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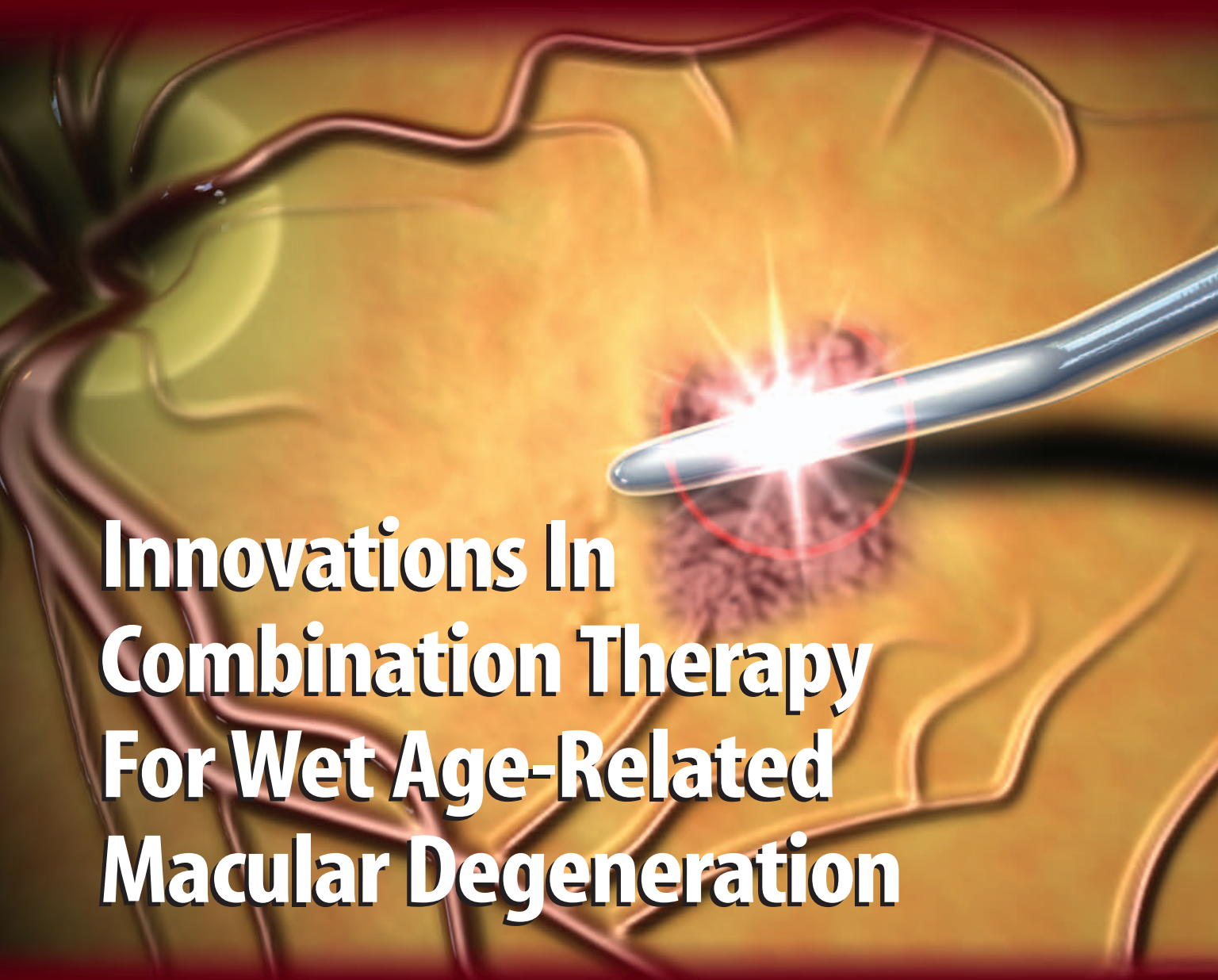

Innovations In Combination Therapy For Wet Age-Related Macular Degeneration

FEATURING:

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TARGET AUDIENCE

This certified CME activity will be designed for vitreoretinal specialists and general ophthalmologists managing vitreoretinal diseases.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

Understand the impact of wet AMD epidemiology and the burden of blindness in an aging population on their ophthalmic practice

Define the pathogenesis of wet AMD and properly educate patients requiring treatment

Evaluate clinical outcomes of combination strategies for pharmaceutical, surgical and radiation therapy in wet AMD

METHOD OF INSTRUCTION

Participants should read the continuing medical education (CME) activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions, and the course evaluation. To answer these questions online and receive real-time results, please visit http://www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 2 *AMA PRA Category 1 Credits*.™ The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation and Retina Today. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this educational activity for a maximum of 2 *AMA PRA Category s Credits*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

FACULTY CREDENTIALS

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DISCLOSURE

In accordance with the disclosure policies of the Dulaney Foundation and to conform with ACCME and FDA guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufac- turers of any commercial products/devices, or providers of com- mercial services; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Carl C. Awh, MD, states that he is a member of the medical advisory board for Neovista, Inc.

Borja Corcóstegui, MD, states that he has no financial relationships to report.

Pravin U. Dugel, MD, states that he is a consultant for Alcon Laboratories, Inc., Genentech, Inc., Neovista, Inc., and Macusight. He is on the speakers' bureau for Alcon Laboratories, Inc., Genentech, Inc., Neovista Inc., and Macusight.

Timothy L. Jackson, PhD, FRCOphth, states that he is consultant for Merck, Inc., and that his employer received research grants from Neovista, Inc.

Joseph O'Sullivan, MD, FRCPI, FFRRCSI, states that he has no financial relationships to report.

Peter Wiedemann, MD, states that he has no financial relationships to report.

All of those involved in the planning, editing, and peer review of this educational activity have indicated that they have no financial relationships to disclose.

CONTENT VALIDATION

In compliance with ACCME standards for commercial support and the Dulaney Foundation's policy and procedure for resolving conflicts of interest, this CME activity was peer reviewed for clinical content validity to ensure the activity's materials are fair, balanced and free of bias; the activity materials represent a standard of practice within the medical profession; and any studies cited in the materials upon which recommendations are based are scientifically objective and conform to research principles generally accepted by the scientific community.

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STATEMENT OF NEED

The increasing incidence of wet age-related macular degeneration and other degenerative retinal conditions due to the aging population has been well documented, with considerable evidence provided by the landmark Beaver Dam Eye Study.[1] Additionally, the progression of AMD has been studied in relation to increased abdominal obesity, which has reached significant levels in our increasingly sedentary society.[2-4]

Recent statistics from the Centers for Disease Control and Prevention (CDC) indicate a staggering increase in projected choroidal neovascular disease associated with rising diabetes in the United States.

In response to these concerns regarding the management of wet AMD and other choroidal neovascular conditions, new treatment strategies and comparisons to established treatment modalities continue to rapidly evolve.[5-9] Rapid advancements continue to produce clinical evidence for interpretation and discussion among experts regarding monotherapy and combination strategies using photodynamic therapy, anti-vascular endothelial growth factor agents (anti-VEGF), and beta radiation therapy.[5-8]

In concert with pharmaceutical, surgical and radiation treatment advances, retinal imaging technologies continue to evolve and move quickly into routine use during both anterior and posterior segment surgery. For example, the preoperative use of optical coherence tomography in cataract surgery for macular edema detection has recently been discussed as an effective tool in the prevention of retinal complications of the most commonly performed ocular surgery.[10] Parallel advances in uveitis treatments and endophthalmitis prophylaxis strategies continue to be critical elements of retinal management in ocular surgery in order to maximize patient outcomes in both routine and advanced surgery.[11,12]

As demand for vitreoretinal services increases with an aging society, ophthalmologists need to arm themselves with the most current knowledge in order to effectively manage degenerative retinal conditions and choroidal neovascular diseases, as well as complications of anterior segment surgery.[13] Healthcare authorities increasingly call for ophthalmologists and other physicians to follow evidence-based recommendations to maximize efficiency, increase effectiveness of care, and ensure optimal patient outcomes.[14]

Like other medical professionals, ophthalmologists routinely turn to expert colleagues for knowledge that will help them to develop the most effective therapeutic strategies. This proposed CME activity will provide evidence-based knowledge with experts addressing the most critical clinical data for consideration in making treatment planning decisions in wet AMD and related diseases. The activity will also provide perspectives to help clinicians plan for near-term future developments in this area.

The challenges faced by vitreoretinal specialists and ophthalmologists managing degenerative retinal conditions are under increasing pressure due to the impact of the aging population and coincident increases in retinal disease.[15] As advances in vitreoretinal treatment options and technology have increased the opportunity for improved patient outcomes, evidence suggests that, like other clinicians, ophthalmologists do not fully use these advances for the benefit of their patients.[16] Similar to the adoption of small-incision cataract surgery, for example, the move towards minimally-invasive vitreoretinal therapies presents a learning curve as surgeons become more comfortable with new techniques and technology, as well as the management of complications.[6,7,17]

Expert opinion regarding emerging clinical data can improve this learning gap so that more patients may benefit from technology advancements that can improve treatment outcomes. Translation of wet AMD therapy research into clinically focused advice is needed because of predicted increases in resultant blindness in the aging population and continuing therapeutic advancements in this area.[5-7]

These gaps between preferred and actual care have established clear learning needs that can be met with an expert-developed educational activity that addresses diagnosis and treatment planning for wet AMD, providing information that can be immediately applied to clinical practice. The rapid growth in strategies for wet AMD and choroidal neovascular treatments imparts a significant burden on clinicians to identify and learn about new clinical therapies. Increasing patient expectations and demand for vitreoretinal care delivery due to population demographic changes in the next decade place mounting pressure on surgeons to deliver superior clinical outcomes to more patients.[18-20]

Busy clinicians may not be fully aware of comparative data and expert opinion regarding best practices for addressing choroidal neovascularization, as well as evolving combination therapeutic strategies. Reliance upon outdated or uncertain therapeutic habits may not provide patients with the best possible option to preserve visual function. Concerns about complications from various treatments options can create an atmosphere of uncertainty among clinicians developing therapeutic plans.[5,7]

An expert-developed educational activity designed to address wet AMD management using combination treatment strategies can provide education that is immediately applicable to care for an aging population.

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Innovations In Combination Therapy For Wet Age-Related Macular Degeneration

Dr. Dugel: The purpose of this roundtable is to discuss the concept of combining radiation therapy with strontium 90 brachytherapy with antivascular endothelial growth factor (anti-VEGF) agents to treat exudative age-related macular degeneration (AMD). The goal of this combination strategy is to reduce the treatment burden of the current standard therapy, which is monthly injections of an anti-VEGF agent, ranibizumab (Lucentis, Genentech, Inc.) or bevacizumab (Genentech, Inc.).

Dr. Jackson, can you begin with an overview of the epidemiology of AMD?

Dr. Jackson: There is no doubt that AMD is one of the most common conditions we face as ophthalmologists. The World Health Organization has cited AMD as being one of the most common causes of vision loss in the developed world.[1] In the United Kingdom, approximately 26,000 patients per year develop wet AMD, and NICE (the National Institute for Clinical Excellence) estimates that approximately 19,000 are eligible for treatment with anti-vascular endothelial growth factor (anti-VEGF). In terms of treatment burden, AMD represents a significant issue at the moment for the National Health Service (NHS) due to the frequency with which we perform anti-VEGF injections, not only in relation to the cost of health care, but also in terms of the patient's treatment burden. Since anti-VEGF agents have become available, retinal clinics have been inundated with patients who need regular injections. Over the long term, as patients are newly diagnosed and increase the pool of those for whom we are performing frequent

PANEL

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> "As patients are newly diagnosed and increase the pool of those for whom we are performing frequent intravitreal anti-VEGF injections, the cumulative cost and treatment burden has the potential to overwhelm our health care system."
>
> -Dr. Jackson

Dr. Corcóstegui: I have seen an increasing number of patients with AMD who have become aware of their treatment options since the availability of anti-VEGF injections. One of the problems that we frequently encounter, however, is that many patients were diagnosed late in the first eye and as a result, severe vision loss has occurred in that eye.

Dr. Wiedemann: In Germany, the number of ophthalmologists is probably six times higher than in the United Kingdom so there is no shortage of physicians to administer the increased intravitreal injections. The cost burden, however, is a different story and reimbursement issues associated with intravitreal injections are of big interest at the moment. We have 16 federal states and in each state there are different treaties between doctors and insurance agencies to pay for the injection and drug (ranibizumab, bevacizumab, or pegaptanib [Macugen, OSI/Eyetech]).

The burden of injections on patients is the same worldwide. Frequent injections are difficult and I believe all of us who administer them would like to see a reduced need for these.

Dr. Awh: I predominantly use intravitreal ranibizumab injections as monotherapy. I administer bevacizumab for patients who are enrolled in the CATT (Comparison of AMD Treatment Trials) study and for patients who have certain insurance issues that dictate the use of bevacizumab. Given the powerful evidence supporting the use of ranibizumab,[2,3] it is difficult for me to depart from its use other than in a controlled clinical trial.

Currently, I do not use any combination therapy; in fact, I cannot think of a single patient for whom I used combination therapy in the last year. Given the excellent results with ranibizumab monotherapy, I am hesitant to use other therapies except in the setting of a clinical trial. The rationale behind combination therapy is sound, but I am waiting to see results from a more powerful study before I recommend this strategy for my own patients.

The treatment burden with anti-VEGF treatments is real. Many of our patients are retired and, although I am continually surprised to see how well the patients tolerate the monthly injections, it can be expensive for them if they have to pay for transportation, or burdensome and expensive for their children or caregivers to make the monthly trips. Most patients and their support networks are willing to comply with frequent anti-VEGF treatments, given the results that can be achieved, but I often find myself addressing the question, "How long this will go on?" I am confident there will be a time when we will look back and remember anti-VEGF injections as an effective, but burdensome treatment for wet AMD; we will have newer treatment options that will allow fewer trips to the doctor's office with equivalent or better visual outcomes.

Dr. Dugel: Are you using combination therapy for exudative AMD in attempt to reduce injection frequency?

Dr. Wiedemann: Currently, I am not using combination treatments, but I agree with the rationale that the pathogenesis of AMD is multifactoral and it may be effective to attack the disease from different angles, such as anti-VEGF agents for angiogenesis and steroids for inflammation. Hitting multiple targets has the potential of fewer injections for the patient, maintaining the improvement that we are able to reach with the current gold standard for AMD, ranibizumab. I think combination therapy would be more common with ranibizumab if the cost of the injections were less cost prohibitive.

Dr. Jackson: There is no doubt that combination therapy is a popular topic. There are some small case series using combination therapies, but the methods and drugs used in each vary too widely to come to any definite conclusions on efficacy. The results of these studies are promising in that it seems that we can use therapies adjunctive to anti-VEGF injections to maintain the visual improvement and reduce the need for injections, but the results of larger studies that are currently under way will be important in translating these theories to clinical practice.

Dr. Corcóstegui: Ranibizumab is, of course, the best treatment currently for AMD; however, in Spain, because of cost, we cannot provide this to many of our patients. For a large number of patients, clinicians are using intravitreal bevacizumab (Avastin, Genentech, Inc.). It would be ideal to have a regimen of combination therapy with which we can lower the cost of treatment with intravitreal ranibizumab.

RATIONALE FOR RADIATION IN COMBINATION WITH ANTI-VEGF

Dr. Dugel: Dr. O'Sullivan, can you explain the rationale for using radiation in combination with anti-VEGF agents?

Joe O'Sullivan, MD: It has been known for some time that radiation has antiangiogenic properties.[4] The main purpose of radiation is to damage deoxyribonucleic acid (DNA), and in cancer treatment radiation targets the DNA in cancer cells. A well-known side effect of radiation, however, is significant vascular damage and an immediate effect on rapidly growing cells, including endothelial vascular cells. From our work in radiation for tumors, we have seen significant effects on microvasculature and a reduction in blood vessel formation.[4]

> "External beam radiation is not precisely localized, which reduces the efficacy and the ability to target a specific area with a high dose of radiation."
>
> -Dr. Wiedemann

Additionally, radiation has been shown to reduce acute local inflammation, so it may also have the benefit of addressing another factor in AMD.[5] Some of the most compelling data that are available showing that radiation is complementary to anti-VEGF are from rectal cancer.[6,7] For treating cancer, drugs like bevacizumab are used to enhance the effects of radiation. In ophthalmology, however, it is the other way around, so we are looking at radiation from a different perspective.

Dr. Jackson: Radiotherapy for AMD has been studied since the early 1990s. One of the studies considered to be a more "modern" review of external beam radiation for AMD was published in 1997.[8] Although there was a good amount of optimism for this concept early on, it has been difficult to review the efficacy of radiation for this application because the studies that have been performed offer no consensus. For example, there are as many published studies that show a positive effect[9-15] as those showing an equivocal or no effect.[16-21]

These studies all seemed to use differing doses and fractionations of radiation and this may explain why the results were so variable, but these early efforts have had a significant effect on how we understand the delivery and dose of radiation today.

Dr. Wiedemann: The main challenge in many of these studies that focus on the biologic effect of radiation for the destruction of angiogenic cells has been avoiding inducing damage to other areas of the retina with an increased dose. External beam radiation is not precisely localized, which reduces the efficacy and the ability to target a specific area with a high dose of radiation. I think that the key is not necessarily in the dose, but the method of delivery.

TARGETED RADIATION

Dr. O'Sullivan: The choice of radiation type is also important. For example, beta radiation is strong enough to cause ionization of electrons from the atoms or molecules in tissue.

Alpha radiation is rarely used in cancer therapy apart from some treatment of bone metastases, because the particles are quite large with essentially helium nuclei. The result is a very damaging radiation over a very short radius. Beta radiation is essentially an electron that is emitted from an unstable nucleus so that the isotope—in this case strontium 90—attempts to stabilize itself and in doing so, emits electrons. X-rays and gamma rays are typically used for external beam radiation and neutron radiation is currently not often used.

The biggest difference between the various types of radiation is their penetrating power. Alpha particles penetrate poorly and can be stopped by a piece of paper. Gamma rays require large lead-lined, lead-and-concrete–mixed walled rooms to protect those outside the room when the radiation is taking place. The penetration of beta rays, however, falls between alpha and gamma rays and can be stopped by fairly simple measures. Treating staff can be protected by simple plastic or very thin metal radioprotection equipment.

Strontium 90 beta radiation is the most intense at the source, and within a few millimeters, there is very little radiation present. Beta radiation penetration can be halted by surrounding tissue in the retina, which is essentially water, so I think that it is appropriate for targeted delivery to the retina. It is capable of delivering ionization or delivering energy deposition, but over a very short radius.

The choice of isotope is also important because different isotopes have varying activity levels and dose intensity. For example, we use strontium 89 for treating metastases from prostate cancer, because its dose intensity is significantly lower than strontium 90. It would take several weeks to deliver 24 Gy of strontium 89, compared with a matter of minutes with strontium 90.

Dr. Dugel: What is the importance of dose and fractionation of radiation?

Dr. O'Sullivan: The higher the energy of radiation emitted from an isotope, the greater the distance or the radius of dose deposition. The factors in this equation include

dose rate, which is the rate that the dose is emitted, the radius or range of radiation. Dose rate does not necessarily determine the length of radius of dose, but rather how long it takes to deliver a particular radiation dose. The range of radiation is dependent on the energy of either the electrons or the type of radiation that being emitted.

> "Strontium 90 beta radiation is the most intense at the source, and within a few millimeters, there is very little radiation present."
>
> -Dr. O'Sullivan

Fractionation is another important component in this equation. In the studies on radiation therapy for AMD, there is an enormous variation in fractionation schemes that were used. For oncology, these various dosing regimens and dose fractionations would deliver no benefit.

In general, when we are attempting to eradicate a tumor, the higher dose of radiation the better. In order to protect normal tissue that is most commonly sitting adjacent to the tumor, however, the dose must be fractionated. The standard fraction size used in oncological treatment is between 1.8 Gy and 2 Gy per fraction, and a curative dose of radiation falls between 70 and 80 Gy per fraction, delivered in 2-Gy fractions. There is considerable experience using large doses of single fraction, however, particularly in palliative care.[22] The most significant difference between a large single fraction and multiple small fractions is the occurrence of early and late effects. With multiple small fractions, normal tissue has time to recover. Larger fractions and a lower number of fractions increase the likelihood of late tissue damage. The goal of radiation for AMD is to induce some late radiation damage, such as induced fibrosis or blood vessel damage, so the choice of a large single fraction, such as 24 Gy, makes perfect sense.

Dr. Dugel: Endothelial cells, which are targeted in radiation therapy for exudative AMD, do not divide nearly as rapidly as cancer cells, which are in a mitotic state—even the abnormal endothelial cells. Can you explain how cell status factors in the choice of fractionation?

Dr. O'Sullivan: Yes. Cancer tumor cells are more likely to be in mitotic or dividing state than normal cells. A cell in a mitotic state is more susceptible to damage by radiation because the nucleus of the cell is larger than a normal cell and the target DNA is easier to attack. The endothelial cells involved in AMD, however, are late-responding normal tissues, which are post-mitotic, and so the effect of radiation on these cells is independent of the cell division phase.

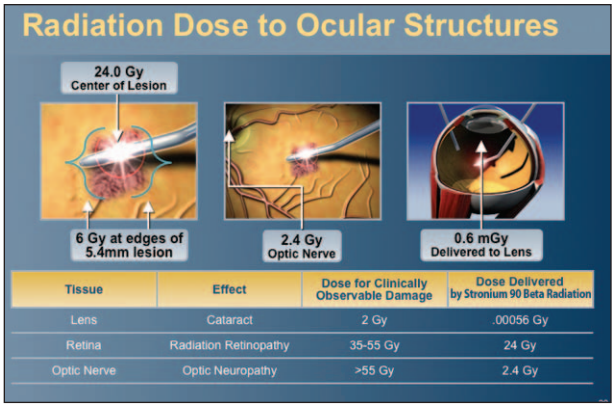

Figure 1. The 24 Gy dose of radiation delivered to the lesion falls off to 6 Gy at the edges. The radiation dose delivered to the surrounding ocular structures is less than what has been observed to produce clinically observable damage.

Dr. Dugel: One of the reasons that such a high dose of radiation can be applied with brachytherapy is that strontium 90 has a rapid falloff rate (Figure 1). The 24-Gy dose is able to be applied to the epicenter of the lesion, where the dose at the edges of the lesion drop to 6 Gy. Can you explain this?

Dr. O'Sullivan: Rapid fall-off is dependent on the energy of the radiation emitted from the isotope, so the isotope strontium 90 is a factor, but also important is the way the radiation is delivered. If you were trying to deliver a large single fraction of 24 Gy to the eye using external beam radiation, a large amount of damage would occur to the surrounding tissues. Epimacular brachytherapy (Vidion ANV Therapy System, Neovista, Fremont, CA) uses 24 Gy strontium 90 brachytherapy. The device brings the actual radiation to the lesion itself with a rapid falloff so that a high dose of radiation can be delivered to a small volume.

The majority of the clinical trials that we have discussed that used radiation for AMD did so with external beam delivery. It is very difficult to deliver to volumes smaller than 4 centimeters in diameter, which would encompass the entire eye of most patients, with external beam.

Brachytherapy delivers the highest dose of radiation possible, but the rapid falloff protects the local areas of the eye outside of the target area, such as the optic nerve, from radiation damage. The volume of tissue affected by the dose is very small, along the order of a few millimeters.

NVI-068 AND NVI-111 DATA

Dr. Dugel: We have talked about why brachytherapy would make sense for delivery of radiation from a hypo-

thetical point of view; however, we do have data from two phase 2 studies. The NVI-068 study[23] evaluated the radiation device itself with a vitrectomy and the NVI-111 study[24] evaluated the radiation device with a vitrectomy and bevacizumab.

Dr. Jackson, what are your thoughts on these two studies, particularly in regard to safety and biological signals?

Dr. Jackson: Both the NVI-068 and the NVI-111 studies enrolled treatment-naïve patients. Patients in the NVI-068 received one of two doses of strontium 90 beta radiation—15 Gy and 24 Gy. The latter was found to be more effective. The second study, NVI-111, evaluated patients who received one treatment with 24 Gy of strontium 90 beta radiation and two injections of intravitreal bevacizumab to determine if a synergy between beta radiation and bevacizumab exists. The results of these studies, when combined, suggest that beta radiation indeed has an effect on its own for improving visual acuity in AMD and when used in combination with bevacizumab. Patients in the NVI-068 study, using 24 Gy radiation alone, had a mean improvement of 4.4 letters at 12 months and the patients in NVI-111 who had 24 Gy radiation with bevacizumab gained an average of 8.9 letters in 12 months (Figure 2). So these data seem to show a definite advantage to combining radiation with bevacizumab.

Dr. Dugel: What is your impression of safety of brachytherapy, as demonstrated by NVI-068 and NVI-111?

Dr. Jackson: Safety can be difficult to address with smaller studies; for example, it is difficult to ascertain the side effects, such as endophthalmitis and retinal detachment, in small groups of patients. By combining these two studies, however, we can obtain useful information on any dramatic side effects or significant safety issues associated with brachytherapy. These data should also be considered alongside the larger studies on the safety of radiation for retinal use that provided the threshold for the amount of radiation that is safe to use intraocularly.[8-10,12,14,18,20,21,25-56]

In the two studies on strontium 90 brachytherapy, however, the impression is that the 24 Gy dose is relatively safe. The adverse events that did occur in these two studies, such as subretinal fibrosis or hemorrhaging, seem to be more attributable to the underlying disease of wet AMD rather than the intervention with radiation.

Dr. Dugel: Two things impress me about the visual acuity data in Figure 1. First, the treatment profile in both studies are very similar; second, there seems to be a synergistic effect demonstrated with brachytherapy and anti-VEGF in the NVI-111. If you look at the visual acuity graphs of the two phase 2 studies, they are parallel to one another, only the results with anti-VEGF treatment are much better. These data indicate, in my opinion, that radiation treatment has a biological signal and is possibly synergistic with anti-VEGF treatment. What are your opinions?

> "There does seem to be an advantage when adding bevacizumab, and one could hypothesize that this is because the different modalities attack different points of the disease process."
>
> -Dr. Wiedemann

Dr. Wiedemann: I am not sure I would conclude that a synergistic effect is present because of the small numbers from which these data are comprised. The vitrectomy itself removes some VEGF from the eye and maybe even traction from the retina, and there is a possibility that this is why the visual acuity is initially raised with the addition of radiation.

There does seem to be an advantage when adding bevacizumab, and one could hypothesize that this is because the different modalities attack different points of the disease process. For me, this is an acceptable combination strategy because high doses can be delivered without destroying healthy tissue.

Dr. Awh: I agree that it is impossible to draw an accurate or definitive conclusion from small studies, but this is the typical progression we use in evaluating new treatments in all branches of medicine. So much of what we do surgically, less so pharmacologically, is driven by our impressions from small studies. So, while the small study data is encouraging, these results will need to be validated by the larger phase 3 trial.

Dr. Corcóstegui: It appears that radiation acts against inflammation and is also complementary to anti-VEGF agents in preventing new vessel growth.

Dr. Dugel: Dr. O'Sullivan, from the point of view of a radiation oncologist, when you look at those curves in Figure 2, do you see a possible synergistic effect with radiation and bevacizumab?

Dr. O'Sullivan: I think it is possible. Without having confidence intervals on the actual curve itself, it is hard to comment, and both studies enrolled small numbers of patients. I think, however, that a hypothesis can be generated based on these curves.

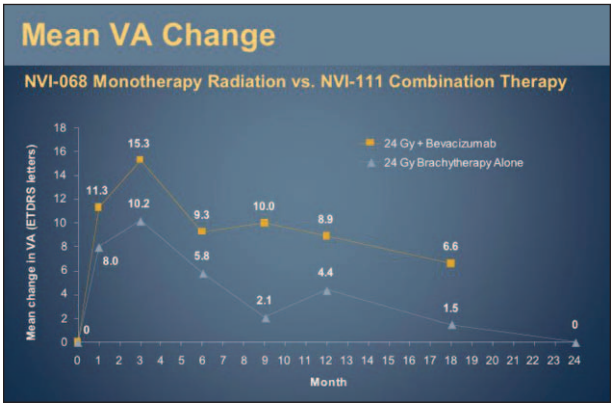

Figure 2. Mean visual acuity change over time of 24 Gy brachytherapy in combination with bevacizumab vs 24 Gy bracytherapy alone.

Dr. Jackson: I agree. Although we can make no conclusions based on these data, we can say that the treatment seems safe, but larger studies are needed to confirm this.

It is my understanding that the onset of a radiation effect usually occurs later, so I was surprised to see that in the vitrectomy/brachytherapy alone group there was an early, sudden increase in visual acuity. As Dr. Wiedemann has expressed, it is possible that the improvement in visual acuity is the result of the vitrectomy, and that the interventions used in these studies are additive, rather than synergistic, to one another.

Dr. Wiedemann: In my opinion, vitrectomy has not been considered in these studies as a second or third treatment modality, nor has it been used to its full capabilities in addressing AMD. To achieve a theoretical effect, one must probably perform a complete vitrectomy. To my knowledge, complete vitrectomies were not performed in either the NVI-068 and NVI-111 studies.

Because of this, I do not think that vitrectomy can be considered a second or third treatment modality in these two phase 2 studies, because a full vitrectomy was not part of the protocol, nor is it in the phase 3 CABERNET study.

Conversely, as we go further out with the data and, if we must perform reinjections, it may be advantageous not to perform a complete vitrectomy so that there is vitreous left to allow for a longer half-life of anti-VEGF agents in the eye. There are many questions that remain unanswered about vitrectomy in this setting and I do not think that these brachytherapy studies are designed to answer them.

Dr. Corcóstegiu: I agree that leaving the posterior hyaloid intact is necessary for successful anti-VEGF injections. I do not subscribe to the theory that the pathogenesis of AMD is related to traction of the posterior cortical bridges.

SAFETY DATA FROM PHASE 2 TRIALS

Dr. Dugel: In addition to complications that may occur with the application of radiation, we must consider complications from the vitrectomy procedure itself. If you look at the combined safety data (Figure 3), you can see that as with all vitrectomies, patients did get cataracts, and a small number of patients had subretinal hemorrhage, subretinal fibrosis, and retinal tears. None of the patients in either study had radiation retinopathy.

Dr. Jackson: It is difficult to comment on safety in such small studies, but what we do see here is that many of the associated complications are just as likely to be associated with the disease of wet AMD itself as with the vitrectomy procedure itself. The obvious exception to that is a peripheral retinal tear, which clearly is not a likely complication of AMD.

It is encouraging that radiation retinopathy has not been detected in these studies, but we will have a better handle on this information with longer 3-year follow-up. As I said earlier, however, to make any conclusions on the safety of radiation used in this manner, larger studies are required.

Dr. Wiedemann: In regard to radiation retinopathy, there are two problems. The first is the duration of follow-up and the second is the method by which you look for signs of this condition. Dr. Jackson noted that we need longer follow-up, which is true. The method of diagnosis is also problematic. For example, if you look for radiation retinopathy only with ophthalmoscopy, the findings may vary from angiography.

Dr. Awh: In terms of radiation, we cannot draw definite conclusions from other studies because the method of radiation delivery is so different. We have to rely on the theoretical risk and I think that the radiation oncologists and the physicists are good at accurately determining the rate of exposure to various structures in the body other than the target tissue. In theory, the amount of radiation exposure with epimacular brachytherapy falls well within what is considered acceptable. We also have the results from the patients who have been treated thus far, and that the farther out the follow-up period, the more confidence we have that there is no significant degree of radiation-related toxicity. If there is toxicity, it must be relatively minor because we have not seen any indication of it all, to my knowledge.

Based on our knowledge of radiation retinopathy, longer-term data will be required to rule out the possibility of this side effect. It is interesting to note, however, that for some modalities, such as proton beam radiation, a significant degree of radiation retinopathy was observed within the

time for which we currently have follow-up with epimacular brachytherapy.[33] The fact that we have not seen any radiation retinopathy in the 2-year time frame of the phase 2 studies is encouraging.

Dr. Dugel: What would you expect to find angiographically and how does this differ from the ophthalmoscopy findings?

Dr. Wiedemann: Angiography detects the finer signs of radiation retinopathy earlier than does examination with ophthalmoscopy.

Whether brachytherapy is safe in terms of radiation retinopathy will depend on what we see in 3- to 4-year follow-up. Most experts in radiation retinopathy would not accept 2-year data as conclusive. The 2-year data, however, are encouraging.

Dr. Dugel: Dr. Corcóstegui, what are your thoughts on the safety data from these trials?

> "We have not seen any abnormalities in the retinal vessels, such as telangiectasis or ischemia, which would be clear signs of radiation retinopathy."
>
> -Dr. Corcóstegui

Dr. Corcóstegui: According to these data, we have not seen any abnormalities in the retinal vessels, such as telangiectasis or ischemia, which would be clear signs of radiation retinopathy. These complications could also be treated with extra injections of anti-VEGF agent. In my opinion, radiation retinopathy is a manageable complication. AMD is destroying the macula and is the more emergent situation.

Dr. O'Sullivan: The safety data look encouraging. With late radiation toxicity, however, such as retinopathy, 3 years is an important milestone. The literature on radiation retinopathy shows that this complication does not occur often at a biological equivalent dose of 50 Gy given in 2 Gy fractions.[54] When it does occur, it is most often described as symptomatic retinopathy, where patients are losing vision, and the majority of the literature on this topic is considering the entire retina being radiated, such as for an ocular tumor or a brain tumor. Considering these factors, I would say "so far, so good." It is difficult to say for sure whether radiation retinopathy will occur; it is up to the retina specialists to determine whether large doses to the macular will be safe. I think that it is encouraging at this point, particularly when these patients are being followed closely for their visual acuity. Much of the existing data on radiation retinopathy has been from patients who were administered doses of radiation but were not being followed for visual acuity until they presented with symptomatic vision loss. The CABERNET study, which should be completed at the end of 2009, will provide longer-term safety data and will be able to answer our outstanding questions on radiation retinopathy.

Dr. Awh: In regard to the safety of the vitrectomy procedure in the phase 2 trials, there is risk with any surgical procedure and with any intravitreal injection. I do not think that there is any additional risk to the patient with this procedure compared to the risk of other vitrectomies of similar duration and complexity. Although the risk may be greater with vitrectomy, we are exposing the patient to a one-time risk of a vitrectomy while reducing the number of times we are exposing him or her to the risks of an intravitreal injection.

Dr. Dugel: The main goals of all phase 2 studies, including these two evaluating brachytherapy are to demonstrate a biological signal and to demonstrate safety. I certainly agree that no conclusions can be made with preliminary data. Based on our discussion, however, it appears that the group concensus is that these two trials provide justification for further investigation for this modality of treatment.

CABERNET SURGICAL PROTOCOLS

Dr. Dugel: Let's talk about the pivotal trials, specifically the CABERNET protocol. Dr. Jackson, you have performed many of these procedures. Can you describe the surgical procedure in the CABERNET protocol?

Dr. Jackson: In terms of the surgery itself, I originally performed a 20-gauge vitrectomy but quickly transitioned to a 23-gauge system. Although I now use a three-port 23-gauge vitrectomy, I enlarge the main incision up to 20-gauge, to allow me to insert the 20-gauge epimacular brachytherapy device. I perform an angiogram and have this available in the OR so that I properly position the device over the area of greatest activity. The radiation dose falls off dramatically with increasing distance from the source, so the placement must be directly on the internal limiting membrane (ILM). I have an oncologist present in the OR and use a timing device, which is activated when the device is lowered onto the ILM. The crosshairs are positioned over the treatment zone, and the timer is counted down over approximately 4.5 minutes. Afterward, the device is moved back to the vitreous cavity and the radioactive pellet is disengaged back to the housing.

From this point, I undertake a careful search of the periphery, suturing the 20-gauge opening (only suturing

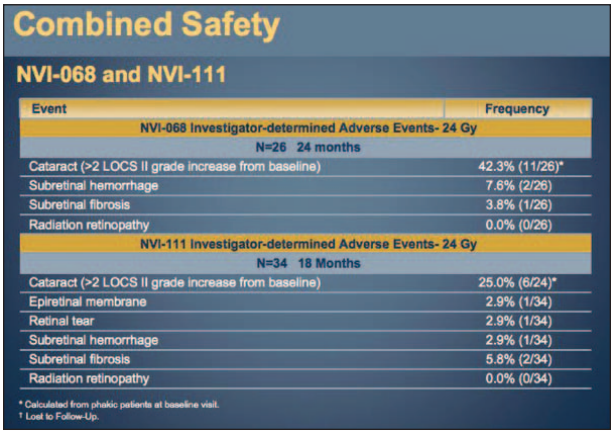

Figure 3. Combined safety data from NVI-068 and NVI-111 phase 2 studies.

the other wounds if they are leaking). The vitrectomy is easy to do in these cases. Often when we are entering the vitreous cavity, we are doing so because there is something rather unpleasant to deal with, such as a retinal detachment; here we have a very focal abnormality, which makes the vitrectomy itself quick and simple.

Dr. Dugel: The protocol of CABERNET allows for detachment of the posterior hyaloid membrane, but leaves this decision up to the surgeon. Do you perform this step?

Dr. Jackson: I let the events of surgery determine my actions regarding the posterior hyaloid membrane. The standard dogma of retina specialists in the United Kingdom is that if you are go into the vitreous cavity, that the vitreous should not be left attached for fear of subsequent retinal breaks occurring. I would much rather have a retinal break occur during the operation and know that it is there so I can treat it, rather than having one occur later on. There is also the potential to create a scaffold for epiretinal membranes. I am starting to challenge this based on my experience with patients who are enrolled CABERNET. For example, I have one patient with asteroid hyalosis for whom it would be difficult to pull off the posterior hyaloid face without a significant risk of trauma. In this case, I have left the posterior hyaloid in place and the patient is doing well in follow-up.

Really, my technique is currently in evolution. I think that I will be performing fewer full vitrectomies as time goes by, but I am still somewhat anxious about leaving vitreous intact if it may cause subsequent complications.

Dr. Awh: Most surgeons perform partial vitrectomies; it is almost impossible to remove every bit of vitreous, which would define a complete vitrectomy. Most times, when referencing complete vitrectomy, we are really talking about a core vitrectomy, or a limited central vitrectomy—vs trying to remove a considerable amount of peripheral vitreous.

I prefer to do more than a limited, or "core" vitrectomy, for these cases.

I do a reasonably thorough vitrectomy for two reasons. Many patients have troublesome vitreous opacities, and appreciate the elimination of their floaters. More importantly, we know there is a potential for peripheral vitreous traction as we introduce instruments into the eye, so debulking the vitreous, particularly in the region where the epimacular brachytherapy device will be inserted, is a reasonable thing to do.

I have used several methods to perform this procedure. For example, I have used a 25-gauge vitrectomy system, removing one of the 25-gauge cannulas after the vitrectomy and enlarging the sclerotomy with an MVR blade to accommodate the 20-gauge epimacular brachytherapy device probe. At the conclusion of surgery, I suture the 20-gauge sclerotomy and the conjunctiva. I have also performed the procedure using a 20-gauge sutureless technique with 20-gauge sutureless cannulas. When I perform the operation with this system, I remove the 20-gauge cannula in order to insert the epimacular brachytherapy device probe because a curved probe will not fit through the cannula. At the end of the case, because of the oblique wound construction that is used to insert the 20-gauge cannulas, sutures are not required. Yet another way of doing this procedure is to use a 20-gauge sutureless technique with no cannulas—there are several techniques for doing that—one in which an oblique 20-gauge transconjunctival wound is created through which the device can be introduced and no sutures are needed.

The exposure time that I use is approximately 4 to 5 minutes. Every probe is calibrated by the radiation oncologist and the physicist so in the clinical trial, they are the individuals who decide how long we are to hold the device in place.

Dr. Dugel: Dr. Corcóstegui, I understand that you are also a minimalist when it comes to vitrectomy, is that correct?

Dr. Corcóstegui: Yes. My technique is to perform a 23-gauge vitrectomy, and in some cases a 25-gauge vitrectomy. I open one of the sclerotomies to place the radiation device. Once placed, the device is activated for approximately 4 minutes and then I remove it. I do not remove the posterior hyaloid, but I do remove a little bit of the peripheral vitreous gel and I check over the peripheral retina to look for breaks or any abnormalities. My technique is simple and I find that it is effective in avoiding postoperative complications.

Dr. Dugel: Dr. Wiedemann, would you advise a complete vitrectomy including removal of the posterior hyaloid?

Dr. Wiedemann: Well, I am not sure I would advise a complete vitrectomy. Fifteen years ago, surgeons regularly left some of the vitreous behind in standard vitrectomy procedures because they did not know better, and although a complete vitrectomy is now the standard, it is not in the CABERNET trial. Therefore, at the moment this question will not be answered by the CABERNET trial and is not really answered by other studies. Theoretically, you could perform a complete vitrectomy and add a third modality of treatment in relieving the mechanical traction by vitreous remnants, but this is yet to be determined.

Dr. Dugel: In your experience, is this a fairly well tolerated procedure?

Dr. Wiedemann: Yes, this is a simple, well-tolerated procedure.

Dr. Corcóstegui: This procedure is easy. The first case was a bit more difficult because we were in training, but we were able to learn the technique quickly and after a 20- to 25-minute vitrectomy procedure, the patient is happy.

Dr. Jackson: One pearl I should mention is that it is critical to steady your hand during the procedure to ensure that there is no movement while delivering the radiation. A hand rest and the hand support are important tools to have.

Dr. Dugel: I agree that this is important. Probably the most critical part of this procedure is keeping the hand still and in the proper distance from the lesion for 4 minutes.

ADDITIONAL STUDIES

Dr. Dugel: The CABERNET trial, which is the pivotal phase 3, multicenter (45 sites) trial, is designed to evaluate the safety and visual acuity outcomes of treatment-naïve patients in two arms: patients treated with epimacular brachytherapy and two injections of ranibizumab 1 month apart, and patients treated with ranibizumab monthly for the first three injections then followed by quarterly injections.

The MERITAGE trial that Dr. Jackson and I are running in two centers evaluates the safety and efficacy of a single procedure with epimacular brachytherapy along with either ranibizumab or bevacizumab injections administered on an as-needed basis. The patients who are enrolled in this trial are not treatment naïve, rather they have active exudative AMD that has persisted despite treatment. Quite frankly, most of the patients I see and treat on a daily basis have persistent AMD and do not fall into the treatment-naïve category.

In my opinion, MERITAGE is designed to answer the most pervasive question with AMD: how do we reduce the treatment burden for our patients?

Dr. Jackson: There are three main reasons why I initiated the MERITAGE trial. First, the trial would enroll patients have been receiving a drug that clearly has an effect on AMD, and one cannot assume that the treatment outcome will be the same as treatment naïve patients. Second, most patients with AMD are already receiving ranibizumab or bevacizumab, so the need for a trial to assess the outcomes of this combination treatment in patients who have already been treated but for whom their disease persists is clearly necessary. Third, I am interested in the question of surgical capacity with this procedure. We have already discussed the difficulties presented by the volume and frequency with which we perform intravitreal injections with ranibizumab. The level of expertise for a vitrectomy is at a higher level, and I am not convinced that we will have the surgical capacity to offer every patient with wet AMD this new treatment, however good it might be. My feeling is that this treatment, if found to be effective in MERITAGE, might be best reserved for those patients who are not responding as well to anti-VEGF agents.

> "Quite frankly, most of the patients I see and treat on a daily basis have persistent AMD and do not fall into the treatment-naïve category."
>
> -Dr. Dugel

Dr. Dugel, I know you have treated many more patients in MERITAGE than I, but my own experience with small numbers is positive thus far. I cannot comment or generalize based on the numbers of cases that I have performed, but I can say that the rationale for the MERITAGE trial makes sense. I also think that it would be unwise to use the CABERNET results and assume that they would be the same as in previously treated patients.

Dr. Dugel: The goal of the MERITAGE trial is to reduce the treatment burden for our patients. In MERITAGE, which is a small study with only 20 patients at the outset, the criteria for enrollment is strict and includes an induction stage as well as a maintenance stage. Some patients who received seven to 19 previous anti-VEGF injections have actually improved vision. These patients have also

suffered some of the side effects that one would experience with vitrectomy alone, such as cataract formation. Pseudophakic patients certainly have improved quite a bit. Even patients with cataracts have improved initially until cataract formation; once the cataracts are removed, I expect that these patients will continue to respond well.

Dr. Awh: The MERITAGE trial targets a very important group of patients. Common sense suggests that monotherapy with anti-VEGF agents is unlikely to the best treatment for every patient. Although some patients experience a benefit from monotherapy, there are many patients who will have no response, inadequate response, or demonstrate a reasonable response, but with a difficult-to-maintain continual dependence on the drug. Once we have identified these patients, it is reasonable to offer them another option in the setting of a controlled clinical trial that may improve their response, or maintain a good response with a lesser treatment burden.

CONCLUSION

Dr. Dugel: In concluding, these data are encouraging; the question that I have is not whether epimacular treatment works, because we do not know. The question is really whether this should be investigated further and I believe we all agree that this is warranted.

Hypothetically, if epimacular treatment is found to be effective, how will this change your practice?

Dr. Wiedemann: If epimacular treatment is found to be effective, I will offer it to my patients as initial treatment to reduce the frequency with which they receive injections. Even when a patient's insurance covers the costs of anti-VEGF injections, many patients are not satisfied to come into the office for this procedure on a monthly basis, so I do think that a good number of patients would be pleased to have this option. I believe, however, that when and if this treatment becomes available to us, there will be other combination therapies that will be in competition, so I will wait to see what happens.

Dr. Corcóstegui: Vitrectomy and the application of radiation with the epimacular treatment is an easy-to-perform procedure. If it proves successful for reducing injections of anti-VEGF while providing good visual acuity results, I would definitely use it for my patients.

Dr. Jackson: The key issue for me is providing more choices for my patients. Currently, there are not many proven alternatives to ranibizumab. I agree with Dr. Wiedemann that this is not necessarily going to be the only treatment modality that emerges over the next 2 or 3 years, but I think if the preliminary results are borne out in the big studies, it will certainly be a choice that I would discuss and offer to all my patients. Depending on the results with CABERNET, MERITAGE, and MERLOT, I hope to be able to offer it to all my patients, both treatment naïve and those who have had suboptimal results with anti-VEGF agents alone.

AMD, as we know, is not just one disease. There will be some patients who do not like frequent injections. There will be some patients who do not respond to anti-VEGF therapy as well as others. Having an additional option for patients has a clear advantage for both patients and clinicians.

> "As ophthalmologists gain more experience with this treatment I think it is unlikely that radiation oncologists will continue to be needed in theater."
>
> -Dr. O'Sullivan

Dr. Awh: I am encouraged by the preliminary data and by the experience that we have had treating our own patients in our practice in the CABERNET trial. I look forward to the day that we have better treatment options for our patients with exudative AMD. The possibility that a combined surgical-pharmacologic approach may prove to be one of these treatments is certainly compelling. I hope that the clinical trials will validate the effectiveness of this novel therapy.

Dr. O'Sullivan: If epimacular radiation therapy proves successful for AMD, the biggest change for me will be hanging out with ophthalmologists rather than urologists. Going forward, however, I think the likelihood is that radiation oncologists will be involved initially, especially in the clinical trial stages. As ophthalmologists gain more experience with this treatment and if it reaches the point where it becomes a treatment option, I think it is unlikely that radiation oncologists will continue to be needed in theater.

Dr. Dugel: Fortunately for our patients, we currently have an effective treatment for exudative AMD, using ranibizumab or bevacizumab. However, we also have a treatment burden faced throughout the world that cannot be sustained. Additionally, we may have reached the physiologic saturation for treatment with anti-VEGF alone.

The next successful treatment model will be sustainable for health care systems throughout the world for physicians and patients. Additionally, it will likely be amenable to combination therapy, having a broad spectrum of physiologic action. Epimacular brachytherapy has the potential to

be an important part of our next treatment model. I concur with the expert panel that epimacular brachytherapy deserves further investigation. ■

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CME QUESTIONS

1. What is the main purpose of radiation for use in humans?
a. To create significant damage to rapidly growing endothelial vascular cells
b. To reduce inflammation
c. To damage DNA
d. All of the above

2. The penetration of beta radiation is:
a. stronger than alpha radiation
b. cannot penetrate plastic
c. is sufficient to detach electrons from atoms or molecules
d. all of the above

3. The 24 Gy dose of Strontium 90 beta radiation falls off to 12 Gy at the edges of the lesion when administered intraocularly with the epimacular bracytherapy device.
a. True
b. False

4. A cell in a mitotic state is more susceptible to damage by radiation because the nucleus of the cell is:
a. smaller than a normal cell, making the target DNA easier to locate
b. larger than a normal cell, making the target DNA easier to attack
c. the same size of a normal cell, with more identifiable target DNA
d. none of the above

5. In the NVI -068 study, patients who received 24 Gy beta radiation alone:
a. had a mean improvement of 4.4 letters at 12 months
b. had no visual improvement
c. had a mean visual improvement of 8.9 letters at 12 months
d. had a mean visual decrease of 1.4 letters at 12 months

6. In the NVI-111 study, patients who received 24 Gy beta radiation with bevacizumab:
a. had a mean improvement of 4.4 letters at 12 months
b. had no visual improvement
c. had a mean visual improvement of 8.9 letters at 12 months
d. none of the above

7. The complications of vitrectomy reported in the combined safety data of NVI-068 and NVI-111 included:
a. cataract
b. subretinal hemorrhage
c. retinal tear
d. all of the above

8. Longer term data are needed on the incidence of radiation retinopathy with epimacular brachytherapy.
a. True
b. False

9. The protocol of the CABERNET trial:
a. requires that small-gauge incisions for vitrectomy be enlarged to 20 gauge for insertion of the epimacular brachytherapy device device
b. recommends that radiation be active and positioned over the treatment area for approximately 4.5 minutes
c. allows for removal of the posterior hyaloid but leaves it up to the surgeon
d. all of the above

10. The MERITAGE trial:
a. does not exclude patients who have received prior treatment for AMD
b. requires that patients be treatment naïve
c. is designed to answer the question of how to reduce the treatment burden for AMD on patients and physicians
d. A and C
e. B and C

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