Radiation Treatments for Neovascular AMD

A conversation with Pravin U. Dugel, MD

Radiation therapy for neovascular age-related macular degeneration (AMD) has been studied since the 1990s, when numerous studies employing external beam radiotherapy returned variable results—some positive, some negative, some equivocal. Investigators at the time used a variety of radiation doses and fractionations, and they relied on external beam radiotherapy, a delivery method that was not precisely localized, limiting its ability to target a specific radiation dose to a specific area of the eye.

Interest in radiotherapy for neovascular AMD has been revived recently with the introduction of several new technologies. The most advanced of these, in regard to clinical investigation, is the Vidion ANV Epimacular Brachytherapy System (NeoVista), a probe that is inserted into the posterior segment after vitrectomy to deliver 24 Gy strontium-90 brachytherapy directly over the choroidal neovascular membrane. This technology has been evaluated in the recently completed CABERNET study in treatment-naïve eyes. Another study in previously treated eyes, MERLOT, has now completed recruitment. A second device, the iRay (Oraya), which delivers low energy x-rays through the pars plana, has been evaluated in a pilot trial, and 1 year results of a larger European trial are expected this year. A third device, from Salutaris Medical Devices Inc., delivers brachytherapy through the posterior sclera, and early results in 6 patients have been presented.

Retina Today *asked Pravin U. Dugel, MD, to provide an update and perspective on these therapies for the focus on AMD in this issue. Dr. Dugel is a consultant to and minor shareholder in NeoVista.*

Retina Today: You recently presented the 2-year results of the CABERNET clinical study of epiretinal brachytherapy.[1] Can you briefly run through the topline results for us?

Pravin U. Dugel, MD: Yes. Just to explain the procedure briefly, epimacular brachytherapy (EMBT) delivers a synergistic triad of increased oxygenation to the retina due to vitrectomy, 24 Gy of targeted beta radiation through the brachytherapy probe, and antiangiogenic therapy with injections of an anti-VEGF agent. CABERNET was a prospective randomized active-controlled phase 3 study with a noninferiority design comparing EMBT plus 2 injections of ranibizumab (Lucentis, Genentech) with anti-VEGF monotherapy using a modified PIER protocol. The primary endpoint was visual acuity, specifically the percentage losing less than 15 letters on the ETDRS chart. The study included 457 treatment-naïve patients, 302 in the treatment arm and 155 in the control arm, with all types of neovascular AMD lesions.

In the original PIER study, at 2 years, 10 injections were required to achieve an end result of a mean loss of 2.3 letters of visual acuity. In CABERNET, in the EMBT group, a mean 6 injections were required at 2 years for a mean visual acuity loss of 2.5 letters. In the control group receiving ranibizumab monotherapy in a modified PIER protocol, with a mean 11 injections at 2 years, there was a mean gain of 4.4 letters.

The bottom line is that CABERNET did not achieve its endpoint with a 10% noninferiority margin. It did, however, demonstrate an acceptable safety profile for EMBT at 2 years.

In an unplanned, post-study subanalysis, it was observed that a subgroup of patients appeared to benefit from the device. There were 44% of patients in the EMBT group who did not require rescue anti-VEGF treatment in year 1 and required a mean of 1 rescue treatment in year 2, and 25% of patients in the EMBT group who did not require rescue treatment at all throughout the 2-year period. However, although there appears to be this subgroup of patients who benefit from the device, the patients in this subgroup cannot be reliably and consistently identified at this time. We cannot look at a patient in the clinic and say "This patient will do well with EMBT." Also, it must be emphasized that this subgroup was identified in an unplanned, post-study subanalysis,

which has implications for the reliability of the finding.

Retina Today: In retrospect, could the trial have been designed differently?

Dr. Dugel: Two things could have been done differently in CABERNET. First, a study of this size should probably not have looked at treatment-naïve patients, but rather previously treated patients, because that is probably where the technology will belong if it is proved effective.

Second, more emphasis should have been placed on probe placement. The primary concern when the study was started in 2006, appropriately, was safety, because that is always an issue with radiation. The technology was thought to be safe because of the way the radiation is delivered, exactly where the pathology is, and because of the radioisotope that was chosen: beta radiation emitted by strontium-90, which has a very rapid decay, about a 10% decrease in energy for every 0.1 µm distance from the epicenter. And sure enough, this was true, the safety profile of the device has been very good.

However, because of that same rapid decay, if the probe is not placed in its proper position, the effective dosage of radiation is not delivered to the target. The probe was designed so that its angled tip should be placed just touching the retina. In the CABERNET protocol, emphasis was not placed on the positioning. The one variable that appears to affect the efficacy of the treatment is the surgeon. If the surgeon was dedicated to placing the tip of the probe on the retina and delivering the radiation the way it was designed, there was a much better chance patients did well.

Another bit of evidence in this regard is the condition of 10 patients in CABERNET who had suspected radiation-based retinopathy. First, all of these radiation changes were nonproliferative, consisting of telangiectasia, dot hemorrhages, etc., and none of them progressed to proliferative radiation retinopathy over the 2-year period. Second, as a group, these patients tended to do well regarding visual acuity gain and number of injections given. This tells us that, when the proper dose of radiation is delivered—as indicated by focal nonproliferative radiation retinopathy—these patients can do well.

So these are 2 lessons learned from the study. But one has to report the bottom line, which is that the study did not meet its endpoint.

Retina Today: So where does EMBT currently stand?

Dr. Dugel: In my opinion, EMBT is not going to be a first-line treatment for neovascular AMD. If it is in our armamentarium, it will probably be a second- or third-line treatment. I say that because promising results have been seen in previously treated patients. The MERITAGE study, a small, 53-patient study, included patients with persistent fluid despite a number of anti-VEGF treatments; some patients had been treated with more than 35 injections over 5 years. In preliminary results in that study, 63% of patients showed some improvement in visual acuity, with 50% gaining at least 5 letters at 6 months, and the need for ongoing anti-VEGF treatment was reduced.[2]

Based on the encouraging results of the MERITAGE study, a larger study in patients with persistent fluid has just finished recruiting, the MERLOT study. This trial is sponsored by the UK government, not NeoVista, and it will be about a year before those results are announced. The results of MERLOT will tell us a lot as to the viability of and potential role for this technology.

Retina Today: EMBT is a fairly invasive treatment, requiring vitrectomy and the use of the radiation probe. In the era of pharmacologic treatment of wet AMD, will invasiveness be part of the consideration of when this treatment is appropriate?

Dr. Dugel: It is a surgical treatment, no doubt. It is thought that this is 1 part of the synergistic triad of benefit, the vitrectomy allowing for increased oxygenation, the EMBT providing focused delivery of radiation, and the established beneficial effect of anti-VEGF treatment.

It certainly is an invasive treatment, and that is part of the reason this will probably not be a first-line therapy. If the technology is proven beneficial, it will be indicated for patients who have had numerous injections but continue to have subretinal fluid and who can't bear the treatment burden of repeated injections.

This is a real issue in the United States and even more so outside the United States: the issue of treatment burden and patient attrition. Our current monotherapy treatment model, while the results are very good and the bar is set very high, is dependent on treatment given on a monthly or near monthly basis. Monthly treatment for a disease that may have a 10- or 15-year cycle, depending on the age of the patient, is simply not sustainable. In a few studies in which less than monthly injections have shown fairly good results, monthly monitoring seems to be essential. Neither monthly injections nor monthly monitoring is sustainable in the long term. It results in attrition of patients, who can't bear the treatment burden. Simultaneously, it also results in attrition of photoreceptor cells. The therapy converts wet AMD into dry AMD, and patients then often lose vision because their photoreceptor cells eventually die.

We are in need of a sustainable treatment model—not

instead of what we have, but in combination with what we have. Where radiation will stand in that treatment model, we really don't know at this point.

Retina Today: Let us move on to the other technologies. The Oraya iRay delivers low energy x-rays from outside the eye.

Dr. Dugel: The Oraya technology is fascinating, particularly the eye-tracking technology. The system includes a low voltage x-ray source, an eye tracking system, and a robotically controlled delivery system. The low-voltage x-rays are delivered to the macula noninvasively through the inferior pars plana in 3 beams, each delivering a third of the total dose to the macula. It is an external x-ray delivery system, so it involves a more potent radiation energy source than the beta radiation that the EBRT device delivers.

Results of a 6-month safety and preliminary efficacy study with this system were recently published.[3] A single 24-Gy treatment was administered in a consecutive series of patients with neovascular AMD, both treatment-naïve and previously treated. In 19 patients who completed 6-month follow-up, no radiation-related adverse events were seen, and there was overall improvement in visual acuity. Patients received an average of 0.4 additional ranibizumab injections after 2 initial mandated injections.

These phase 1 results are interesting and encouraging. A larger trial, called INTREPID, completed enrollment of 226 patients in Europe last year, and we await the 1-year results, expected in the second quarter of this year.

Retina Today: The newest entry is a device, apparently yet unnamed, from Salutaris Medical Devices.

Dr. Dugel: Few of us know much about this technology. I have seen 1 presentation, by Reid F. Schindler, MD, at Retina 2012 in Hawaii.[4] He announced short-term results of a phase 1 study in 6 patients.

In this procedure, called episcleral brachytherapy, the surgeon places a probe behind the posterior sclera and applies 24 Gy of radiation. The probe is illuminated, and the surgeon verifies placement using indirect ophthalmoscopy. All patients reportedly experienced some improvement in vision (at least 4 letters), and no reported serious adverse events were seen. The therapy was given in conjunction with anti-VEGF treatment.

Retina Today: Final thoughts on the overall status of radiation for treatment of wet AMD?

Dr. Dugel: Although preliminary results with these technologies appear promising, as with all kinds of new technology that are exciting, they should be investigated, but we also have to keep the early results in perspective.

In phase 1 trials we look for 2 things: 1 is the entity being investigated safe, and 2 is there a biological signal? But to move from phase 1 to a larger phase 2 or 3 study is a large leap. And as we have seen, the results don't always bear out. So while we can say that phase 1 results are interesting and encouraging, we have to wait for more definitive data.

It's crucial for the sake of our patients to ask interesting questions, to do good, honest studies, but, most important, to report the results as transparently as possible. That's why, even when we have interesting results, it's important to put them in perspective. For instance, take the subanalysis of the CABERNET study. Although it's interesting to see that there seems to be a subgroup of patients who benefit, it must be taken in proper perspective as a post-study unplanned analysis because that has implications as to the reliability of the data. It's very important for the sake of the scientific community that we try to be as transparent as possible.

Will there be a role for radiation in the treatment of neovascular AMD? These studies are well worth doing because this question remains to be answered. Right now we have a monotherapy treatment model that is not sustainable. Once the studies are done, we need to report the data openly, honestly, and transparently. At the end of the day, the data will determine appropriateness of all technology. That is the way it should be. We are scientists, and science should dictate what we do. We must remember that the bar is set very high. The results of monotherapy, though not sustainable in the long term, when given appropriately, are extremely good. We mustn't forget that. ■

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