A REVIEW OF DATABASED PUBLICATIONS AND PRESENTATIONS IN THE SELECTION OF ANTI-VEGF AGENTS

BASED ON A LIVE ROUNDTABLE DISCUSSION HELD DURING THE 2014 ANNUAL MEETING OF ARVO
Participants

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Pravin Dugel, MD: We are at a point in our careers when we have many excellent therapies for diseases of the retina. In the past, we had some patients for whom we could offer no treatment. Now, we have multiple choices. In our discussion, we focus primarily on neovascular age-related macular degeneration (AMD) and our practical considerations for choosing from the three most commonly used anti-VEGF agents. In a departure from many discussions of this nature, we will begin by addressing the impact of drug costs.

Weighing the Costs

Dr. Dugel: As far as overall cost is concerned, meaning personal and societal, it would seem bevacizumab (Avastin, Genentech) has an advantage over ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron). What are your thoughts?

Dante Pieramici, MD: That depends on the cost to whom. For most patients who have insurance or Medicare, the difference in cost is not large. Patients either have secondary insurance that pays for the drug, or they are enrolled in a patient assistance program that pays for it. There is a cost to society. There’s certainly a difference in cost to Medicare, but I’m taking care of patients, so they are my primary concern.

Szilard Kiss, MD: I agree with you. Looking at the bottom line, $50 vs $2,000 seems like a significant difference, but you have to consider who is paying that price. We are in the business of taking care of patients, rather than trying to save money for an insurance company.

Carl Awh, MD: We all have a concern for society, but this idea that we should make treatment decisions for our patients based on cost to society is inconsistent with everything else we do in our practices. Our primary duty to our patients is to provide excellent care. Personally, I want my doctor to decide what’s best for me, and then I hope I have the resources to pay for that treatment. If we, as a society, can’t pay for what we believe are the best treatments, then we need mechanisms to address that, but I don’t think it’s the doctor’s responsibility to solve that problem.

Dr. Dugel: We have two excellent companies in the United States, Genentech and Regeneron, and outside the United States, Bayer and Novartis. These companies have very effective programs for patients who don’t have the resources to pay for their treatments. Has that been your experience in your practice, Dr. Pieramici?

Dr. Pieramici: Yes, absolutely. It’s been a savings for patients and also for our practice, because if we had to bill the outstanding difference to these patients, we probably wouldn’t be able to collect from many of them.

Dr. Awh: I agree. We have introduced systems in our practice to ensure that patients are enrolled in these programs and approved for coverage. This process has removed much of the anxiety we had in the early days when we weren’t familiar with buy-and-bill drugs. I think some practices may resist using ranibizumab or aflibercept because they don’t understand that
programs such as these can relieve much of the financial risk for a practice.

**Dr. Dugel:** Dr. Kiss, I can’t resist asking you a difficult question. In April, the Centers for Medicare & Medicaid (CMS) began reporting what physicians bill for services provided by Medicare, and the information was picked up by various news outlets. Do you think this will have an impact on how we, and our colleagues, use these expensive drugs?

**Dr. Kiss:** I hope it doesn’t, but it may. Some of my patients who read the newspaper articles asked me about the data. I’m in a unique situation, because about 3 years ago, for various reasons, I stopped using bevacizumab and switched patients to either ranibizumab or aflibercept. When patients ask why I’m using these medications, I tell them I believe the overall efficacy of ranibizumab and aflibercept is about the same, and I don’t trust my source of bevacizumab. (See “How Compounding Can Affect Efficacy” on page 6.) Then, I explain how the reported numbers don’t tell the whole story. For example, the physician’s fee for an injection administered in Manhattan is $128, while the company’s fee is $2,000. That $2,128 is shown in the overall reimbursement numbers in the CMS database. When patients understand that — and when I explain that I’m giving them what I would want for my own eye and what I think is best for them — they can put the numbers into context.

**Dr. Awh:** I think it’s important for all physicians, not just retina specialists, to not be defensive about delivering what we consider the best care. If we happen to have received a large sum of money from Medicare, it’s because we treated a large number of patients, and we treated them with a drug that we thought was best. We don’t set the prices for these drugs. We select the drug that we want to use, and we are simply the conduit for sending the money to the pharmaceutical companies.

**Dr. Dugel:** I completely agree with you. I hope other groups, especially the pharmaceutical companies, will join us in educating our patients and the public as to what those numbers really mean and providing the proper context for their interpretation.

This sets the stage for the next part of our discussion. There’s a tremendous amount of pressure for us to use or not use certain drugs. So it’s more important than ever that we understand the science behind these drugs.

### Efficacy Assessment

**Dr. Dugel:** Dr. Awh, is there any indication that one anti-VEGF agent is more efficacious than another?

**Dr. Awh:** All of these drugs work well to improve vision in patients with neovascular AMD. The studies do seem to show some differences in efficacy, depending on how one measures it. If you’re considering reduction in macular thickness, then ranibizumab seems to be superior to bevacizumab, but I think it’s impossible to make a decision without considering all of the factors that we’ll be discussing, safety in particular.

**Dr. Pieramici:** I agree. These are great guidelines, but there may be differences in how individual patients respond to one drug or another, and individual patient safety and durability will vary as well.

**Dr. Dugel:** Those are important points. First, how do we measure efficacy? Second, how do we individualize care versus treating the median? Let’s first discuss visual acuity as a measure of efficacy. Dr. Kiss, have you seen any data to indicate that one of these three anti-VEGF agents produces better visual acuities than the others?
**Dr. Kiss:** In terms of improving visual acuity, I think all three drugs are similar in efficacy. I think the primary driver of differences in mean efficacy isn’t the drugs themselves but how we use them. There seems to be a correlation between the number of injections and the ultimate visual outcome. We’ve all had individual patients whom we’ve switched from one drug to another who may be showing a suboptimal response on OCT, but whose vision has improved. Overall, I think the treatment patterns rather than the drugs themselves may be having an effect on an individual.

**Dr. Dugel:** Let’s discuss the concept of “switch” patients. Do some patients respond better to one drug than another?

**Dr. Pieramici:** I think so, but that response may be dose-related. One patient may respond well to a specific drug at a dose of, say, 0.5 mg for ranibizumab, whereas another patient may need a slightly higher dose, such as the 2.0 mg dose of aflibercept. It’s not that one drug is inherently better than the other but that there happened to be a slight molar dose difference. When we switch drugs, a patient’s tachyphylaxis or tolerance may come into play. A slight change in the molecule may rejuvenate the efficacy of that drug. We’ve all seen that in a few patients.

“I think it’s important for all physicians, not just retina specialists, to not be defensive about delivering what we consider the best care. If we happen to have received a large sum of money from Medicare, it’s because we treated a large number of patients, and we treated them with a drug that we thought was best. We don’t set the prices for these drugs. We select the drug that we want to use, and we’re simply the conduit for sending the money to the pharmaceutical companies.”

— Carl Awh, MD

**Dr. Dugel:** In all of the switch data I’ve seen, the anatomy may improve, but the function doesn’t usually improve. I don’t know if that’s because the switch occurred too late, or if that’s just the way it is or if we’re using the wrong biomarker. Often, it seems that in switch studies, the regimen, as opposed to the actual drug, makes the difference. What are your thoughts, Dr. Awh?

**Dr. Awh:** I think the regimen is key. Few physicians are able to maintain a monthly or bimonthly schedule for their patients in the real world. As we depart from that regimen and treat PRN or use a treat-and-extend approach, I think many patients are undertreated, and, therefore, our patients don’t achieve the full potential that these drugs can provide. Unfortunately, that is the reality of trying to get patients and their family members with busy lives into a busy doctor’s office on a regular schedule.

Another factor that may affect efficacy is variability in the concentration of drug being used. (See “How Compounding Can Affect Efficacy” on page 6.)

**Dr. Dugel:** Let’s discuss how you manage suboptimal or nonresponse to treatment.
How Compounding Can Affect a Drug’s Efficacy

Dr. Awh: We are injecting small amounts of drug, so the concentration of drug in these small volumes must be reliable. In both CATT and in IVAN, all bevacizumab came from a single source and was highly regulated. Some have looked at the reliability of the concentration of bevacizumab in vials obtained from compounding pharmacies, and there is reason for concern. When we use compounded bevacizumab, there is no assurance that we’re administering the same amount of drug used in the clinical trials.

Dr. Dugel: The bevacizumab that was used in the CATT study — the way it was formulated and packaged — isn’t available to us.

Dr. Kiss: You are correct. We at Weill Cornell looked at 11 suppliers of bevacizumab around the country. I really didn’t understand how you can have different concentrations, different aggregations, when you draw up a drug until I spoke with personnel at a good manufacturing practices (GMP) facility. For example, I learned that small independent compounding pharmacies often use non-porous protein filters that may actually filter out the medication. The bevacizumab may be safe in terms of no contamination, but the concentration may not be what you expect. We also found that some preloaded syringes from various compounding pharmacies were empty. These are issues we can’t ignore.

Dr. Dugel: People who haven’t looked at this issue closely would be astounded at the lack of regulatory requirements for compounding pharmacies. We hear about the disasters, but we don’t hear about the possibility of receiving a compound that has very little activity. We have no way of assessing drug concentration and activity when the compounded product is delivered. A poorly compounded or transported product may lead us to misinterpret a patient’s response as suboptimal.

Dr. Pieramici: It may take 2, 3 or 4 months to figure that out, but by that time, the patient may have fibrosis or decreased vision.

References

Suboptimal Response to Therapy

Dr. Dugel: Several questions arise when we’re faced with what appears to be nonresponse to therapy. How do you define nonresponse? When do you consider switching therapies? Do you base that decision on vision?

Dr. Awh: Probably the easiest and most reliable way to determine nonresponse is with OCT, because that’s an objective measure. However, even if the anatomy is relatively unchanged, if the vision is improving, I consider that a success. I’ve seen many patients with modest improvements in anatomy have major improvements in vision. Once a patient reaches an anatomic plateau, I will sometimes switch drugs with the hope that this will gain a bit more vision. In my experience, however, additional improvements in vision occur only if the anatomy improves with switched therapy. Anatomy is the key.
Dr. Pieramici: If visual acuity is worsening, I try to find an anatomical correlate for that. OCT drives my decision-making. I look at OCT qualitatively not just quantitatively. I review all of the scans to make my assessment. If the anatomy and the vision are stable and I think fluid is present that might benefit from another drug, I will try another drug to see if I can further improve the anatomy and perhaps the vision. That decision is anatomically driven.

Dr. Kiss: I agree. I think anatomy, as evaluated by the OCT, is ultimately our best VEGF meter, combined with visual acuity.

Dr. Dugel: OCT is a great barometer for measuring the effect of anti-VEGF drugs, but I think we have to be careful when we talk about combination therapies, because I don’t think OCT is a good barometer for other factors, such as inflammation.

I’ve been underwhelmed by switching drugs because I think the patient’s genetic makeup, as opposed to the drug itself, determines how he will respond. (See “Using Genetics to Personalize Treatment” on page 8.) I think if a patient is going to respond well, he’s going to respond well to any of the three drugs. I like to perform VEGF challenges. I simply inject a drug and check the patient for a response in 1 or 2 weeks instead of 4 weeks. I also use indocyanine green angiography (ICGA) to guide therapy.

Durability Versus Efficacy

Dr. Dugel: Is there any evidence that one anti-VEGF agent is more durable than another?

Dr. Pieramici: On average, aflibercept may squeak out a couple more days of benefit, but I think the other drugs are about the same.

Dr. Awh: I agree that there are no major differences in durability among the three drugs. At ARVO this year, Dan Martin and colleagues reported that treatment with ranibizumab was among several predictors of fewer injections, but it’s difficult to know if the effect is from durability or efficacy.¹

Dr. Kiss: I wasn’t surprised by those findings. The primary indicator for retreatment is fluid, so if fluid levels decrease, you’re not giving as many injections.

Dr. Dugel: If you look at the treatment regimen in the HARBOR study, the median was 14 injections but the treatment window is enormous.² So, if you’re treating with 14 injections based on that study, you’re undertreating half of your patients. This disease is so patient-driven and so variable that even if a particular drug may give a few days durability advantage, that advantage may be moot. Overwhelmingly, the treatment will be driven by the patient … more specifically, the patient’s genotype.

People rarely talk about the variability of the disease. In the original ANCHOR and MARINA studies, 5% of patients in the sham arm received no treatment and their vision improved by 3 lines.³,⁴ In VIEW 1 and VIEW 2, there was a greater than 40% difference in efficacy with the same drug and the same regimen.⁵ Again, it is a variable disease that I believe is entirely patient-driven.

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Using Genetics to Personalize Treatment

Dr. Dugel: Dr. Awh, you’ve been a champion of personalized medicine based on genetics. Take us to the future. How do you imagine we’ll be using genetic knowledge to personalize and individualize treatment?

Dr. Awh: Genetic testing already enables us to identify patients who are at risk for developing advanced AMD. That, in itself, is important, because clinical trials have consistently shown that visual acuity at the start of treatment is a key predictor of final visual acuity. The earlier we identify disease and begin treatment in patients, the better. Patients known to be at higher risk of progression can be examined more at frequently and may be more compliant with home vision monitoring and nutritional supplements.

What’s more, our analysis of AREDS data has shown that we may be able to reduce the risk of progression for patients through genetically guided nutritional therapy. Rather than treating all patients with the AREDS formulation, we can use genetic testing to identify subgroups of patients who may respond better to zinc alone or to antioxidants alone, rather than to the combination of zinc and antioxidants. Our analysis suggests that genotype-directed nutritional therapy could substantially decrease the percentage of patients who progress to advanced disease. Our work is preliminary, but I think that this approach, or something quite similar, will prove to be correct.

Dr. Dugel: Will genetics also guide our treatments?

Dr. Awh: I absolutely believe we will one day use genetic markers and biomarkers to identify potential best and worst responders to available treatments. This knowledge will be helpful to both the doctor and the patient when they discuss treatment options, especially if the preferred treatment involves multiple injections. This will help to set expectations, to make decisions regarding changes in therapy, and to select optimal treatments when we have drugs with different mechanisms of action.

In a paper published in April in *Ophthalmology*, researchers reported that polymorphisms in the VEGFR2(KDR) gene significantly influence visual outcomes in patients receiving ranibizumab treatment for neovascular AMD. The study shows, for the first time, that genetic variation partially explains the wide range of responses to ranibizumab treatment. This is the type of using Genetics to Personalize Treatment

Dr. Kiss: Medicare claims data provide a good snapshot of how physicians are actually using these drugs in the “real world.” In our review, my colleagues and I found very little difference in treatment intervals for ranibizumab and aflibercept, whether we were looking at a first-line treatment in a treatment-naïve patient or a second-line switcher. I agree that it’s primarily an individual patient-specific decision rather than the specific medication injected.

Patients who are newly diagnosed with AMD often know someone who has had injections, so their concerns about having a needle in the eye are easily overcome. The next question is usually, “How many injections will I need?” I can try to use FA and ICGA findings to determine the need to treat, but ultimately, it comes down to their genetics, their individual variability.

Dr. Dugel: Durability may not be the issue. Perhaps the question we should be asking is: Do any of these three drugs reduce treatment burden more than the others? We often equate the number of injections to treatment burden, but the burden is not
the injection itself, which takes only a few seconds. The burden encompasses what it takes for patients to come in frequently for injections.

How do we determine how a patient will respond? It's really trial and error. If we're going to treat and then try to extend the interval between treatments, our decisions are based on the individual patient's response. That's why we're seeing what we're seeing in the market scan data, which is that none of these drugs has an advantage over another related to treatment burden.

Dr. Pieramici: What was surprising from the claims data was that doctors were using aflibercept the same way they were using ranibizumab. We were hopeful that this drug (aflibercept), based on clinical trial data and FDA approval labeling would reduce the burden for patients, but this is not the case.

Systemic Safety

Dr. Dugel: After seeing the CATT data and the IVAN 1 and IVAN 2 data on ranibizumab and bevacizumab, do you think systemic safety issues exist?
**Pros and Cons of Genetic Drug Delivery**

**Dr. Dugel:** At least two companies are working on genetic drug delivery systems, one that is injected into the eye and one that is surgically placed under the fovea. Are you excited about having a mutated adenovirus gene act as a drug delivery device?

**Dr. Awh:** It’s intriguing technology, but I think it will be important for us to know who among our patients needs lifetime, continual delivery of these medications. With genetic testing and other biomarker assays, we may be able to identify those patients. On the other hand, if we can identify patients likely to respond well to a shorter course of therapy, then they might not be the ideal group of patients for genetic drug delivery. We want more options, and converting the eye to an anti-VEGF factory is intriguing.

**Dr. Dugel:** On the one hand, we talked about the benefits of personalized medicine and the advantage of having numerous choices. On the other hand, we’re talking about delivery systems that, to a certain extent, take away our ability to personalize treatment. For example, would it be beneficial to have a molecule with both anti-VEGF and anti-platelet-derived growth factor (PDGF) properties? I’m not so sure. There may be instances when I want to give one or the other, or I may want to give a different kind of anti-VEGF agent. I want to be able to individualize my treatment, but I don’t necessarily want everything packaged together. How do we reconcile that with having a delivery system?

**Dr. Kiss:** I may be a fool in 10 years, but I think the only way we’re going to deliver biologics long-term is through gene therapy. With that being said, I have two concerns. First, how do we individualize therapy when the patient has a drug on board that takes away the VEGF component? Second, what are the long-term effects of anti-VEGF therapy?

We talk about individualizing therapy with genetics, and that’s one arm of research that is advancing, but we can already individualize therapy with imaging. By performing a

**Dr. Kiss:** I think that’s yet to be determined. Overall, the drugs are safe, safer, it appears, in the AMD population than in the diabetic population, which tends to be a systemically sicker patient population. Significant differences in safety may become apparent only after we’ve studied hundreds of thousands of patients.

However, I think we would be remiss to ignore the biology and the safety signals from these trials. There are differences between these two drugs in clearance and in systemic exposure, independent of how they’re binding VEGF. I’ve discussed these factors with my patients. It’s not something I ignore, even in my AMD patients.

**Dr. Dugel:** There never will be a definitive study, because the sample size would need to be too large. Yet, retina specialists have to make decisions. Dr. Pieramici, your group has looked at the systemic exposure of aflibercept, bevacizumab and ranibizumab in diabetic macular edema. What have you found, and how have your findings influenced your day-to-day practice?

**Dr. Pieramici:** When we started using anti-VEGF agents, particularly bevacizumab, in patients with diabetes, we saw a response in the fellow eye, suggesting that some of the intravitreal drug was entering the systemic circulation at a high enough level to inhibit VEGF in the other eye.

There’s no doubt the length of systemic exposure of these drugs is different based on the Fc (fragment, crystallisable) portion of
the molecule. Ranibizumab, lacking the Fc is degraded systemically in a short time period, whereas bevacizumab and aflibercept persist at levels above the IC50 for longer periods. In theory, they can potentially inactivate VEGF systemically for weeks.

Some controversy exists regarding the levels of VEGF being measured in the plasma and the serum, but even if we look only at the levels of the drugs themselves, they are at active levels systemically. So there is biologic plausibility that this could be having a systemic effect. We can’t ignore these data, particularly when treating high-risk patients, such as older people who may have a history of heart attack or stroke, babies with retinopathy of prematurity or patients with diabetes and hypertension.

So, again, we need to individualize patient care. Not all of our patients are like the 70-year-old patients who participated in the clinical trials.

Dr. Dugel: How has your study changed the way you practice?

Dr. Pieramici: Many of my patients are having bilateral anti-VEGF injections, which exposes them to a double dose of an anti-VEGF agent. I consider double-dosing carefully in high-risk patients, when deciding drug selection.

Dr. Dugel: The European Public Assessment Report (EPAR) on aflibercept stratified arterothrombotic events, based on the knowledge that VEGF suppression causes
hypertension, which is more likely to cause cerebrovascular events; whereas, high cholesterol is more likely to cause cardiovascular events. Patients were also segregated according to age, with patients 85 years or older considered most vulnerable. In the first year, in this most vulnerable patient population, there were more cerebrovascular events, mainly transient ischemic attacks, in the aflibercept group, but there were more cardiovascular events in the ranibizumab group. In the second year, the cardiovascular events tended to normalize, but the increased number of cerebrovascular events in the aflibercept group persisted. Dr. Awh, how do you look at the EPAR data? Do you change your practice based on those data?

**Dr. Awh:** There seems to be a difference in how these drugs are cleared from the eye and from the body, and we know we’re affecting serum levels of VEGF, but we really don’t know the impact of those changes. Generally, my feeling is if we don’t understand something, it’s better to minimize variations from normal.

**Dr. Dugel:** Do you consider systemic exposure when choosing a drug?

**Dr. Awh:** The fact that systemic exposure is probably less with ranibizumab than with bevacizumab is something I consider. That is a small factor, however, because we’re not sure of the impact of the systemic exposure.

For elderly patients with useful vision in one eye, these injections may be essential for them to live full and normal lives. I believe that even if we were certain that these eye injections resulted in a slight increase in the risk of some systemic problem, most would choose to continue treatment. At present, we don’t have to present our patients with these options, but consider this: plenty of 80-year-olds will eat a steak tonight, knowing it that may increase their risk of heart disease, but they derive great pleasure from eating that steak! We make these types of informed decisions all of the time. Choosing a treatment that protects vision, even one that poses a small risk, is an easy choice for most people.

**Dr. Dugel:** Dr. Kiss, how much do systemic safety data influence how you choose a drug, and how you monitor the patient?

**Dr. Kiss:** It’s highly influential. In my group’s claims analysis studies, we looked at a normal population of people without diabetes, age-matched controls with diabetes without diabetic macular edema, and patients who have DME. We found that patients with DME are much sicker than clinicians may realize. They are sicker in terms of their cardiovascular, cerebrovascular and kidney health. When we look at these patients, we’re looking at an extreme, and looking at the extremes may give us important information even within a normal population.

In any sick population, I try to minimize the systemic exposure by going to a surrogate. That surrogate is not only the
Clinical trial data but also the pathophysiology of how these molecules are eliminated from the eye and how they are recycled. Because of the Fc fragment, I think bevacizumab and aflibercept may have higher systemic exposure, which the EPAR analysis and the DME trials may confirm.

**Dr. Dugel:** Interestingly, the Fc portion may also have a local effect, although we don’t know this. A recently published paper examined the effects of intravitreal ranibizumab and aflibercept on monkey eyes. The researchers found that the reduction of the choriocapillaris endothelium thickness, the number of fenestrations and the areas with hemolysis were more pronounced after aflibercept. The inference is that these factors may lead to further geographic atrophy. Dr. Pieramici, what is your opinion?

**Dr. Pieramici:** The Fc domain of anti-VEGF drugs is worrisome for a number of reasons that we have discussed. Based on the knowledge we have, if I were to design a drug today, I would eliminate that.

Another concern is that the newer trials are excluding patients who have a history of stroke and other cardiovascular problems. In my clinic, a large percentage of patients are undergoing renal dialysis and have had strokes and heart attacks.

**Pipeline Potential**

**Dr. Dugel:** Anti-VEGF monotherapy with any of the three drugs in this class has some great benefits, but we are also starting to see some shortcomings. Some of those shortcomings may be related to sustainability, because we know there’s a large gap between the regimens used in the clinical trials and what we are able to do in our clinics.

Regardless of the anti-VEGF agent and regardless of the disease, we often see an initial improvement and then a plateau. With neovascular macular degeneration, we can stop a blood vessel from growing, but that blood vessel doesn’t usually go away. That’s why I’m quite interested in the antiplatelet-derived growth factor (PDGF) agent (Fovista, Ophthotech). Physiologically, it makes sense to me to clinically strip the pericytes and expose the endothelial cells, allowing an anti-VEGF agent, in combination, to penetrate the cells more effectively. The phase 2 data showed a 62% comparative benefit from baseline visual acuity in the combination arm versus ranibizumab monotherapy.

**Dr. Awh:** I think the mechanism is compelling, although we must interpret this phase 2 data with cautious optimism. There are great analogies between cancer treatments and how we treat wet AMD. Our oncologist colleagues are constantly combining drugs and developing new regimens to more effectively attack cancer, and this is parallels that logic. It makes sense to attack the disease from multiple angles. The phase 2 data were encouraging enough to proceed with the phase 3 trial, but I am reluctant to hypothesize what the vision outcomes might be in phase 3. I hope this will add to our ability to treat our patients.
Dr. Dugel: I agree that we should take those data with a grain of salt, but it was the largest phase 2 trial ever performed in retina. I was particularly impressed that all of the biomarkers consistently aligned; despite their well-known variability.

There are three hurdles that I hope we will overcome in the future: 1) more sustained drug delivery; 2) a different mechanism of action, other than anti-VEGF; and 3) more personalized medicine. I think an anti-PDGF agent fits into the second category. I believe we have hit the ceiling, so to speak, with anti-VEGF therapy. An anti-VEGF agent alone probably will not give us a better overall result in terms of anatomy or visual acuity. We may be able to get a more sustained result, depending on different molecules and molecular makeup, and the sustained delivery devices, but in terms of anatomy and visual function, we may have hit a ceiling.

As we look at the SEVEN UP trials and others, we seem to be converting some of our wet AMD patient into dry AMD patients. We may even be accelerating that conversion, but I think as we treat these patients 5, 6, and 7 years from now, we have to think about treating dry AMD.

Dr. Pieramici: I agree. I think about geographic atrophy more and more in my anti-VEGF patients. These are the patients I continue to inject for years and many develop significant central atrophy. This may be the natural disease process, but some evidence suggests we may be enhancing this process with persistent anti-VEGF therapy. When treating a patient who has a small amount of fluid and some pericentral geographic atrophy, I wonder if it is more prudent to hold the injection rather than potentiate the atrophy. This is what concerns me about long-acting drug delivery systems. I think they may move us away from individualized care in some respects and we may be over-treating some patients and risking unnecessary side effects.

Fundamentally these are aging diseases, and we are treating them far downstream when we should be treating them upstream by preventing the development of the early or intermediate stage changes.

Dr. Dugel: Researchers first looked at anti-PDGF as an antifibrotic agent for proliferative vitreoretinopathy. It has very strong antifibrosis activity, which I think is attractive.

Regarding VEGF pathobiology, our purpose in using anti-VEGF agents isn’t the same as the original purpose for anti-VEGF agents. In colon cancer and breast cancer, which have no permeability issues, it was used to normalize vessels, and that’s what it does. When you suppress VEGF, you prematurely normalize vessels. It provides you with a pathway to the disease. So we shouldn’t be surprised that when we take away the tip cells, which are naked endothelial cells, we’re left with a hyper-mature or prematurely matured abnormal blood vessel complex covered by pericytes that we may have to treat forever. I agree that a combination therapy will be very attractive.

It is clear in this discussion with experts that we’re moving from defining the role of anti-VEGF drugs to a new phase of refining the role of anti-VEGF drugs in the treatment of neovascular AMD. This refining process includes the consideration of the cost/benefit ratio to society; the safety risk/benefit ratio to the patient; the individualization of patient care; finally, and perhaps most importantly, the combination of complementary drugs to improve outcomes. We are indeed turning a new page ... and the thoughts imparted in this discussion will prove prophetic.
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