The Ins and Outs of Physician-Industry Collaboration

A panel discussion with Jeffrey Nau; Namrata Saroj, OD; Chirag P. Shah, MD, MPH; Rishi Singh, MD; and Charles C. Wykoff, MD

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Our leaders in Washington originally passed the sequester as part of the Budget Control Act of 2011 (BCA), aka the debt ceiling compromise. It was designed to force the hand of the Joint Select Committee on Deficit Reduction to come to a deal to cut $1.5 trillion over 10 years. If the committee had done so, and Congress had passed it by December 23, 2011, then the sequester would have been averted. Our representatives were not able to manage a deal, and so the sequester was essentially put into action. However, while the BCA originally dictated that the sequester cuts would take effect at the beginning of 2013, adding the sequester with Bush tax cuts and the payroll tax cut became a politically untenable option known as the fiscal cliff. Facing this unpopular problem, our leaders agreed to avert the cliff by delaying the sequester until March 1, 2013. Not exactly a long-term solution.

How does this affect our lives as retina specialists? To start, all Medicare services will be reduced by 2%; thus, reimbursements for all office visits and procedures will be lowered. The sequester also significantly affects the finances of physician-administered drugs under Medicare Part B. The focuses of our practices have dramatically shifted with the availability and broad use of anti-VEGF drugs. These medications are now the primary therapy for AMD and vein occlusions, and are also gaining traction in the treatment for diabetes. Using these medications in our practices is no small task. To start, many practices have had to invest in structural changes, building out injection rooms and making other changes to accommodate frequent patient visits. In addition, practices must track inventory and drug usage, verify patient insurance to guarantee payment, and carefully track the receipt of primary insurance payments and the secondary insurance payments that accompany Medicare claims for each and every vial of drug used. Failure to receive full payment for vials of the drug can be extremely costly to say the least. Worse, sometimes practices may be completely unaware of deficits in payments. Fiscally responsible practices spend significant overhead dollars to administer these medications on a daily basis.

Currently, Medicare Part B reimburses physicians for the cost of the drug plus an extra 6% to offset the fixed costs of handling the drug within our practices. The sequester, however, changes the reimbursement model. Under the new regulations, physicians will be reimbursed for the cost of the drug but the extra 6% will be reduced to 4.3%. The New York Times and other publications have touted this as a simple 1.7% decline, less than the 2% Medicare cut. But the correct calculation shows that this is actually a 28% reduction (1.7/6) in fees paid to our offices to handle the costly drugs. Some retina practices, already struggling to keep track of the utilization of these medications, may find that this squeezes their margins toward the red and forces them to reconsider their treatment options to primarily off-label therapy such as bevacizumab (Avastin, Genentech) or generic triamcinolone.

If you haven’t already, we suggest you take a sharp look at your practice infrastructure to see what effect sequestration will have on your practice.

Richard Kaiser, MD; and Jonathan Prenner, MD
Chief Medical Editors
Intravitreal anti-VEGF therapy has revolutionized the management of retinal vascular diseases, resulting in immeasurable clinical benefit to hundreds of thousands of patients affected by these potentially blinding conditions. The continuing development of anti-VEGF therapy is the result of a partnership among ophthalmologists, industry, and clinical trial participants. However, the cost of anti-VEGF therapy is great. In 2010, the combined Part B expenditures for ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) were $2 billion. Additionally, delivery of anti-VEGF therapy has substantially increased office-based imaging, evaluation and management services, and procedures. In 2012, more than 4 million retinal optical coherence tomography (OCT) scans (CPT code 92134) were performed in the Medicare fee-for-service population. Intravitreal injections (CPT code 67028) increased from approximately 1 million in 2009 to 2 million in 2012 in the same population.

This unprecedented growth has attracted the attention of the Centers for Medicare & Medicaid Services (CMS). As a result, the Office of the Inspector General (OIG) for the Department of Health and Human Services (HHS) issued a report in 2012 called Medicare Payments for Drugs Used to Treat Wet Age-Related Macular Degeneration. The OIG was created to protect the integrity of HHS programs and the well-being of beneficiaries by detecting and preventing fraud, waste, and abuse; by identifying opportunities to improve program economy, efficiency, and effectiveness; and by holding accountable those who do not meet program requirements or who violate federal laws. The OIG comprises more than 1800 professionals, including lawyers, accountants, and investigators to conduct audits, evaluations, and investigations. The OIG collaborates with the Department of Justice when necessary. For fiscal year (FY) 2011, the OIG reported expected recoveries of about $5.2 billion, consisting of $627.8 million in audit receivables and $4.6 billion in investigative receivables. The OIG also identified about $19.8 billion in savings estimated for FY 2011 as a result of legislative, regulatory, or administrative actions that were supported by their recommendations. Such savings generally reflect third-party estimates (such as those by the Congressional Budget Office [CBO]) of funds made available for better use through reductions in federal spending. The OIG reported FY 2011 exclusions of 2662 individuals and entities from participation in federal health care programs; 723 criminal actions against individuals or entities that engaged in crimes against HHS programs; and 382 civil actions, which included false claims and unjust enrichment lawsuits filed in federal district court, civil monetary penalty settlements, and administrative recoveries related to provider self-disclosure matters. The financial success of the OIG process has been identified by Congress as both a source of health care revenue and evidence that fraud, waste, and abuse are significant factors in escalating health care costs.

The objectives of the OIG study on age-related macular degeneration (AMD) were:
- to compare the Medicare payment amount for ranibizumab to physicians’ acquisition costs;
- to determine the average Medicare contractor payment amount for bevacizumab when used to treat wet AMD and compare it to physicians’ acquisition costs;
- to examine Medicare contractor payment policies for bevacizumab; and
- to examine the factors considered by physicians when choosing bevacizumab.

The study used Medicare claims data to identify 2 stratified random samples: (1) a sample of 160 physicians who received Medicare payment for ranibizumab, and (2) a sample of 160 physicians who received Medicare payment for bevacizumab. The study sent electronic surveys asking physicians to provide the total dollar amount and quantity purchased of both drugs in the first quarter of 2010. The study also asked physicians...
to describe the factors they consider when choosing which drug to use for the treatment of wet AMD. The study compared physician acquisition costs to Medicare payment amounts obtained from CMS and Medicare contractors. Additionally, it analyzed Medicare contractor payment policies and the reasons physicians reported for administering bevacizumab instead of ranibizumab.

The study found that in the first quarter of 2010, physician acquisition costs for ranibizumab and bevacizumab were 5% and 53% below the Medicare payment amount, respectively. Medicare contractors’ payment amounts for bevacizumab when used to treat wet AMD differed by as much as 28%, although payment policies were similar. Additionally, the majority of physicians who administered bevacizumab to treat wet AMD reported the substantial cost difference compared with ranibizumab as a primary factor in their decision.

OIG Recommendations

Based on the findings of its AMD study, the OIG recommended that CMS (1) establish a national payment code for bevacizumab when used for the treatment of wet AMD; and (2) educate providers about the clinical and payment issues related to ranibizumab and bevacizumab.

As required by law, CMS replied to both recommendations. They “non-concorded” with the first recommendation and concurred with the second. In their reason for declining the first recommendation, they cited the 2009 fiasco in which CMS proposed creating a national Medicare payment rate of $7.185 per 1.25-mg dose, which was calculated by taking the payment amount for the 10-mg dose of bevacizumab and dividing by 8. The OIG study confirmed the inadequacy of the 2009 proposal by finding that ophthalmologists paid, on average, $26 including drug and compounding costs per 1.25-mg dose of bevacizumab. The OIG noted that the average Medicare contractor payment of $55 per dose was 53% higher than the acquisition cost. The implication is that this payment may be too high. For ranibizumab, ophthalmologists paid $1928 (net of discounts) per vial in the first quarter of 2010, which was 5% below the Medicare payment amount of $2023. This finding demonstrates that the average sales price plus 6% methodology for Part B drug payments is working, at least for CMS. The OIG study provides ophthalmologists with an interesting perspective on payment policy at CMS.

Continued Reviews

Although the OIG study of AMD is complete, the OIG work plan for 2013 includes further scrutiny of ophthalmology payments. The OIG will review Medicare claims data to identify questionable billing for ophthalmologic services during 2011 and will also review the geographic locations of providers exhibiting questionable billing for ophthalmologic services in 2011. The criteria used to determine questionable billing are not described in the work plan. This year, the OIG will also report the results of an ongoing review of the appropriateness of ambulatory surgery center payments, and it will begin a study on the safety and quality of surgery in ambulatory surgery centers and hospital outpatient departments. The results of these studies will likely affect all of ophthalmology.

In 2010, Medicare allowed more than $6.8 billion for services provided by ophthalmologists, which is more than 10% of the total Part B pie. With such numbers at stake, we can expect continued OIG interest in the provision of ophthalmic care.

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Competencies in Cornea: Ocular Surface Disease

By Francis S. Mah, MD

As part of the Road to Recertification article series in New Retina MD, Francis S. Mah, MD, provides an overview of some of the ocular surface disease topics that retina specialists may want to review in more detail for Maintenance of Certification. As with every article in this series, Dr. Mah’s overview is not meant to take the place of a comprehensive review course; rather, its purpose is to highlight some key areas within the cornea subspecialty and to encourage a more thorough review prior to taking the Demonstration of Ophthalmic Cognitive Knowledge examination.

—Diana V. Do, MD

Diagnostic Testing for Ocular Surface Disease

When a patient presents with signs and symptoms of ocular surface disease (OSD), it is important to tailor the diagnostic testing to the individual. After slit-lamp, visual acuity, and intraocular pressure evaluations, fluorescein staining of the cornea and conjunctiva is commonly performed, as is staining with lissamine green or rose bengal. Lissamine green is generally better tolerated by patients, as rose bengal can cause stinging. Rose bengal, however, has the advantage of being viral static, which can address keratitis from a herpes simplex virus.

Other tests for OSD include Schirmer testing, which measures tear production via filter paper strips that are inserted into the eye. If performed with anesthesia, the test can identify basal tear rate. Schirmer testing is, however, not considered to be the most reliable test for dry eye. There are some new OSD tests available including the TearLab Osmolarity System, which is an objective and qualitative test for diagnosing dry eye disease via tear osmolarity evaluation, and the Tear Science LipiView ocular surface interferometer, which evaluates the tear film.

The advantages of the TearLab system are that it provides more evidence on the composition of a patient’s tears, and it is also billable through insurance. The downside of the TearLab system is that the results vary depending on a patient’s recent activity. For example, if a patient puts in an artificial tear within 1 hour prior to testing, the osmolarity will decrease, improving the score, but if a patient has been reading in the waiting room for the last hour, the osmolarity will increase, making the dry eye seem more severe than it truly is.

The LipiView system shows, in a colorimetric format, how the tear film appears in terms of oil level, which is helpful for patients with meibomian gland disease and blepharitis. It does not, however, assess tear volume. This system is very expensive, and currently, there is no current procedural technology (CPT) code assigned to it.

Another newer test that is available is the RPS InflammaDry Detector (Rapid Pathogen Screening). This test measures the amount of matrix metalloproteinase number 9 (MMP-9) in the eye, which has been linked to the incidence of dry eye.

There is a validated questionnaire, the Ocular Surface Disease Index (OSDI), that can be given to patients to assess their probability of having dry eye disease.

For patients with blepharitis, performing a tissue culture is theoretically useful, but this is considered more academic. For eye allergies, cytology may also be potentially useful to look for the presence of IgE or eosinophils, but again, this is considered an academic pursuit.

Dry Eye Disease Treatments

The first line of treatment for tear deficiency is artificial tears or lubricating eye drops. By the time patients have seen or scheduled a visit with an eye care professional, most have already tried artificial tears. After artificial tears, there are a lot of other typical management methods. The American Academy of Ophthalmology’s (AAO’s) Dry Eye Syndrome Preferred Practice Patterns state that a patient discussion is important to the examination and in determining the next steps of managing dry eye.

Cyclosporine 0.05% (Restasis, Allergan Inc.) given twice
per day was shown to provide clinical improvement, and there are several studies demonstrating that with extended use, there is continued improvement. Cyclosporine’s mechanism of action is to increase aqueous production. Although the product’s US Food and Drug Administration (FDA) label states that it is not to be in conjunction with punctal plugs, there have been studies showing that these 2 methods of treatment when used together have an additive and even synergistic effect.

There are numerous types of punctal plugs. Collagen punctal plugs are degradable depending on the tear volume. Silicone plugs are permanent. They can also cause irritation if not seated well in the punctum, in which case removal is required. There are data showing good retention rates after 1 year. A common concern with intracanalicular plugs is that because they are inserted directly into the punctum, there is a risk for infections, and the only way to remove them is surgically.

Although not verified by large clinical studies, there is evidence suggesting that omega-3 fatty acids may be useful in the management of dry eye disease, particularly meibomian gland dysfunction.

Another option for treatment of dry eye is steroids. Lodoxeprednol etabonate 0.5% (Lotemax, Bausch + Lomb) is the only FDA-approved medication for the treatment of inflammation on the ocular surface, but steroids have been used for this purpose for many years with success, sometimes alone or in conjunction with cyclosporine. Careful follow-up is necessary, however, to monitor the patient for side effects associated with this method of treatment including cataract formation and intraocular pressure rise.

Laser or cautery can also be used to permanently close the punctae, but it is important that the patient is aware of the potential complication of overflow tearing (epiphora). More aggressive surgical techniques include tarsorrhaphy, which involves sewing the eyelids together to narrow the exposure of the globe.

Contact lenses can also be used as a kind of bandage for patients with dry eye, but the use of contact lenses must be monitored, as they can present a risk for infection in dry eye patients.

Off-label treatments for keratitis include N-acetylcysteine, which we use primarily for filamentary keratitis to dissolve mucous.

The LipiFlow system (Tear Science) is a thermal pulsation system that uses controlled heat and pressure to stimulate the natural oil that is necessary for a healthy tear film. There is currently no CPT code for this system, and so the cost is out-of-pocket for patients.

Intense pulse light (IPL) therapy is primarily used for patients with ocular rosacea and blepharitis, but it’s basically a light treatment that helps to decrease the inflammation and the redness associated with blepharitis and meibomian gland dysfunction and that secondarily helps the dryness and the inflammation that’s around, specifically blepharitis but also dry eyes.

Oral doxycycline and oral and/or topical azithromycin can also be used off label to treat patients with blepharitis.

**Chalazia and Hordeola**

Chalazia and hordeola are associated with ocular rosacea, meibomian gland dysfunction, and blepharitis, and are caused by plugged meibomian or oil glands. The first-line treatment is to use a warm compress, such as a warm wet washcloth, and lid scrubs. It is important to keep the warm compress on the eyes for a good 5 to 10 minutes at a time, twice a day. The lid scrubs, which can be a washcloth and mild soap like baby shampoo, should be used to massage the eyelid and express the glands to debulk mucus and remove any bacteria from the eyelids.

Oral doxycycline, topical cyclosporine, or erythromycin can also be used in conjunction with warm compresses and lid scrubs.

Another option is steroid injection, but this can cause degeneration and necrosis of the overlying skin. Incision and drainage is an option for more chronic inflammation from chalazia and hordeola or for cases that have not resolved after the use of warm compresses and medications.

**Contact Lens Wear**

The most significant issue regarding contact lenses is infection, and these cases are often the result of a patient who sleeps in his or her contacts. Sleeping in contacts is associated with a14-fold higher risk of infection. Contact lens care is also a major issue— instructing patients as to the proper way to clean lenses is important to avoiding infections.

Patients should also be told that decreasing contact lens wear time is important so that enough oxygen can reach the cornea.

Gas-permeable lenses are associated with an increased incidence of giant papillary conjunctivitis, which induces papillary changes and an allergic reaction on the eye’s surface. Often, this can be resolved simply by switching the kind of contact the patient is wearing or his or her contact lens solution.

Partial limbal stem cell defects can occur when contact lenses and hygiene are abused. The corneal epithelium is irregular, resulting in epitheliopathy and keratitis. A contact lens holiday is usually helpful in these cases, as is ensuring that the lens fits correctly when the patient resumes contact lens wear.
The safest contact lenses available are rigid gas-permeable lenses. Although they are associated with a low risk for infection and allow the greatest amount of oxygen to the cornea, they are also, unfortunately, the most difficult for patients to wear. The second safest, theoretically, are the daily wear disposable lenses. The contact lenses with the worst safety record are the extended-wear soft contacts.

**Exposure Keratopathy and Filamentary Keratopathy**

There are 3 main causes of exposure keratopathy: (1) eyelid procedures such as blepharoplasty or a trauma procedure that change the ability of the lids to cover the cornea; (2) neuropathy that causes the inability to detect dryness; and (3) neurological conditions caused by either stroke or trauma that affect the normal blink reaction.

The first-line treatments for exposure keratopathy are topical eye drops and ointments. If these fail, a temporary tarsorrhaphy can be performed. If a permanent tarsorrhaphy is required due to severity of lack of response to other measures, it can be reversed. A Gonderson flap can also be used, removing the corneal epithelium, dissecting the conjunctiva, bringing it down over a debrided cornea, and suturing the eyelids.

Filamentary keratitis is a chronic condition that is related to dry eye, in which mucus and exfoliated epithelium attach to the surface of the cornea. Some underlying conditions that can contribute to this are graft vs host disease, chemical reactions, shingles, and blepharitis.

Management of filamentary keratitis includes lubricating eye drops and ointment. Patients can be treated with cyclosporine or steroids, and then doxycycline to address potential blepharitis. Topical N-acetylcysteine can help decrease the amount of mucus; however, this should not be applied indefinitely, as mucin production is necessary for a healthy cornea.

**Recurrent Erosions**

Recurrent erosions occur either due to previous corneal abrasions or genetics. If the patient has no memory of any trauma that would have caused a corneal abrasion, an examination of the fellow eye should be performed. If there are signs of an anterior basement membrane dystrophy, the cause may be genetic.

The typical management for corneal erosions are prophylactic antibiotics and possibly a patch. A bandage contact lens can also be used. Osmotic contact can be used at night to keep the cornea deturgesced during the night and prevent blisters from forming. Typically with recurrent corneal erosions, when patients sleep, tears go into the cornea, and blisters form due to the loose basement membrane of the corneal epithelium. These bullae can tear when patients wake up in the morning, causing additional erosions. Osmotic agents pull fluid out from the cornea to prevent bullae from forming. Osmotic drops can also be used in the morning to pull fluid from a blister.

Stromal micropuncture can be performed if the area of the recurrent erosions in anterior basement membrane dystrophy is not in the visual axis. Epithelial debridement and phototherapeutic keratectomy may be performed using an excimer laser, alcohol, or a diamond burr.

**Persistent Corneal Epithelial Defect**

When treating patients with corneal epithelial defects, the first step is to determine the underlying cause, which can be herpes simplex virus or shingles, for example. The second step is to examine the corneal surface to ensure that there is no ring of fibrous tissue preventing the epithelium from migrating over the epithelial defect. The process of removing this ring or line of fibrous tissue is referred to as “freshening up the edges.”

Artificial tears, lubricating eye drops, or serum eye drops can be applied to the eye. I use doxycycline because it helps to decrease inflammation around the eyes and enhances the oily tear film. Contact lenses can also help, but because they are associated with infection, it is recommended that a broad-spectrum topical antibiotic also be used. Tarsorrhaphy is considered the final-line of treatment for patients with persistent epithelial defects.

Persistent epithelial defects are often seen in patients with diabetes who have neuropathy.

**Conclusion**

This article provides a brief review of some of the common topics that may be touched upon in the maintenance of certification examinations in ocular surface disease management. You can find a complete list of topics at the American Academy of Ophthalmology website: http://one.aao.org/CE/MOC/POCTopics.aspx.
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The Ins and Outs of Physician-Industry Collaboration

A panel discussion with Jeffrey Nau; Namrata Saroj, OD; Chirag P. Shah, MD, MPH; Rishi Singh, MD; and Charles C. Wykoff, MD
A quick review of retina fellowship outlines at several institutions reveals rigorous courses aimed at mastery of medical treatment and surgical techniques. Many of the programs also include clinical research opportunities via assisting faculty members involved in clinical trials. Nowhere in these syllabi, however, do business matters appear, such as considerations in signing a contract, managing a practice, or engaging with industry. New Retina MD was launched 3 years ago because there are few resources for retina specialists that tackle these practical issues. In this issue, we have gathered a panel of physicians in the early stages of retina practice and representatives from the pharmaceutical industry to discuss important aspects of working with industry. The collaborations of physicians and industry can be productive in maximizing the efforts of companies in their research and development (R&D) efforts, but how to go about establishing these relationships and working together in a way that maintains the highest level of patient care is not clearly defined.

Adding to the complexity of physician-industry relationships, in 2010, the Affordable Care Act (ACA) was signed into law. A provision included in the ACA was the Physician Payments Sunshine Act (Section 6002; PPSA). The PPSA requires full reporting of all financial transactions that take place between physicians and/or teaching hospitals and manufacturers of pharmaceuticals and biologic agents and medical device companies. The PPSA is designed to promote transparency in these transactions and make this information available to the general public.

The PPSA has not taken effect, but it will in the near future. In a recent article in The Atlantic, it was noted that there is frustration among some in the physician community that the institution of the PPSA has been delayed. In an open letter to Jacob L. Lew, former White House Chief of Staff, Marcia Angell, MD, of Harvard Medical School and the former editor-in-chief of the New England Journal of Medicine, and colleagues expressed their disappointment regarding the delay and their concerns about direct-to-consumer advertising and marketing to physicians. Clearly, there is concern among those in the medical community that there is a need to curtail some aspects of interactions between the pharmaceutical and medical device industries and physicians, but at what cost to the positive relationships that take place in R&D and overall innovation?

The discussion below seeks to address some important considerations involved with industry collaboration. New Retina MD welcomes the feedback of our readership regarding this topic. Please e-mail any comments to rrenshaw@bmctoday.com.

Rachel M. Renshaw: This question is directed to the physicians on the panel. What has been your involvement with the ophthalmic pharmaceutical and medical device industries?

Chirag P. Shah, MD, MPH: Most of my involvement with industry has been through my work on clinical trials and speakers’ bureaus.

Rishi Singh, MD: I first began working with industry as a fellow under Peter K. Kaiser, MD, at the Cole Eye Institute, Cleveland Clinic. He was immensely valuable in helping me establish contacts. What I soon began to realize was that these relationships were important to create for a multitude of reasons. Industry-sponsored trials allowed a clinician scientist like myself to ask and answer questions. In return, the companies needed expertise as to how they should design clinical trials and as to what inclusion and exclusion criteria to consider. Finally, working with industry offered hope to our patients by allowing us to participate in early phase clinical trials. My experiences during fellowship helped when I transitioned to an attending staff surgeon at Cleveland Clinic.

Charles C. Wykoff, MD: This is an exciting time in retina because of the major advances in our treatment capabilities over the past 20 years, which are in part a product of industry involvement and collaboration with retina specialists and researchers. I have been involved with companies as a consultant, on steering committees, and on speaker bureaus. I find research personally fascinating. The most interesting and rewarding experiences have revolved around research, for example, developing investigator-sponsored trials (ISTs), and having exposure to premarket sponsored trials, instruments, and technologies.

Ms. Renshaw: From an industry standpoint, what do you see as being the greatest benefit of being able to work closely with doctors on R&D and postmarket projects?

Namrata Saroj, OD: I view collaboration between industry and physicians as symbiotic—we all gain. When a company is developing a new product, the guidance that physicians provide is critical to make sure that the company is on the right track to achieving something that is needed in clinical practice. This in turn helps physicians because they have a direct input and can better help their patients with what is being developed.

Jeffrey Nau: I agree with Namrata. Having physician input...
is extremely helpful because a company may see data differently. The physician can look at large data sets and interpret them with a day-to-day clinical practice perspective, and, often, the collaborations between physicians and industry are the keys to pushing products over the finish line.

**Getting Involved**

**Ms. Renshaw:** What would be your advice to physicians early in their careers, such as in residency or fellowship, regarding how to engage with industry?

**Dr. Saroj:** The most important advice would be to be proactive in engaging with industry. Reach out to the companies you are interested in working with. Local industry representatives are a great resource through which to establish initial contact.

Getting involved in clinical trials is a good first step. Most universities and clinical practices that provide training are actively involved with clinical trials, so, even though residents and fellows cannot be principal investigators (PIs), they can be active subinvestigators and, in the process, become familiar with the process and the companies involved.

Once a physician is out of fellowship, continuing with company-sponsored clinical trials as well as developing and initiating investigator-sponsored trials are also good ways to engage with industry. Other opportunities to consider are speaking at scientific meetings and becoming involved with commercial activities, like speaker programs.

**Mr. Nau:** The most successful retina specialists with whom I have worked all have 1 thing in common: they became involved with clinical research early on. Building relationships with industry during fellowship will ultimately pay dividends as physicians go into private practice because those in industry know them and recognize that they are willing to work hard. It’s natural that people tend to gravitate toward those they know and trust.

I echo Namrata’s comment about establishing contacts with local representatives. We receive a lot of feedback from the field as to physicians’ levels of interest in getting involved with us. I would suggest that a physician make contact with the local representatives, and then put substance behind any queries in terms of suggesting an area in which he or she is particularly interested. Having the local representative from a company understand what a doctor’s interests are and what drives him or her in the clinic or as a research interest are important steps to getting a foot in the door.

**Ms. Renshaw:** Drs. Shah, Singh, and Wykoff, did you receive any mentoring from either your chief residents or your attendings as to how to get involved with industry?

**Dr. Shah:** I had great mentors during my residency and fellowship including Carl D. Regillo, MD; Allen C. Ho, MD; Sunir J. Garg, MD; and Julia A. Haller, MD. They are all very actively involved with research and industry, and often passed opportunities on to me and my co-fellows. If you work hard and do a good job, you end up forming your own independent relationships. As Jeff noted, those relationships carry on to your career as an attending.

My mentor in practice at Ophthalmic Consultants of Boston is Jeffrey S. Heier, MD, who has helped introduce me to many research collaborators in industry and routinely gives me guidance. Following in the footsteps of people who have done it already can be a very helpful route to take.

**Dr. Singh:** If your mentors are involved in a lot of clinical research, it’s a good idea to participate at a trial’s earliest stages as an injecting physician or even as the masked physician because it allows you to see the inner workings of a trial. It’s also a good idea to find out how other aspects of clinical trials, such as designs, budgets, and grant writing.

Much of a retina surgery fellowship is focused on how many surgical cases are performed, which is of course necessary. Few, however, are structured to teach fellows how to run a practice and how to build industry relationships, so a fellow should not forget to use these 2 years to ingest as much information as he or she can regarding the more practical information. This information might not be taught directly, but it is there if you know where to look.

**Dr. Wykoff:** It’s not that you must become involved with industry early on. Rather, it’s more important to focus on research that interests you—find passion in what you do, and you will be successful. I had great mentoring relationships with many of the retina specialists at Bascom Palmer Eye Institute; however, industry-sponsored research and consulting associations were not commonly discussed. If you have good ideas, work hard, and do the right thing for patients, opportunities, including those with industry, will fall into place.

A good place to start is often simple, retrospective analyses. As your experience increases and you become more familiar with publishing and presenting, you naturally get better at asking the right questions, and your analyses become more refined. Doing a PhD in molecular biology gave me a great foundation for research. It wasn’t until I finished training that I began to interact with industry from a research perspective.

**Other Considerations for Engagement**

**Dr. Saroj:** For someone starting in a private practice without prior research involvement, industry-sponsored research might be a good way to begin interacting with industry in your role as a PI and learn the tricks of the trade in regard to running a clinical trial.

As stated previously, letting your local drug company representatives know of your interest is key. Even if there are
procedures that employees have to follow. Any time changes
make scrutiny and will likely have organizations within its
whom it is conducting research, however, will undergo much
more scrutiny and will likely have organizations within its
main umbrella to oversee compliance.

**Mr. Nau:** It is important that, before you actually take the
step to become engaged with industry-sponsored clinical
research, you step back and consider whether you are truly
ready to take on the added responsibilities of trial recruitment,
data collection and analysis, and writing and submitting papers.
If you engage and do not perform, it can be more detrimental
to you career than if you never became involved at all.

**Dr. Saroj:** Yes, it is key that, once someone becomes an
investigator, he or she is committed and actively involved in
the trial at his or her site.

**Dr. Wykoff:** In addition to retrospective studies, I would
add that it’s important to also consider becoming involved in
non-industry–related research, such as trials sponsored by the
Diabetic Retinopathy Clinical Research Network and the
National Eye Institute. It may be helpful to take this route
before getting into directly industry-related and industry-
sponsored trials.

**Guidelines for Interaction**

**Ms. Renshaw:** How do PhRMA and AdvaMed govern the
relationships between physicians and industry? What is the
level of oversight, and what are the differences between the
pharmaceutical and medical device industries?

**Mr. Nau:** The PhRMA code was adopted in 2002 in
response to multiple violations of the federal anti-kickback
statute and the general lack of governmental oversight to
step in and clearly define the guidelines. The code is fairly
strict as to how companies can interact with medical profes-
sionals, but it is a set of guidelines, not law, so it is open
to interpretation. The AdvaMed code of ethics for device
manufacturers mirrors that of PhRMA.

I would say that the biggest differences between the
PhRMA and AdvaMed codes are not necessarily related
to the codes themselves, but rather more related to the
size of a company and whether that company has a com-
mercial organization attached to it. If a company is strictly a
research-based company and does not have a commercial
entity (doesn’t sell anything), then obviously those codes are
interpreted a bit differently because they don’t have to worry
about anti-kickback rules. A large pharmaceutical company
that is marketing products to the same physicians with
whom it is conducting research, however, will undergo much
more scrutiny and will likely have organizations within its
main umbrella to oversee compliance.

**Dr. Saroj:** All companies have compliance guidelines and
procedures that employees have to follow. Any time changes
occur, employees have to be retrained and reeducated to
ensure that all the rules are understood and followed. As Jeff
said, the scope of these guidelines can depend on the com-
pany’s function, size, and if it has any marketed products.

In addition, not only do we ensure that, from the com-
pany’s perspective, employees are compliant, but we also make
efforts to ensure that the physicians with whom we interact
are educated on these guidelines and understand how we
can all interact in a compliant manner.

**Mr. Nau:** I think it can be confusing to new physicians
why a company can or cannot do certain things and how
the financials work when it comes to research, consulting, or
speaking. Pharmaceutical and medical device companies are
tightly controlled with regard to compliance. For example,
if a physician comes to us [Genentech] with a proposal
to present at an ophthalmology conference in a country
where our drugs are not approved, we cannot provide travel
reimbursement because it might suggest inducement. Many
times, these decisions are out of our hands, and, although it
may appear that we are being over-conservative, this is how
industry is and how we live at the moment.

**Ms. Renshaw:** Jeff, you were previously with a small startup
company. How did you find the compliance aspect different
from a larger company like Genentech?

**Mr. Nau:** Because we didn’t have a compliance person, we
had to pretty much police ourselves. In smaller companies, it’s
easier to do, particularly when there is no product in the mar-
ter. We did, however, follow the AdvaMed code closely.

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**PROACTIVE APPROACHES FOR BUILDING RELATIONSHIPS WITH INDUSTRY**

- Contact industry representatives to express your
  interest in being involved
- Be specific about your interests
- Be sure you are ready to participate fully and will be
  able to meet deadlines and complete any projects to
  which you commit

**Opportunities**

- Volunteer to participate in clinical trials as an investi-
gator, trial recruiter, or data collector/analyst
- Suggest your own research ideas (eg, investigator-
  initiated studies, subanalyses of existing data)
- Volunteer to be a speaker at scientific meetings
  (local, regional, and national)
- Participate as a speaker in promotional programs
- Volunteer as a consultant (advisory boards, as ad-hoc
  expert discussions)
- Volunteer to participate in employee training and
  preceptorships
**Feature Story**

**Ms. Renshaw:** This question is for the doctors on the panel: do you have any rules that you have set for yourself in terms of interacting with industry?

**Dr. Wykoff:** It is important to remember that the main goal of any company is profit. With this in mind, I approach any relationship, including those with industry, with my patients’ best interests in mind, and I try to be as academically rigorous as possible with data analysis.

**Dr. Shah:** The best rule is to stay academically honest and put your patients first.

**Dr. Singh:** It’s important to have a good moral compass and maintain scientific integrity even to a fault, so that you don’t attribute your name to anything that involves questionable science.

**Ms. Renshaw:** Does increased scrutiny on physician-industry interaction help or hurt innovation in pharmaceutical and medical device research?

**Dr. Singh:** At the Cleveland Clinic, we cannot accept samples or have sales representatives attend any of our continuing medical education courses without invitations. In fact, when sales representatives visit the OR, they have to wear orange scrubs that resemble prison jumpsuits to distinguish them from employees of the Clinic. Additionally, every employee must disclose his or her financial relationships with industry, which is publicly available on our website (www.ccf.org). I think that these strict rules have had a positive effect on maintaining our clinical judgement free from industry influence.

**Dr. Wykoff:** I think transparency is a good thing, both for physicians and patients. When implemented appropriately, I don’t think that it affects R&D in a negative way.

**Dr. Shah:** Although the rules in Massachusetts are stricter than they may be in other states, they are not as strict as the Cleveland Clinic. We are not allowed to participate in company-sponsored dinners or receive gifts. I don’t think this affects innovation or the ability to have a healthy relationship with industry and maintain good research.

**Mr. Nau:** The only situation in which I would be concerned about increased scrutiny having a negative effect on innovation is one in which the needle swings too far to the conservative side to allow no interaction with industry. Many of our collaborations provide fruitful outcomes, so it is important that industry and the physician base resist this scenario.

**Dr. Saroj:** I agree with Jeff. We do need comprehensive guidelines and regulations, but we also need to interact with one another to ensure that we [industry] are addressing the needs of treating physicians and patients.

**Dr. Singh:** The new PPSA is worrisome for many physicians because, although it is designed to increase transparency, which I think we all agree is good, it may lead to misconceptions among patients. For example, if we are running a clinical trial for which industry provided funding in the amount of $100,000, it may appear to some people that these monies are a profit, when they are actually going toward patient costs. If the PPSA goes forward without proper guidance and education, it has the potential to hurt future collaboration between physicians and industry.

**Ms. Renshaw:** What are some proactive measures that physicians can take with their patients to avoid these misconceptions?

**Dr. Singh:** We have begun preparing statements on our interpretation of the PPSA, both from our perspective and our patients’, to explain how the disclosures appear and how they should be viewed.

**Dr. Saroj:** From what I understand, research monies will be listed separately specifically as research, so this may help alleviate some of the concerns that patients might have.

**Ms. Renshaw:** This has been a very educational discussion. Thank you all for your participation.

*The information provided reflects the opinions of the participants in their individual capacities and not those of their employers or institutions.*

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Patient Selection is a Key Component of Success for Ocriplasmin Injection

By Brandon G. Busbee, MD

Ocriplasmin (Jetrea, Thrombogenics) is a novel therapy that offers a medical alternative for the management of vitreomacular adhesion (VMA)/vitreomacular traction (VMT) and small macular holes. Prior to the US Food and Drug Administration approval of ocriplasmin, the traditional management approach for patients with symptomatic vision loss from VMA/VMT was surgical intervention to release the adhesion and/or traction. A large majority of our patients, however, had mild to moderate symptoms from VMA for which surgery was not advisable based on the risk-benefit ratio. Ocriplasmin now allows for a nonsurgical alternative for selected patients who either want to avoid surgery or are not candidates for retinal surgery to relieve symptomatic VMA.

Who May Benefit?

The data from the MIVI-Trust clinical trials for ocriplasmin provide guidance as to which patients will benefit most from injection. Figure 1 shows that ocriplasmin was more successful in adhesions 1500 µm or smaller.

Additionally, patients who experienced VMA resolution gained more vision compared with placebo (Figure 2). Based on this information, choosing the right patients for injection with ocriplasmin will prove highly important in producing VMA resolution and potential vision gain.

Based on subgroup analysis, the biggest “winners” in these clinical trials were small full-thickness macular holes 400 µm or smaller—for these smaller holes, there was almost a 50% closure rate with 1 injection (Figure 3). A large majority of those patients who achieved closure also gained 2 or more lines of vision (Figure 4). There were 19 patients with macular holes larger than 400 µm. None of these holes closed, so we know that attention to macular hole size will dictate appropriate patient selection to maximize potential success.

In other subgroup analysis, data showed that although...
significantly more patients with epiretinal membrane (ERM) responded to ocriplasmin than placebo (8.7% vs 1.5%), ocriplasmin was not as successful in achieving VMA resolution in patients with ERM vs those without ERM (8.7% vs 37.4%). Based on these data, we can probably rule out most patients with ERM as candidates for ocriplasmin injection.

The response to ocriplasmin appears to be rapid. The endpoint for VMA resolution was 28 days, and most patients who experienced resolution did so within 7 days. On average, we will most likely know quickly who is going to respond favorably to ocriplasmin. This can direct education and discussion about subsequent vitrectomy in a short time interval for patients who do want visual improvement from their VMA and did not have success with their single injection of ocriplasmin. Although the effects of ocriplasmin on future vitrectomy have not been formally evaluated at this point, consensus from those physicians who have experience in this situation is that ocriplasmin may have a beneficial effect on releasing the hyaloid during subsequent vitrectomy.

**Patient Counseling**

Many of the patients that we see in retina practice are accustomed to the idea or experience of an intravitreal injection. Those who have received previous intravitreal injections know what to expect in regard to the process.

Many of the patients in my practice who may be good candidates for ocriplasmin injection have been people that I have been following for a long time with moderate-to-poor vision from VMA. For these patients, I have already discussed the option of vitrectomy after a period of observation. My impression is that the idea of only having to undergo 1 injection with the potential of VMA resolution is going to be very appealing.

It is critical to know your patient. Some people can live with moderate blurred vision in 1 eye. For highly motivated patients, this will likely not be the case and injection should be considered as an option. The age of the patient is also important, because if he or she is phakic, vitrectomy can increase the likelihood of cataract formation.

I will advise my patients that, if the drug works, they will see improvement in their vision within the first month after injection, again based on the data from the clinical trials.

**Other Considerations**

Ocriplasmin is unique in that it must be stored frozen. In offices that are not equipped with a -4°F (-20°C) freezer, it must be acquired prior to introduction of ocriplasmin. We run several clinical trials from my practice that require us to have a -4°F (-20°C) freezer, but this accounts only for our main office and not for our satellite offices at this time. We are currently considering installing freezers in our key satellite locations to minimize patient travel. However, with a 1-injection treatment, it may be reasonable to have a centralized office to administer ocriplasmin. This will be individualized across the country dependent upon practice needs.

For administration of ocriplasmin, the vial is first defrosted and the solution diluted with saline prior to injection. Once defrosted, the drug must be administered within a few hours, so this must be taken into account if a doctor is traveling to remote office locations. For example, if I am in an outlying community and I see a patient who I think will benefit from an anti-VEGF agent, I just pull the vial out of

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Figure 3. Smaller macular holes (≤400 µm) closed at a significantly higher rate with a single injection of ocriplasmin.

Figure 4. Seventy-seven percent of patients gained 2 or more lines of vision when they achieved full-thickness macular hole closure with a single injection of ocriplasmin.
a refrigerator and inject it, but I cannot do the same thing with ocriplasmin because of the storage requirements. However, I believe Thrombogenics has implemented a program to facilitate small -4°F (-20°C) freezers in offices that do not already have them.

**The Effect on Vitrectomy Volume**

I do not think that the availability of ocriplasmin will have a direct effect on the number of vitrectomies that we perform. First, as with any new drug, the reimbursement issues must be resolved and consistency in how the drug is covered must be established before we will see widespread use.

Additionally, it is important to remember that 26% of patients in the MIVI trials experienced VMA resolution—that leaves about three-quarters who did not. This may actually create a slight increase in vitrectomies for VMA. Think of a scenario in which a patient is a good candidate for ocriplasmin and is injected with ocriplasmin but there is no resolution of the VMA. Subsequently, this same patient may be more motivated than prior to injection to improve his or her vision. This may result in a desire for a vitrectomy when previously it was not a serious consideration.

**Summary**

Overall, having ocriplasmin available provides a significant advantage to our patients who we may have just observed in the past in patients with symptomatic VMA. It is important, however, to properly select these patients to maximize our results and patient satisfaction.

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Radiation Therapy for Neovascular Age-related Macular Degeneration

By Andrew A. Moshfeghi, MD, MBA

Approximately 1 of every 3 people over the age of 70 years in the United States is affected by dry or wet age-related macular degeneration (AMD). Affected patients typically initially have non-neovascular or dry AMD. AMD can be mild, intermediate, or advanced. Mild and intermediate AMD are characterized by a spectrum of signs typified by soft drusen, focal atrophy of the retinal pigment epithelium (RPE), or RPE hyperplasia. Advanced AMD is characterized by dry AMD with fovea-involving geographic atrophy (8-10%) or by transformation of dry AMD into wet AMD with choroidal neovascularization (10-15%).

Although we have no demonstrated treatments for advanced dry AMD with center-involving geographic atrophy, numerous treatments have proven to be beneficial for wet AMD. Historically, thermal laser photocoagulation and verteporfin photodynamic therapy (PDT) were helpful for slowing the rate of vision loss in wet AMD patients but did not result in improved vision after the initiation of treatment in the average patient. In addition, these treatments were not curative, with most patients requiring additional laser or additional PDT treatments to maintain CNV control.

Is There a Basis for Using Radiation in AMD?

There is a strong biologic rationale for combining radiation with anti-VEGF therapy for the management of choroidal neovascularization (CNV) secondary to neovascular AMD. Radiation has been explored previously for its obvious downstream effect of vasotoxicity. However, its upstream characteristics also make it a desirable choice for combination with anti-VEGF agents. Specifically, radiation has been shown to be antiangiogenic, antiinflammatory, and antifibrotic. It is these 3 characteristics that make it appealing not only for CNV modulation and control, but also possibly to mitigate the irreversible damaging effects of subretinal fibrosis. Two different radiation approaches for the management of wet AMD have been evaluated over the years: external beam and brachytherapy with a radioactive plaque.

External Beam Radiation Therapy (EBRT): Historical Approaches

An extensive review of the historical approaches of external beam radiation therapy (EBRT) using radioactive isotope...
sources or proton-beam irradiation for the treatment of neovascular AMD is beyond the scope of this piece. It is sufficient to point out that no statistically significant dose-dependent treatment effect was evident in pooled trial data, nor was a statistically significant difference in the rate of common intraocular complications observed. Importantly, no cases of radiation retinopathy, radiation-induced optic neuropathy, or secondary malignancies were reported. A shortcoming of these analyses was that a limited period of follow-up might have been too short to observe these effects, which are known to typically occur several years after radiation exposure. These early radiation trials were also not double-masked. Early studies with radioactive plaque brachytherapy for wet AMD were performed, but were limited by the need for 2 surgeries (plaque placement, plaque removal) and the anteriorly directed radiation beam resulting in a high rate of secondary cataracts. For such a common disease, the invasiveness of traditional plaque brachytherapy is not a pragmatic solution. However, these early studies did help later investigators calculate appropriate dosimetry for contemporary studies.

Contemporary Radiation Approaches to Wet AMD

In the past decade, several novel treatment approaches have emerged. The first, from NeoVista Inc, is a twist on traditional plaque brachytherapy. Instead of applying a radioactive isotope on the outside of the eye, NeoVista’s Vidion technology applies radiation through a transvitreal epiretinal approach in conjunction with vitrectomy surgery. After pars plana vitrectomy is complete, the surgeon advances a proprietary strontium-90 radiation probe directly over the area of CNV, holding it manually in place for approximately 3 to 5 minutes to deliver a dose of approximately 24 Gy to the target tissue. This selective application avoids undue radiation exposure to the lens, surrounding retina and orbital tissue, and presumably the optic nerve as well. This epimacular brachytherapy treatment (EMBT) is a 1-time treatment that is supplemented with prn delivery of intravitreal anti-VEGF agents. Phase 1 trials with this approach demonstrated no dose-limiting toxicity with the 24 Gy dose and promising visual acuity results.

Two pivotal registration trials followed on the heels of this early work. The CABERNET study evaluated treatment-naive patients, and the MERLOT study examined previously treated patients. CABERNET enrolled 457 treatment-naive wet AMD patients in a 2:1 randomization (EMBT: quarterly ranibizumab in a modified PIER protocol). Patients in the EMBT group were to receive 24 Gy of EMBT with 2 injections of ranibizumab followed by ranibizumab prn. In the no-radiation group received a modified PIER protocol ranibizumab dosing regimen. The main outcome measure in this prospective noninferiority study was the proportion of patients losing less than 15 ETDRS letters. At year 2, the control group received 11 ranibizumab injections and, visual acuity was, on average, 1 line better than in the radiation group, which received 6 ranibizumab injections. Unfortunately, the prespecified efficacy endpoint was not achieved. Although nonproliferative retinopathy complications in the EMBT group were observed in 10 patients in the CABERNET study, no cases of proliferative radiation retinopathy were observed.

The MERIGE study was a prospective, nonrandomized study of 53 previously treated patients in the United Kingdom. Patients received EMBT or prn ranibizumab with a 12-month coprimary endpoint of visual acuity preservation and change in anti-VEGF dosing frequency. Before enrollment, participants had received an average of 12.5 anti-VEGF injections. After a single treatment with EMBT, 81% maintained stable vision, with a mean of 3.49 anti-VEGF retreatments in 12 months. Mean ± standard deviation change in visual acuity was -4.0 ± 15.1 ETDRS letters.

As NeoVista’s Vidion EMBT was a twist on traditional brachytherapy, Oraya’s IRay device is a twist on traditional EBRT. The IRay is a stereotactic, robotic, radiotherapy platform designed to deliver focused, low-energy radiation to the central macula through the pars plana, thereby avoiding the crystalline lens. The device is powered using a standard electrical 110-V socket and does not utilize a radioactive isotope source. The eye is stabilized with a suction apparatus and tracked with the IGuide, which uses infrared cameras and fiducials to actively track eye movements and appropriately direct radiation. Excess movement in the X, Y, or Z planes immediately interrupts the delivery of radiation with additional safety measures utilizing an automated gate for releasing the eye from the IGuide, opening a leaded patient head shield, release of handgrips, and activation of an emergency shutoff button. Following axial length determination with a standard A-scan ultrasound, the dose of radiation is delivered via 3 separate locations through the inferior pars plana that overlap on the macula to deliver the total dose of approximately 16 to 24 Gy in various studies. The radiation spot size is fixed, so lesions greater than 4 mm are not suitable for this treatment.

Early clinical trials with the device in Mexico employed 16 Gy and 24 Gy doses along with adjunctive ranibizumab in 3 different protocols: (1) 16 Gy plus 2 ranibizumab injections
A common misconception when interpreting the results of the INTREPID study is to view them through the lens of treatment-naïve study results. Followed by prn ranibizumab; (2) 16 Gy plus prn ranibizumab; and (3) 24 Gy plus 2 ranibizumab injections followed by prn ranibizumab. These studies determined that patients had preserved or improved vision along with a diminished need for ranibizumab using an optical coherence tomography (OCT)-guided retreatment protocol. Moreover, the 16 Gy plus prn ranibizumab group (ie, no mandated ranibizumab injections were given primarily) demonstrated a possible independent biologic effect on the CNV lesion of 16 Gy radiation alone.10-13

These early studies with the Oraya device formed the basis for the larger INTREPID study in previously treated wet AMD patients. This randomized, prospective, double-masked, multicenter, controlled clinical trial was based in Europe with more than 225 patients enrolled. The study had 4 arms in a 2:1:2:1 randomization scheme, with allotment favoring the radiation groups over the sham control groups. All groups received a baseline injection of ranibizumab followed by randomization to 4 treatment groups: (1) 16 Gy followed by prn ranibizumab; (2) sham 16 Gy radiation followed by prn ranibizumab; (3) 24 Gy radiation followed by prn ranibizumab; and (4) sham 24 Gy radiation followed by prn ranibizumab.

In this previously treated patient population, visual acuity was essentially unchanged after 12 months of treatment among the radiation treatment groups, and progressive ability to dehydrate the macula on OCT was demonstrated. The study met its primary efficacy endpoint by demonstrating an ability to reduce the number of prn ranibizumab injections in the active radiation treatment groups by 32% compared with the sham radiation plus prn ranibizumab groups (unpublished data). Also, post-hoc analysis looked at the best responders to stereotactic radiotherapy and identified a group of patients that experienced a 54% reduction in the number of injections and a mean visual superiority of 6.8 ETDRS letters compared with equivalent patients in the control group.

Putting the Clinical Trial Results in Perspective

Let’s put this in perspective. Consider that at the beginning of year 2 in the CATT study, the patients could be thought of as now being “previously treated” patients. In this previously treated patient population, patients received 5 to 11 injections to result in a net loss of vision in each of the 6 subgroups by the end of year 2.14 Similarly, in year 2 of the CATT study, only those patients receiving monthly injections did not gain any fluid on OCT, while those in the prn treatment groups all gained fluid in the second year. The CATT study used retreatment criteria that were representative of what average retina physicians employ in everyday practice for their patients with wet AMD. Namely, these criteria entail treating until there is absence of any intraretinal fluid and subretinal fluid. The INTREPID trial retreatment criteria, created prior to the revelation of the results of the CATT study, employed less-strict retreatment criteria than those of the CATT study, namely an increase in central retinal thickness of 100 µm or more compared with the last visit. Despite having a higher tolerance of fluid before initiating retreatment with ranibizumab, the INTREPID study demonstrated visual acuity stability with continuing dehydration of the macula on OCT with far fewer injections than was seen in the second year of the CATT study. In the INTREPID study, the radiation treatment groups received half as many injections as were performed in the prn treatment groups in the CATT study.

A common misconception when interpreting the results of the INTREPID study is to view them through the lens of treatment-naïve study results. In this study evaluating previously treated wet AMD, patients received 5.5 prior anti-VEGF treatments on average before study enrollment, with three quarters of those patients having received ranibizumab specifically.

By contrast, NeoVista’s CABERNET study, evaluated only treatment-naïve patients and did not meet its efficacy endpoint. Why might this be? The 3 most obvious reasons are vertical dose instability with EMBT with variation in the surgeon’s microscopic hand movements over 3 to 5 minutes, the CABERNET study’s evaluation of only treatment-naïve patients, and the possible confounding effect of pars plana vitrectomy on the study results with respect to possible altered pharmacokinetics of subsequent ranibizumab injections in the prn follow-up period.

Summary

In summary, there appears to be a role for radiation in the management of neovascular AMD. The NeoVista EMBT device did not meet its primary prespecified endpoint. As of March 2013, NeoVista is no longer operational.

Oraya’s device met its prespecified endpoints in the INTREPID study, and, is currently planning a pivotal trial. The first patient treated with the Oraya device outside a clinical trial occurred in February of 2013 in the United Kingdom, where marketing approval has been granted. The Oraya device has the CE Mark in the European Union and is available commercially in the UK and Switzerland.

Finally, a new entry into the radiation therapy arena, Salutaris MD (http://bmctoday.net/retinatoday/2013/01/article.asp?moorfields-eye-hospital-and-salutarismd-to-collaborate-on-treatment-for-wet-amd), is evaluating a novel episcleral (Continued on page 23)
Retina Case Management

With Dean Eliott, MD; Dante J. Pieramici, MD; and Carl D. Regillo, MD

Surgical Rounds is a new column in New Retina MD. In this inaugural installment, we present various case scenarios to a panel of surgeons, who then describe how they would approach each case. The expectation is that, although some of the approaches will be similar, there will be interesting variations based on surgeon preference, demographics, and individual OR settings.

In this installment, Dean Eliott, MD; Dante J. Pieramici, MD; and Carl D. Regillo, MD, participate. Primary vitrectomy, pneumatic retinopexy, and scleral buckling are among the approaches described. During the discussion, it was noted that many younger surgeons are no longer trained in buckling techniques and perform “straight” vitrectomies for most cases. It is the consensus here, however, that a buckling approach remains valuable should that it should continue to be taught in fellowship programs.

Your feedback regarding this column is welcomed. If you have case scenarios that you would like to see discussed here, please e-mail me at rrenshaw@bmcstoday.com. Surgical Rounds is presented in the spirit of education—it is you, the surgeon and reader, who can help make the content of this column as relevant as possible to your practice. I look forward to hearing from you.

– Rachel M. Renshaw, Editor-in-Chief

Case No. 1: A 70-year-old patient, pseudophakic, with superotemporal macula-on detachment. No lattice or retinal tears.

Dean Eliott, MD: For this case, I think a vitrectomy with gas would be a reasonable approach. If the patient were phakic, I would consider a pneumatic retinopexy procedure, but I usually do not use this for pseudophakic patients.

My philosophy for pneumatic retinopexy is that I will choose this procedure for a patient who is phakic with 1 or 2 relatively small superior breaks that are in close proximity to each other, with a limited area of detachment and no inferior pathology.

Dante Pieramici, MD: This is a good case for a primary vitrectomy with an intraocular gas bubble. I will most likely use a 20% SF₆ gas bubble as the detachment is superior and not complex. A pneumatic retinopexy is also a very reasonable choice but if there is a physician in the OR within 24 hours who can add the patient to their schedule we find, in our practice, a primary vitrectomy to be more effective and a much more comfortable procedure for the patient. I also tend to perform 360º laser retinectomy for most cases. I don’t use heavy laser, rather a gentle pattern straddling the vitreous base.

Carl D. Regillo, MD: I always consider pneumatic retinopexy first whether a patient is phakic or pseudophakic as long as they fit the established pneumatic criteria, which does not make any distinctions in regard to lens status.¹⁻⁵ If I see a single superotemporal tear as in this case, I will choose pneumatic retinopexy. I like using C₃F₈ gas with pneumatics in order to have a large bubble. I would opt to repair this detachment with vitrectomy if I am not confident that I can detect all the breaks, and that is more often in cases with larger detachments and eyes that are pseudophakic.

I do not perform 360º laser with vitrectomy for patients with retinal detachment. I selectively treat all breaks and suspicious areas and, more often than not, will choose a longer-acting gas. The advantage of having a long-acting gas is if the retina starts to detach inferiorly from early PVR, the gas buys me some time by keeping the macula attached longer.

Dr. Pieramici: Some surgeons would consider a combination vitrectomy buckle in a case such as this; however, it may be overkill.

Case No. 2: A 70-year-old patient, pseudophakic, with macula-on inferotemporal retinal detachment. Lattice superiorly, small tear superonasally in an attached retina.

Dr. Eliott: I will most likely perform a primary vitrectomy for this case. Because the patient is pseudophakic, I can probably easily remove the peripheral vitreous and see all of the pathology with scleral depression. There is a possibility that I would use a vit-buckle in this case, because of the inferotemporal nature of detachment, but I usually reserve buckles for phakic eyes or eyes with high myopia.

Dr. Pieramici: This sounds like a case for which I will likely perform a primary vitrectomy. I will apply more laser in this case than Case No. 1, because there is a large amount of pathology in the other quadrants. I would use C₃F₈ gas instead of SF₆ gas, as a longer inferior tamponade would be possible.

If the patient had high myopia, I might consider adding a buckle, so as to support the vitreous base 360º.
Dr. Regillo: For this case, I will do primary vitrectomy. I don’t think there is enough additional pathology to necessitate a buckle. I would laser the pathology, use $C_3F_8$ gas, and expect this patient to do well with side positioning after surgery.

Dr. Pieramici: How would you instruct this patient to position and for how long?

Dr. Regillo: I have them position mostly full-time on their side for 5 days.

Dr. Eliott: I instruct patients to position facedown for 3 days postoperatively, encouraging them to position longer, up to 5 or 7 days if possible. I use $C_3F_8$ gas for most cases, with the exception of cases like case No. 1 where there was no inferior pathology.

Dr. Pieramici: I am not as strict. I tell patients to be facedown for 45 minutes at a time with 15-minute breaks following an initial period of 6 hours of strict positioning. In theory, 15 minutes per hour of upright positioning could inadvertently translocate the retina in the presence of residual fluid. I tell patients to lie on their side at bedtime.

Case No. 3: A 40-year-old, phakic, no cataract development, macula-on superotemporal tear, posterior vitreous detachment (PVD). There is no additional pathology.

Dr. Regillo: I will choose a pneumatic retinopexy for this patient.

Dr. Pieramici: I think this patient is a good candidate for a pneumatic retinopexy, provided they are not too uncooperative. Alternatively, a primary buckling procedure would be reasonable. The buckle reduces the need for intraocular gas. Because we have many patients who live at significantly higher elevations, gas bubbles can create travel challenges.

Dr. Eliott: Because there is a PVD in this case, I will choose a pneumatic retinopexy. If this patient did not have a PVD, I would go with a buckle.

Case No. 4: A 40-year-old, phakic, no cataract development, PVD, inferotemporal tear. Lattice in 2 additional quadrants.

Dr. Pieramici: In a younger patient such as this, a vitrectomy with a buckle or primary buckle may be a reasonable approach. I would assume this patient has high myopia because of the detachment and the patient’s age.

Dr. Regillo: I will use a segmental scleral buckle for this patient to address the temporal tear and detachment and use indirect laser or cryotherapy for the lattice in the other quadrants where the retina is attached.

Dr. Eliott: I will probably perform a vitrectomy with a buckle. I like to add a buckle in these types of cases because there is pathology elsewhere. If there was no PVD, I would favor a primary (encircling) buckle.

Dr. Pieramici: I also like to use an encircling band. I commonly use a 40-50 band, putting a little extra piece of the buckle material underneath the band and extra imbricating sutures in the quadrant where the tears are located to achieve localized imbrication while reducing “fishmouthing” of the breaks. I generally find that drainage is not necessary. However, if the case involves extensive subretinal fluid for which drainage is necessary, I will most likely perform a vitrectomy with a scleral buckle and drain internally.

Case No. 5: A 50-year-old, phakic, macula-on retinal detachment, temporal giant retinal tear (GRT).

Dr. Pieramici: This is a patient who will require a vitrectomy. In this type of case I will also combine with a 40-50 band aiming for a low buckle. If the GRT is 360º a buckle is not necessary. I will typically use $C_3F_8$ gas in a patient such as this. When dealing with GRTs, regardless of their location, I primarily use gas instead of silicone oil.

Dr. Eliott: Because the GRT is temporal, 1 of the edges will be located inferiorly, which causes me some concern, so vitrectomy with a low buckle and $C_3F_8$ gas makes the most sense. Assuming that there is an inverted posterior flap, a vitrectomy is necessary, and perfluorocarbon would be used to uncurl the posterior flap. Don’t always use a buckle in cases of GRT, but when 1 of the edges is located inferiorly, I usually do.

Dr. Regillo: Much of my decision on how to handle this case will depend on the exact location and size of the GRT. There is a significant difference between a smaller, superior GRT such as one that extends from 12 to 3 o’clock and a larger, inferior GRT such as one that extends from 3 to 9 o’clock.

“There is a significant difference between a smaller, superior GRT such as one that extends from 12 to 3 o’clock and a larger, inferior GRT such as one that extends from 3 to 9 o’clock.”

– Carl D. Regillo, MD
intraoperatively in GRT detachments. I do not use oil on the first attempt at retinal detachment repair, even with GRTs.

Dr. Pieramici: Would either of you use steroids in this type of patient? I often recommend intravenous solutedrol at the time of surgery in most of my detachment cases, except in patients with diabetes. I rarely place patients on postoperative steroids.

Dr. Eliott: I do not.

Dr. Regillo: In detachment cases I will use sub-Tenon steroids. I don’t use steroids anymore for less involved vitrectomies such as for macular pucker or macular hole, but I still do in retinal detachment cases. Steroids have potential antiproliferative effects, and they minimize inflammation. I inject 0.5 mL of triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) in 1 of the 2 inferior quadrants, and this will provide a relatively high dose of corticosteroid for 3 to 6 weeks after surgery.

Dr. Eliott: Do you have any problems from spikes in intraocular pressure (IOP)?

Dr. Regillo: Not very often, and if this does occur, I don’t necessarily attribute IOP rises to steroids because I often see the effect in the first week postoperatively and this is not in line with a steroid effect.

We would like to thank the panelists for their participation with their approaches to these cases.

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**Break It Down**
(Continued from page 20)

delivery device for its version of brachytherapy for wet AMD. After a positive small safety study in the United States, a larger trial is planned at Moorfields Eye Hospital in London.

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Program Highlights of the Inaugural Vit-Buckle Society Meeting

By Steve Lenier, Contributing Editor

The first meeting of the Vit-Buckle Society (VBS) will take place April 11-14, 2013, in Miami Beach, FL. The program has been planned to make things interesting and engaging for those attending.

Rohit Ross Lakhanpal, MD, FACS, who is Vice President of the VBS, says the planned format for presentations is much more participatory and interactive than simply giving a lecture. “The goal is to try to stimulate discussion,” he said, noting that at bigger meetings, it’s sometimes intimidating to contribute from the audience, particularly for younger doctors. Dr. Lakhanpal said this meeting is purposely being kept as low-key as possible and that individuals will be walking around the audience with microphones to keep things moving.

He said the presentations will be made more interesting by the fact that they will be based on surgical videos, rather than typical text slides, and he believes that both the content and the presentations will capture and keep the audience’s attention.

“I think the key thing is to show people there are a lot of different ways to do things, and it’s not only based on where you were trained. It’s going to be very nontraditional—that’s what the VBS is about,” he said.

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(PVR), phakic vs nonphakic status, and the factors that can determine the best management of each case. Dr. Lakhanpal said that, in contrast to many meetings, they will not be looking for a consensus, but rather seeking to highlight differences in how people manage cases, so that others may decide to incorporate some of those ideas into their own techniques.

Andrew Schimel, MD
Center for Excellence in Eye Care, Miami
Dr. Schimel will present multiple cases in which a complication or difficult situation is encountered during vitrectomy. The discussion will focus around managing complicated scenarios in a stepwise fashion, which he said was one of the most valuable aspects of his fellowship training. Dr. Schimel noted that the surgeons who performed the cases presented will remain anonymous.

Tien P. Wong, MD
Retina Consultants of Houston
Dr. Wong will give a presentation on management of recurrent retinal detachment. The videos will include several PVR cases in which the retina redetached, and Dr. Wong will show how he fixed the recurrent detachments. He hopes to have a good discussion with a lot of people in the audience. “Some cases involve extensive PVR, some subretinal PVR,” said Dr. Schimel.

(Continued on page 26)
Creating income still continues to be the Holy Grail for investors. The US Federal Reserve’s policies have resulted in interest rate levels of approximately 1.89% on the 10-year Treasury note. Tying up your money for 10 years at that rate, however, is quite undesirable, not to mention the fact that you risk loss of principal should interest rates rise. As a result, investors are moving to a number of other yield-oriented investments, including dividend-paying stocks and high-yield bonds. Another often overlooked investment that merits attention is the master limited partnership (MLP).

What Is an MLP? These securities are frequently based in the oil and gas industry, particularly pipeline transportation and energy storage. MLPs run the gamut from well-established multinational companies to small, recent entrants to the market. An investment in an MLP can provide the investor with current yields in the 5% to 6% range, with a recent initial public offering (IPO) reaping initial yields near 9%. They are also an additional method by which to participate in the energy boom that some say will make the United States energy-independent by 2025.

Just as with any other investment, there are risks. MLPs are capital intensive, so rising interest rates can make their yields less attractive. MLPs have a strong history of raising their distributions, however, which helps to offset the negative effects of rising rates. There is also the potential for price volatility, based upon the fluctuation of different energy commodities. Although many MLPs earn large portions of their income through transportation fees and are therefore less exposed to commodity prices, some are actually engaged in the exploration and production of energy products. Investors should be able to identify the main sources of their MLPs’ income as a way of properly diversifying the risks in their portfolio.

Tax Considerations With MLPs There are more than 100 traded MLPs on the market today, and all operate differently from stocks. Their shares are frequently referred to as units, and, although they are traded on stock exchanges in similar fashion to standard stocks of public companies, their taxation presents some challenges. By definition, you, the investor, are buying into a partnership, and partnerships issue a schedule K-1 form for tax reporting purposes. This makes filing your tax return more complicated. Distributions are partially taxed as income and partly deferred, meaning they are treated as a return of capital, which reduces your cost basis in the MLP’s units. K-1s are often issued well after the 1099 from typical investment accounts, leaving the tax filer to play the waiting game. Also, the unrelated business income of MLPs can create taxable events in individual retirement accounts (IRAs) under certain circumstances. Investors with many individual stock positions may be unaware they will need the additional tax forms, so be certain to check with your accounts’ advisors or custodians before assuming that your 1099 will suffice.

To simplify matters, several firms have begun offering mutual funds and exchange-traded funds. These investments issue the traditional 1099 for tax return purposes and provide the added benefit of diversification. The advantages of tax simplicity, however, can come at a cost. The index funds may not track their underlying index as closely as is customary due to the fund company’s tax filing status. Funds may be taxed as regular corporations, which causes them to reduce their net asset value (NAV) to account for deferred tax liabilities. Investors should consult the funds’ prospectuses for more detailed information regarding their taxation.

Furthermore, the tax differences between individual MLPs and mutual funds are worth reviewing with a tax professional. The investment vehicle and account type (ie, retirement, nonqualified, corporate) that provides the greatest benefit or least deterrent will vary by investor.

An investment in an MLP can provide the investor with current yields in the 5% to 6% range, with a recent initial public offering reaping initial yields near 9%.
The tax complexities can seem daunting, but yield seekers who believe in the energy boom will want to consider MLPs carefully.

Diversify, Diversify

Today’s investment market certainly is challenging for the income investor. The Federal Reserve has shown little sign of impending policy changes, which could extend this low-interest-rate environment for at least another few years. MLPs currently offer average yields on par with high-yield bonds and greater than those of the more traditional dividend-paying stocks, while still providing the potential for capital appreciation. The tax complexities can seem daunting, but yield seekers who believe in the energy boom will want to consider MLPs carefully. We always advise that the best approach is to maintain a diversified portfolio. This includes looking outside the traditional stock/bond spectrum, where MLPs may create a unique investment opportunity. Given the increasing number of MLP participants in the IPO market and new MLP focused funds, investors have a constantly expanding selection from which to choose.

Securities offered through Purshe Kaplan Sterling Investments, Member FINRA/SIPC, Headquartered at 18 Corporate Woods Blvd., Albany, NY 12211 are not FDIC insured, not bank guaranteed, may lose value, including loss of principal, and are not insured by any state or federal agency.

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Eugene W. Ng, MD, MBA, is a vitreoretinal surgeon. He is the founder of his solo private practice in Hawaii. Dr. Ng holds an MBA from Harvard Business School and previously worked as a life sciences investor at several investment management firms. He currently advises biotechnology firms and buyside investors on strategic and investment projects in life sciences and healthcare. Dr. Ng is a New Retina MD Editorial Board member and may be reached at 808 266 0577; or at pacret888@gmail.com.

Vit-Buckle Society Corner

(Continued from page 24)

Dr. Wong. “It should be really exciting to have Dr. Stanley Chang, who is the keynote speaker of the meeting, and others in the audience who have significant experience with PVR discuss these cases.”

Audina M. Berrocal, MD
Bascom Palmer Eye Institute, Miami

Dr. Berrocal will discuss new instrumentation techniques for pediatric retina cases, particularly the new 25+ instrumentation from Alcon for smaller eyes. The new line of instrumentation includes a light pipe and vitrector that are slightly shorter than the standard 25+ instruments, making them a bit stiffer.

Pravin U. Dugel, MD
Retinal Consultants of Arizona, Phoenix

Dr. Dugel will discuss patient selection for ociprlasmin (Jetrea, ThromboGenics). He said that, until more evidence is gathered, there are only 2 types of patients who should be considered for injection with ociprlasmin: those with a medium to small macular hole (<400 µm), and those with vitreomacular traction with adhesions of 1500 µm or less. His presentation will also examine subanalyses that further help elucidate which patients will benefit most with ociprlasmin.

Regarding the meeting format, Dr. Dugel said, “It’s a fairly young group of physicians, and I don’t think anybody wants to be just talked to. I think my presentation will be more of a discussion than anything else.”

Summary

The presentations highlighted here are only a few of the talks that will be given at the VBS meeting, but they provide an idea of what physicians can look forward to. The interactive approach distinguishes those who attend the first annual meeting from just attendees to full-fledged participants.

Thomas Albini, MD, is an Assistant Professor of Clinical Ophthalmology at the Bascom Palmer Eye Institute. He specializes in vitreoretinal diseases and surgery and uveitis. He is the Membership Chair of the VBS and a member of the New Retina MD Editorial Board. He can be reached at +1 305 482 5006 or at talbini@med.miami.edu.
In a pooled analysis of Studies DME-1 and DME-2 [see Clinical Studies (14.3)], the AE rate of 2.1% (21 of 987) in patients treated with 0.5 mg LUCENTIS, 0.3 mg LUCENTIS, and 0.1 mg LUCENTIS vs. control was 12.1% (119 of 987) in patients treated with control. Of these AEs, the most common were injection site reactions (9.3% vs. 10.4% vs. 10.8%, 9.3% vs. 10.4% vs. 10.8%, 9.3% vs. 10.4% vs. 10.8%, and 9.3% vs. 10.4% vs. 10.8% for 0.5 mg LUCENTIS, 0.3 mg LUCENTIS and 0.1 mg LUCENTIS vs. control, respectively). The rates of AEs were similar between the three treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-5% of patients. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iris or vitreous inflammatory reactions. No serious reactions were observed in DME or RVO patients with the highest levels of immunoreactivity.

7.4 Drug Interactions

Drug interaction studies have not been conducted with LUCENTIS. LUCENTIS intravitreal injection has been used adjuvantly with verteporfin photodynamic therapy (PDT). Tenos of 1015 patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no studies of LUCENTIS in pregnant women. In a study of placental and embryo-fetal development in pregnant cynomolgus monkeys, skeletal abnormalities were seen in fetuses at the highest dose tested of 1 mg/kg which resulted in trough exposures up to 3.6 times higher than predicted C_{max} with single eye treatment in humans (see Nonclinical Toxicology (13.2)). Skeletal abnormalities were not seen in monkeys at 0.3 mg/kg which resulted in trough exposures equivalent to single eye treatment in humans. Animal reproduction studies are not always predictive of human response. It is also not known whether ranibizumab can cause fetal harm when administered to pregnant women; however, it is not known whether ranibizumab can cause fetal harm when administered to pregnant women or can affect fetal development (including teratogenicity) and reproductive capacity. LUCENTIS should be given to a pregnant woman only if clearly needed.

8.2 Nursing Mothers

It is not known whether ranibizumab is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 72% (1366 of 1908) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age (see Clinical Studies (7.4)). No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not affect the rate of treatment failures in the clinical trials. However, a higher rate of treatment failures in the clinical trials. However, a lower rate of treatment failures in the clinical trials.

9.6 Use in Specific Populations

Neovascular (wet) age-related macular degeneration

In the clinical studies, patients with neovascular AMD were enrolled as neovascular, neovascular or exudative, choroidal neovascularization, or vascular leakage (including death of unknown cause).

Neovascular (wet) age-related macular degeneration

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LUCENTIS IS the first and only FDA-approved anti-VEGF drug for DME shown to improve vision

- Nearly 40% of patients improved ≥3 lines vs 15% with sham²
- Rapid and significant vision improvement as early as day 7 that continued through year 3²

INDICATION
LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with diabetic macular edema (DME).

IMPORTANT SAFETY INFORMATION
LUCENTIS is contraindicated in patients with ocular or periocular infections or hypersensitivity to ranibizumab or any of the excipients in LUCENTIS.

WARNINGS AND PRECAUTIONS
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored during the week following the injection to permit early treatment, should an infection occur.

Increases in intraocular pressure (IOP) have been noted within 60 minutes of intravitreal injection. IOP and perfusion of the optic nerve head should be monitored and managed appropriately.

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

A pooled analysis of Studies DME-1 and DME-2 showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

ADVERSE EVENTS
Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

In clinical trials in diabetic macular edema, the most common ocular side effects included conjunctival hemorrhage, cataract, increased IOP, and vitreous detachment. The most common nonocular side effects included nasopharyngitis, anemia, and nausea.

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time.

For additional safety information, please see LUCENTIS Brief Summary on adjacent page.

REFERENCES: