided about whether it is a viable treatment option. Because the delivery of external beam radiation is not localized, its ability to target only affected cells without collateral damage to healthy tissue is significantly reduced. Low-dose beta radiation inhibits angiogenesis and has been used in the treatment of ocular tumors.5

EPIMACULAR BRACHYTHERAPY
Investigational treatments using epimacular brachytherapy provide targeted delivery of beta-ionizing radiation after vitrectomy.

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rectomy.6,7 Epimacular brachytherapy combines a three-port pars plana vitrectomy with a surgical device that delivers beta radiation. The device (Vidion Anti-Neovascular [ANV] Therapy System; NeoVista, Inc., Fremont, CA) comprises a strontium-90 source within an endoscopic probe that is held over the AMD lesion for approximately 4 minutes and then removed from the eye. The Vidion ANV is designed to deliver targeted beta radiation to leaking blood vessels that affect central vision without causing damage to surrounding tissues. The treatment delivers the highest dose (24 Gy) to the center of the lesion, but the optic nerve receives only 2.4 Gy and the lens 0.0006 Gy.

Strontium isotopes are also used in cancer treatments, most notably strontium-89 for the treatment of prostate cancer. Isotope choice is a crucial factor when opting to use radiation treatments, as different molecules have various treatment times. The choice of strontium-90, coupled with dosing rate and fractionation, is what enables epimacular brachytherapy with the Vidion ANV to deliver high doses of radiation to treat the lesions without causing damage to the surrounding tissues. Two earlier phase 2 studies showed that epimacular brachytherapy had good potential to treat neovascular AMD,6,8 and preliminary findings from other ongoing studies are supporting earlier conclusions.

CLINICAL TRIALS

NeoVista, Inc., is currently conducting three clinical trials delivering epimacular brachytherapy with the Vidion ANV in patients with AMD. Macular Epiretinal brachytherapy versus Lucentis Only Treatment (MERLOT), a large randomized controlled clinical trial, is under way to evaluate the Vidion ANV system in patients who continue to require regular anti-VEGF injections. The trial has a targeted recruitment of 363 subjects in the United Kingdom. Patients in the MERLOT study are randomized to either epimacular brachytherapy or anti-VEGF monotherapy (control). Both groups can receive ranibizumab (Lucentis; Genentech, Inc.,) rescue treatment based on predefined retreatment criteria. The coprimary outcome measures are the mean number of anti-VEGF injections during 12 months and mean Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity.

In the United Kingdom, MERLOT has been awarded portfolio status as part of the government’s “Best Research for Best Health” initiative.

The Macular Epiretinal Brachytherapy in Treated Age-Related Macular Degeneration Patients (MERITAGE) study enrolled patients who had as many as 23 previous injections of anti-VEGF therapy before receiving epimacular brachytherapy. All patients who entered the study had to have received at least five maintenance injections in the 12 months preceding enrollment or three injections in the 6 months preceding enrollment. Preliminary observations suggest that a single procedure of epimacular brachytherapy reduced patients’ need for ongoing anti-VEGF therapy, indicating that the Vidion ANV system may reduce the burden of treatment in these resource-intensive patients while maintaining good visual outcomes.9 Additionally, 63% of patients showed some improvement in visual acuity, with 50% gaining at least five letters at 6 months.

The CNV Secondary to AMD Treated with Beta Radiation Epiretinal Therapy (CABERNET) study is a phase 3 multicenter, randomized, controlled trial of epimacular brachytherapy using a prototypic device. The trial recently completed its recruitment target of 450 patients at 45 clinical centers worldwide. Unlike MERLOT, which targets patients who have commenced anti-VEGF therapy, CABERNET recruited treatment-naïve patients. The 1-year results of this study are expected to be available early next year.

With phase 3 results from CABERNET on the immediate horizon, epimacular brachytherapy may become a viable therapeutic option capable of reducing the treatment burden to health care systems globally.

Pravin U. Dugel, MD, is managing partner of Retinal Consultants of Arizona and founding member of the Spectra Eye Institute in Sun City, Arizona. Dr. Dugel is also a clinical associate professor with the Department of Ophthalmology, Doheny Eye Institute, University of Southern California, Los Angeles. He is a consultant to Akon Laboratories, Inc.; Abbott Medical Optics, Inc.; Genentech, Inc.; Regeneron Pharmaceuticals, Inc.; OraCyte Therapeutics, Inc.; and MacuVision, Inc. He is also a consultant to and a minor equity owner of NeoVista, Inc. Dr. Dugel may be reached at pdugel@gmail.com.

The IRay: a Noninvasive, Robotically Controlled X-Ray Irradiation Therapy of Neovascular AMD

BY DARIUS M. MOSHFEGHI, MD; ANDREW A. MOSHFEGHI, MD, MBA; AND PETER K. KAISER, MD

Historically, the treatment of choroidal neovascularization (CNV) due to neovascular age-related macular degeneration (AMD) with radiation has been ineffective.\(^1,6\) Two possible explanations for these observations are the relatively poor targeting scheme employed\(^7\) and the lack of immediate onset of action. Poor targeting in previous methodologies led to large treatment volumes, which were associated with unacceptably high rates of complications.\(^5,6\) Additionally, the 3- to 4-month delay in onset of action often allowed the CNV to progress, causing hemorrhage, fibrosis, and increased lesion size.\(^2\) At the time that radiation was initially introduced as a possible treatment modality for CNV secondary to neovascular AMD, rapid-onset and potent pharmacotherapeutics against CNV like anti-vascular endothelial growth factor (anti-VEGF) agents such as ranibizumab or bevacizumab (both from Genentech, Inc.) were not available as treatment adjuncts.

The IRay system (Oraya Therapeutics, Inc, Newark, CA) is an experimental device that uses a robotically controlled treatment platform to deliver low-energy X-rays precisely and reproducibly to the macula of patients with wet AMD in an office-based setting. The X-ray source is an off-the-shelf device similar to technology used for dental X-rays. The IRay does not require the patient to wear specialized shielding in the treatment room. Treatment planning with the IRay includes axial length measurement and the optic disc edge-to-fovea center distance. To limit radiation exposure of the optic nerve, patients with an optic disc edge-to-fovea center distance less than 3 mm are ineligible for treatment.

HOW IT WORKS

When treatment is initiated, the robotically controlled device moves the X-ray point source 150 mm from the plane of the macula following a predetermined offset directly over the macula. Three 3.5-mm beams are introduced through the inferior pars plana at the 5-, 6-, and 7-o’clock positions. Each beam consists of variable Gy (for example, 5.33 Gy) at a distance of 150 mm from the point source. The beams overlap precisely on the macula.

LITERATURE

Many studies that have reported anatomic outcomes after radiation therapy relied on ophthalmoscopic or angiographic descriptors and lacked uniformity in terminology and trained readers.\(^7,8,11\) Despite this, research has indicated that radiation ultimately produced a beneficial anatomic effect with reduced leakage, lesion size, and/or the rate of lesion growth over time.\(^5,8,11\) Optical coherence tomography was not used in any of these studies.

Complications due to radiation were noted in only three studies.\(^5,6,9\) These were self-limited in the case of a strontium-90 brachytherapy patient\(^7\) and resulted in a severe loss of visual acuity in two other studies, both of which employed proton beam radiotherapy.\(^5,6\) There were no cases of radiation retinopathy reported in any of the external beam radiotherapy or palladium-103 plaque brachytherapy treatments.\(^8,11\) Published risk factors for radiation retinopathy include (1) high total dose (typically 40 to 50 Gy)\(^18,21\), (2) high dose per fraction (reported higher with fractions greater than 2 Gy)\(^18,19,21\), (3) high dosing rate, (4) large volume of tissue irradiated\(^21,23\), and (5) presence of mitigating factors such as concomitant chemotherapy or pre-existing vasculopathy.

Much of our understanding of radiation retinopathy comes from head and neck oncology where the eye is secondarily irradiated, such as in the case of nasopharyngeal cancer.
the macula to achieve a single 4-mm spot of total dose (16 Gy). By selecting the inferior pars plana, which is offset from the limbus, the beams pass through the eye unimpeded by the brow or nose, avoiding the lens and the optic nerve. A lid speculum pulls the lower eyelid out of the path of radiation. The eye is constantly stabilized and tracked using an I-Guide (Oraya Therapeutics, Inc.) suction-based contact lens system to ensure that any eye movement is accounted for in the treatment (discussed later). The use of orthovoltage X-rays with the I-Guide system has been validated in cadaveric eye studies, demonstrating that a cohesive 4-mm treatment spot is reproducibly achieved using three overlapping spots without affecting the optic nerve and lens. Less than 1 Gy is delivered to the optic nerve.

SAFETY FEATURES

At the beginning of the treatment, the patient’s head is positioned on the headrest and secured with a restraint that doubles as a radiation shield. The eye is then independently secured in position with the I-Guide, a vacuum-coupled contact lens interface under low suction to maintain ocular stability during treatment while detecting eye motion. The device operator, positioned to the left of the patient, enters the relevant treatment details into the IRay system and selects the treatment dose (16 or 24 Gy). Before treatment is initiated, the patient is instructed to grasp the handholds, as safety is of paramount concern. The IRay will automatically interrupt the treatment if the handholds are released, the head shield/restraint is opened, or the I-Guide is removed. The most important safety feature is an active eye tracking system. The IRay employs infrared cameras that track the eye using the reflective fiducials on the I-Guide in the x, y, and z dimensions as well as any rotational movements. If any of these parameters exceeds preset thresholds on an individual or combined basis, an immediate gating event will be initiated, interrupting the radiation treatment until the eye is returned to its baseline position. Also, there is an emergency shut-off button next to the operator.

CLINICAL TRIALS

More than 60 patients have been treated in a phase 1 study of the IRay device, and results from that trial led to the design and initiation of the phase 3 trial. The phase 1 study was conducted in Mexico City with Virgilio Morales Canton, MD, and colleagues at Asociacion Para Evitar La Ceguera. It evaluated two radiation doses (16, and 24 Gy) and different treatment regimens. Ranibizumab was used in combination with radiation to avoid the delay in treatment effect traditionally associated with radiation. Two protocols were implemented: (1) ranibizumab at time zero, followed by IRay radiation application (16 or 24 Gy) between days 1 and 14, another ranibizumab dosage at day 30, followed by monthly as-needed ranibizumab treatment based on prospectively defined retreatment criteria and (2) 16-Gy radiation at time zero, followed by monthly as-needed ranibizumab based on prospectively defined retreatment criteria. Unlike previous studies in AMD, these trials were the first to include treatment-naïve and previously treated patients. Long-term follow-up is ongoing.

Oraya Therapeutics, Inc, announced in January 2010 that enrollment is under way for what it called the first masked and sham-controlled study to demonstrate the efficacy and safety of radiation therapy for wet AMD. The phase 3 clinical trial is being conducted at seven European sites and will include a minimum of 150 patients previously treated with anti-VEGF inhibitors (ranibizumab or bevacizumab), with approximately one-third of patients receiving sham treatment in the IRay device and the remainder receiving traditional radiation dosing with the IRay system.

Peter K. Kaiser, MD, is a professor of ophthalmology at the Cleveland Clinic Lerner College of Medicine and a member of the Vitreoretinal Department at the Cole Eye Institute, Cleveland Clinic. He is a consultant to and equity owner of Oraya Therapeutics, Inc. Dr. Kaiser may be reached at pkkaiser@aol.com.

Andrew A. Moshfeghi, MD, MBA, is an assistant professor of Ophthalmology, Vitreoretinal Surgery & Diseases at the Bascom Palmer Eye Institute of the University of Miami’s Miller School of Medicine. He is a consultant to Oraya Therapeutics, Inc. Dr. Moshfeghi may be reached at (561) 515-1500, amoshfeghi@med.miami.edu.

Darius M. Moshfeghi, MD, is an associate professor of Ophthalmology at Stanford University, and founder and director of the SUNDROP Network. He is a consultant to and equity owner of Oraya Therapeutics, Inc. Dr. Moshfeghi may be reached at (650) 323-0231, dariusm@stanford.edu.

carcinoma or choroidal malignant melanoma. It is difficult—if not impossible—to separate out the volume of tissue irradiated from any of the other risk factors. Two studies that reported a severe loss of visual acuity after radiation therapy used proton beam therapy and treated a large portion of the retina compared with plaque brachytherapy or external beam radiotherapy. In fact, to ensure that radiation was delivered to the area of interest, the treatment zone had to be significantly enlarged such that 50% of the total dose (12 of 24 Gy) was being delivered to 34% of the total retinal volume. Further implicating volume as the causative factor as opposed to dose was that no dosing effect was observed between the two groups (16 Gy and 24 Gy), despite a 50% increase in dose.

FUTURE APPROACHES

Two companies, NeoVista, Inc. (Fremont, CA), and Oraya Therapeutics, Inc. (Newark, CA), are evaluating technologies designed to provide more targeted delivery of radiation. The Vision Anti-Neovascular (ANV; NeoVista, Inc.) therapy system utilizes a surgically delivered intraocular exposure of radiation to the macula with strontium-90 in an epiretinal plaque brachytherapy technique over leaking blood vessels that affect central vision without damaging surrounding tissues. The IRay system (Oraya Therapeutics, Inc.) is an investigational, stereotactic, radiosurgical device that uses a noninvasive, robotically controlled platform to deliver low-energy X-rays. Both devices have been shown in early-phase clinical trials to accurately and reproducibly deliver radiation to the macula in a small volume, limiting the risks of bystander effects and subsequent radiation retinopathy that are seen when larger volumes of the retina are treated. Both of these new radiation approaches utilize a concomitant VEGF-inhibitor strategy, thus limiting the likelihood of progressive visual acuity decline, hemorrhage, and fibrosis while the radiation effect is maturing. Neither therapy is approved by the FDA for use in humans in the United States, although pivotal trials are under way. Postapproval surveillance will be important to ascertain what long-term effects, if any, may exist for this chronic macular disease with these novel radiation delivery systems.

Peter K. Kaiser, MD, is a professor of ophthalmology at the Cleveland Clinic Lerner College of Medicine and a member of the Vitreoretinal Department at the Cole Eye Institute, Cleveland Clinic. He is a consultant to and equity owner of Oraya Therapeutics, Inc. Dr. Kaiser may be reached at pkkaiser@aol.com.

Andrew A. Moshfeghi, MD, MBA, is an assistant professor of ophthalmology, vitreoretinal surgery and diseases, at the Bascom Palmer Eye Institute of the University of Miami’s Miller School of Medicine. He acknowledged no financial interest in the products or companies mentioned herein. Dr. Moshfeghi may be reached at (561) 355-8608; amoshfeghi@med.miami.edu.

Darius M. Moshfeghi, MD, is an associate professor of ophthalmology at Stanford University and founder and director of the SUNDROP Network. He is a consultant to and equity owner of Oraya Therapeutics, Inc. Dr. Moshfeghi may be reached at (650) 323 0231; amoshfeghi@stanford.edu.