Epimacular Brachytherapy: Reducing Neovascular AMD Treatment Burden

Concurrent use of epimacular brachytherapy and anti-VEGF injection shows promise.

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Age-related macular degeneration (AMD) may affect as many as 2.5 million people in the European Union.[1] The prevalence rate is approximately 3.3% in those older than 65 years of age, and up to 1.1 million people may have bilateral AMD.[1] In the United States, up to 3 million people are expected to have the symptoms of the disease by 2020,[2] and 155,000 new cases are predicted to be diagnosed yearly.[3]

Despite its high prevalence and potential to severely reduce vision, public awareness of AMD is surprisingly low. According to the AMD Alliance, 75% of those recently surveyed were not familiar with the disease or the impact it may have on a person's quality of life.[4] In Europe, the cost to treat patients with AMD is up to eight times higher than the cost to treat those without the disease, with annual costs of approximately 1.5 billion per country.[5]

Anti-vascular endothelial growth factor (anti-VEGF) agents are widely accepted as first-line treatment for neovascular AMD. Large randomized controlled trials have showed the benefit of ranibizumab, and evidence is emerging that the parent drug bevacizumab also confers benefit. Data from MARINA, ANCHOR, PIER and HORIZON studies show that patients require injections on a monthly basis to achieve the best vision outcome. When ranibizumab is administered every 3 months or on an as-needed basis, vision results are not as good. More recently, case studies have shown that long-term treatment with anti-VEGF agents may result in tachyphylaxis, potentially affected by both local and systemic factors.[6,7]

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An ideal treatment for neovascular AMD would maintain or improve a patient's vision while limiting the number of follow-up treatments. In clinical oncology, combining anti-VEGF treatments and radiation has been successful.[8,9] In this specialty, concurrent dosing of radiation, chemotherapy, and antiangiogenesis has had more success than any of the individual elements alone or any combination of two components.[10]

External beam radiation has been used previously to treat AMD. This treatment modality delivers a therapeutic dose to large volumes of tissue and must travel through surrounding tissues to access its target, which can cause collateral damage. The results were often

similar to or only marginally better than the natural history.[11-14] Further, those studies that did show a benefit did not produce visual results that would be acceptable in the era of anti-VEGF therapy.

Figure. The Vidion beta-radiation device.

RADIATION REVISITED

Despite the generally disappointing results with external beam radiation, the hypothesis that radiation can treat neovascular AMD remains tenable. Radiation preferentially damages proliferating cells, and this applies to many of the cells that contribute to AMD genesis and progression. Specifically, radiation has been shown to target endothelial cells, fibroblasts, and inflammatory cells.[15,16] The crux of the problem in treating AMD with radiation is delivering a lethal dose of radiation to a small area (the CNV complex), while delivering sublethal (repairable) or no damage at all to surrounding tissues.

Recently, there have been attempts to provide more targeted delivery of radiation, through epimacular brachytherapy. Epimacular brachytherapy combines a three-port pars plana vitrectomy with a surgical device that delivers beta radiation. The device (Vidion Anti-Neovascular Therapy System, NeoVista, Fremont, CA; Figure 1) comprises a strontium 90 source within an endoscopic probe. It is remotely advanced, held over the AMD lesion for approximately 4 minutes, and then removed from the eye.

There are two potential benefits to using this type of radiation system for the treatment of neovascular AMD. First, the procedure is performed in conjunction with vitrectomy. It has been theorized that vitreous surgery can improve oxygen tension, which may play a role in CNV formation.[17-19] Moreover, oxygenation enhances the effects of radiation damage by increasing free radical formation and ultimately inducing double-stranded DNA breaks.[20,21] Therefore, a combination of anti-VEGF therapy, vitrectomy, and radiation may be uniquely suited for the treatment of AMD.

Second, although Vidion delivers a high therapeutic dose to the retina, the dose to collateral eye structures (optic nerve, lens) and the whole body is low. The concept of brachytherapy is increasingly utilized in oncology; for example in radioactive seed treatment of the prostate, wherein the radioactive source is placed close to or within the target tissue to deliver a precise dose and minimize damage to healthy tissue.

The Vidion device delivers the radiation directly to the lesion, and the radioactive isotope strontium 90 has a very rapid falloff with increasing distance from the source. 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. Utilizing this approach, damage to the healthy tissues surrounding the lesion is minimized. Two separate preliminary studies on epimacular brachytherapy have shown no serious adverse events related to the device and a high percentage of patients maintaining or improving vision.[22,23]

Another manufacturer is investigating radiation treatment using an X-ray based system. The IRay system (Oraya Therapeutics, Newark, Calif.) delivers a total dose of 24 Gy in three simultaneous beam fractions of 8 Gy. An advantage of this system is that it is office-based, and unlike Vidion it does not entail any surgical risk. The corollary of this is that the improved oxygenation that may occur following vitrectomy may reduce the therapeutic effect of radiation. There is also the potential risk of collateral damage from X-rays, as a much larger volume of tissue receives the maximum dose of 24 Gy, although the device uses three separate beams targeted on the macula to reduce the maximum exposure to other ocular structures. A phase 2 study has been registered at clinicaltrials.gov.

STUDIES OF EPIMACULAR BRACHYTHERAPY

A large, randomized controlled clinical trial is now under way to evaluate the Vidion system in patients who continue to require regular anti-VEGF injections. The MERLOT trial has a target recruitment of 363 subjects in the UK. The trial receives support from the National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN). The CCRN was created as part of the UK Government's Research and Development strategy. The CCRN aims to provide support for studies that are sci-

entifically robust and address areas of importance to the National Health Service. Patients in the MERLOT study are randomized to either epimacular brachytherapy or anti-VEGF monotherapy (control). Both groups receive ranibizumab rescue treatment based on predefined retreatment criteria. The co-primary outcome measures are mean number of anti-VEGF injections over 12 months and mean ETDRS visual acuity.

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The interim results from a preceding study of 50 patients were recently reported.[24] The 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 (n=16) suggest that a single procedure of epimacular brachytherapy reduced patients' need for ongoing anti-VEGF therapy. Importantly, 63% of patients showed some improvement in visual acuity, with 50% gaining at least 5 letters at 6 months. This was better than expected, as patients were already receiving anti-VEGF treatment and tended to have refractory disease.

The CABERNET study is a large randomized controlled trial of epimacular brachytherapy using a prototype device. The trial recently completed its recruitment target of 450 patients. Unlike MERLOT, which targets patients who have commenced anti-VEGF therapy, CABERNET recruited treatment-naïve patients.

SUMMARY

Radiation preferentially damages the cells that mediate vision loss in AMD. It was therefore somewhat unexpected that early studies of external beam radiation failed to show significant benefit. Interest in radiation treatment has recently been rekindled, using devices that provide more focal delivery and less collateral damage than external beam therapy. Large randomized clinical trials of epimacular brachytherapy are under way. If these replicate the findings of phase 2 studies, then patients may look forward to fewer anti-VEGF injections and a reduced burden of treatment. ■

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