Applying Research to Practice for Patients with Diabetes

AN EXPERT DISCUSSION FROM **RETINA SOCIETY 2015**

featuring

David M. Brown, MD
Retina Consultants of Houston

W. Lloyd Clark, MD
Palmetto Retina Center

Peter K. Kaiser, MD
Cleveland Clinic

moderated by

John W. Kitchens, MD
Retina Associates of Kentucky

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ESTIMATED TIME TO COMPLETE
60 minutes
TERM OF CREDIT
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TARGET AUDIENCE

This certified CME activity is intended for all eye care specialists involved in the care of patients with diabetes.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Discuss results and clinical implications from the 3-year data of the VIVID and VISTA study.
- Discuss results and clinical implications from the DRCR.net Protocol T study.
- Describe issues relating to the use of compounded drugs for the treatment of diabetic eye disease.
- Effectively communicate with the primary care clinician as it relates to treating diabetic eye disease.

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FACULTY

David M. Brown, MD
Retina Consultants of Houston
Baylor College of Medicine
Houston, Texas

W. Lloyd Clark, MD
Palmetto Retina Center
University of South Carolina School of Medicine
Columbia, South Carolina

Peter K. Kaiser, MD
Cole Eye Institute
Cleveland Clinic
Cleveland, Ohio

John W. Kitchens, MD
Retina Associates of Kentucky
University of Kentucky College of Medicine
Lexington, Kentucky

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Restoring Vision in Patients With Diabetes: An Expert Discussion From Retina Society 2015

The following roundtable discussion was held in conjunction with the 2015 Retina Society Meeting in Paris, France, Oct. 7-11, 2015.

Editor's note: *This roundtable occurred before the 2-year results of Protocol T were published.*

VIVID AND VISTA

John W. Kitchens, MD: We will start this discussion with the VIVID and VISTA 3-year data. Dr. Brown, can you give a summary of the results?

David M. Brown, MD: The VIVID and VISTA 3-year data[1] were presented during the paper section of the 2015 Retina Society Meeting. Patients originally randomized to aflibercept continued with their treatment intervals—either monthly aflibercept or every-8-week aflibercept (q8)—for the full 3 years. The control arm, which originally received focal laser at randomization and then "as needed" (prn) focal laser every 3 months through 24 months, were switched to prn aflibercept for months 24 to 36. In my opinion, the encouraging thing is that in the aflibercept groups, the visual acuity gains were maintained even in the study arm that received 2 mg every 8 weeks (2q8) (almost exactly the gain of the arm that received 2 mg every 4 weeks [2q4]), implying that a 2q8 regimen can maintain the average patient with diabetic macular edema (DME) at a very good visual acuity gain. For the control arm, about 40% of patients in the study were rescued in the first 2 years, and then another 45% received prn therapy in the third year. Even with rescue and prn, these patients improved over baseline, but not nearly as much as those who were originally randomized to aflibercept.

The key take-home for me is that there should be no delay in starting anti-VEGF therapy. If a patient has significant edema, there will be vision left on the table if you wait for either vision loss or other triggers to institute therapy.

Dr. Kitchens: Did the study include retinopathy regression?

Dr. Brown: Yes. Retinopathy regression was maintained in both aflibercept arms, including the 2q8 arm. It was nice to see that every-other-month aflibercept appeared to maintain the retinopathy regression for a prolonged period. It still does not answer two questions: what happens if (1) the patient receives far less injections, like in the Protocol I study[2,3]; or (2) what the average patient needs in year 3.

Peter K. Kaiser, MD: Is it surprising to anyone that the difference did not increase in that second and third year?

Dr. Brown: It is surprising to me.

Dr. Kaiser: It is surprising to me, too. I was expecting that the long-term anti-VEGF would continue to improve retinopathy scores and it did not appear to do that.

Dr. Kitchens: Dr. Kaiser, does the data we have on retinopathy regression change how you approach these patients?

Dr. Kaiser: That is an interesting question, because I was asked recently by an endocrinologist if in my practice we still use panretinal photocoagulation (PRP) and why we would use laser treatment and potentially decrease a patient's night vision, contrast sensitivity, and color vision when all that is needed are injections.

I explained that to get the benefit, injections are needed every 1 to 2 months for a long period of time, maybe even for life. Therefore, I am not ready to sell my laser just yet. The positive side effect of improvement in diabetic retinopathy when treating DME is great, and certainly meaningful. But, I am not going to do injections in absence of edema to get this benefit.

For me, the next question to answer is whether I am I ready to give a patient injections to avoid doing PRP. The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S study[4] findings did offer some compelling data with less peripheral visual field sensitivity loss, less vitrectomies, less DME development, and similar visual and neovascularization regression results with anti-VEGF injections. But, we do not know what happens when the injections stop. I still think PRP performed at the appropriate time is a sight-saving treatment and will still have its place.

Dr. Brown: I think the retinopathy regression data helps reinforce to patients that the intraocular injections are improving their condition. I show the patient and their family that there are less hemorrhages on the pictures and that the retina looks "happier." In terms of preventing PRP, I agree with Dr. Kaiser. If a patient has neovascularization, I perform panretinal photocoagulation because I think it is more cost effective. And if that patient loses insurance or gets lost to follow-up for whatever reason, I do not have to worry about an eye with neovascular glaucoma or vitreous hemorrhage needing vitrectomy. PRP is a quick answer for proliferative disease.

PROTOCOL T

Dr. Kitchens: We will switch over to DRCR.net Protocol T,[5]

a landmark study in the treatment of diabetic retinopathy and macular edema. The 1-year results were published earlier in 2015. Dr. Kaiser, tell us about the top-line results.

Dr. Kaiser: DRCR.net Protocol T looked at the three different drugs that we commonly use for center-involving DME—bevacizumab, ranibizumab, and aflibercept—in a head-to-head comparison over 2 years. The primary outcome at 1 year showed that patients receiving aflibercept had a statistically significant improvement in visual acuity versus patients receiving ranibizumab and bevacizumab, with visual results between the ranibizumab and bevacizumab groups essentially equal. In addition, to get those results, there were significantly less injections required.

The difference in vision was small and likely not clinically meaningful, and patients in the aflibercept group had only one less injection than patients in the ranibizumab and bevacizumab groups. Among those with poor vision at baseline (worse than 20/40) or worse edema (greater than 400 µm central subfield thickness) the difference in favor of aflibercept was even more significant and clinically meaningful. From a safety standpoint, there was no difference. It is important to note that the 0.3-mg dose of ranibizumab was used in this study, which is the approved US dose; 0.5-mg ranibizumab is the dose used outside the United States.

Dr. Kitchens: Dr. Brown, what is the take-home point from the Protocol T study?

Dr. Brown: The top take-home from Protocol T is that aflibercept won the match, specifically in eyes with worse vision and worse edema. The study results indicated that all the anti-VEGF agents did equally well at reducing edema and improving vision in patients with better vision or less edema at study entry. But, in patients with increasingly more edema and worse vision, aflibercept outperformed bevacizumab and ranibizumab.

Of note with Protocol T is that the study enrolled eyes that were as good as 20/30 +2. No other study prior to this has done that because for registration trials people want 3-line gainers, and it is generally thought that improvement beyond that is not likely. Counterintuitively, there were many 3-line gainers, even in those 20/30 +2 patients.

For me, one of the take-home points from Protocol T is that even patients with relatively good visual acuity can improve, and we are waiting too long to treat with any anti-VEGF if we wait until patients have had visual loss to the extent where they cannot be refracted to 20/40 or so.

Dr. Kitchens: Dr. Clark, how has this study changed your practice?

W. Lloyd Clark, MD: I think the big issue for the clinicians in my practice relates to patients with more severe disease. In South Carolina, we see a disproportionate number of patients with severe disease, so Protocol T data is clinically relevant given our patient population. I did not expect that from the Protocol T results going into the trial.

Dr. Kitchens: Dr. Brown, you have often said that you split your use of anti-VEGF agents equally between the three drugs. Have these results changed how you do things?

Dr. Brown: Yes, certainly for DME, I find that my patients fall into either a bevacizumab kind of a patient or an aflibercept kind of patient. Most of that is predicated by insurance status. Even if a patient has 20/40 or better vision, as long as he or she has good insurance coverage, I will typically initiate treatment with aflibercept, because I think I can get more anatomical deturgescence of the retina and likely less injections over time with aflibercept versus bevacizumab.

Dr. Kitchens: Dr. Kaiser, has Protocol T changed your practice?

Dr. Kaiser: It has changed my practice in that I start all my patients on bevacizumab, regardless of their insurance coverage because I want to see if a patient will respond to bevacizumab. Certainly, if his or her vision is worse than 20/50 or there is more than 400 µm retinal thickness at baseline, I will switch to another anti-VEGF sooner now because of the Protocol T study results. In patients with good vision, I always start with bevacizumab. The study implies that if I treat these patients long enough, they will probably do well.

I agree that with patients who have 20/40 or better visual acuity, it does not matter as much, but there is still a difference even in these patients. For instance, we only have 1 year's worth of data with nine to 10 treatments for retinal thickness. The question is what happens in that second year when treatments are much less? Is the difference greater or is it less? The data from the second year of Protocol T will be very important for how I treat my patients in the future.

Dr. Kitchens: Dr. Kaiser, you have said previously that you start all patients with DME on bevacizumab. In those patients with good visual acuity versus worse visual, what is your cutoff? When do you decide to switch them?

Dr. Kaiser: The vision cutoff from Protocol T is worse than 20/40, but that is on an ETDRS chart and not directly convertible to Snellen notation. There is no hard and fast visual acuity where one would always go with aflibercept. With that in mind, I still start almost all my patients on bevacizumab. My threshold to switch to aflibercept in the patients who have poor vision or swollen retinas is very low. In northeast Ohio, where I practice, many insurance companies, even after Protocol T, require us to prove that a patient has failed bevacizumab prior to being able

to switch to a more expensive drug. Now I have much more ammunition to say earlier on that they are failing treatment and need to switch.

Dr. Kitchens: Dr. Kaiser, theoretically, why do you think we see a difference in the Protocol T results between these drugs?

Dr. Kaiser: I think there are two factors to consider. One is obviously aflibercept's higher binding affinity. However, I think it is more due to aflibercept's blockade of placental growth factor and other members of the VEGF family. DME is multifactorial. There are inflammatory and ischemic components. We know that placental growth factor is involved in vascular leak. The fact that this drug blocks many cytokines, whereas ranibizumab and bevacizumab only block VEGF-A, is probably the main reason we are seeing a difference in this disease.

Dr. Clark: I think Dr. Kaiser's explanation is intriguing and makes a lot of sense. I think about it more in terms of affinity. The corollary is what we see in non-AMD diseases other than DME. When we look at patients with retinal vein occlusion, we see this rapid and dramatic improvement even with a single injection of aflibercept. Now we see this response with other agents as well, but it looks, at least based on clinical trials as well as anecdotal experience, that there is a greater response in these high-VEGF-load diseases to aflibercept relative to the other agents. They very well may both be at play, but it looks like an affinity story.

COMPOUNDED DRUGS

Dr. Kitchens: Dr. Clark, talk to us about compounded drugs and whether they present any issues within your practice.

Dr. Clark: Our group has gradually shifted away from compounded drugs in favor of on-label drugs because of an overall uneasiness with compounding in terms of ocular safety. For patients with particularly good vision, I think it is more of a toss up because we have a drug that is significantly less expensive. It may not be quite as effective, but in eyes that do not have a severe disease, there may be a similar outcome. I would probably say our practice patterns are a little more between the two on-label drugs as opposed to bevacizumab.

Dr. Kitchens: Dr. Brown, what about your practice?

Dr. Brown: I think that one problem is that you can cheat up the dose a little bit with on-label branded drugs that come in vials compared with compounded drug. With the compounded drug, there is only the exact amount in the syringe and there seems to be much more variability with our compounded bevacizumab potentially due to interactions with the plastic syringe. It has been well demonstrated that proteins aggregate with the plastic syringe walls. In places like Bascom Palmer Eye Institute in Miami or Cleveland Clinic Cole Eye Institute, where the drug is compounded within the facility and it is extremely fresh, this problem may not exist.

We have gone to a pharmacy that has met all the credentials

Bilateral DME Treated With Laser and Injections

Presented by John W. Kitchens, MD

At the time of initial presentation this patient was a 65-year-old woman who had a 13-year history of type 2 diabetes. She had a history of proliferative diabetic retinopathy involving both eyes and had undergone prior pan retinal photocoagulation bilaterally, as well as cataract surgery with intraocular lens placement in both eyes.

At the time of her initial presentation, she had 20/25 vision and no macular edema in her right eye and mild diabetic macular edema with 20/30 visual acuity in her left eye. Ten months later, she developed focal diabetic macular edema in her right eye and was treated with focal laser therapy. One year after her initial presentation, the patient's center-involving diabetic macular edema worsened in her left eye and reduced her vision to 20/40 (Figure 1).

It is at this point that we began monthly aflibercept injections.

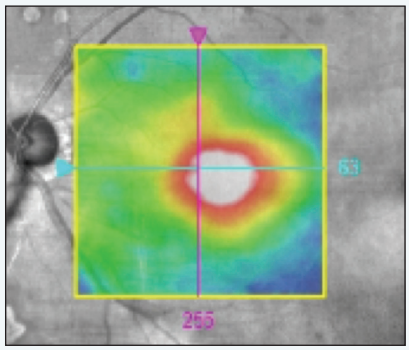

Figure 1. Worsening center-involved DME prior to initiation of anti-VEGF therapy.

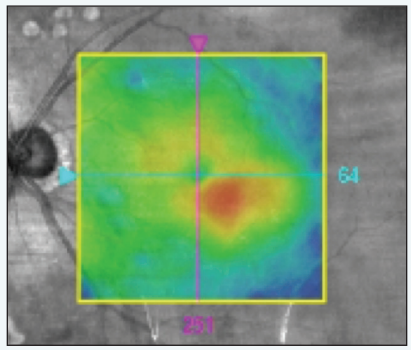

Figure 2. After monthly treatment with aflibercept. Patient was eventually extended to every 2 month dosing.

After three monthly injections, her edema improved significantly, as did her visual acuity (20/25; Figure 2). We were able to extend her injection schedule to every 2 months and maintain a dry macula.

for the new certifications. It makes us feel a little bit better. But I do wonder if the drug was stored at the right temperature and for how long? The shelf life of those drugs is not as long as a drug in a glass vial under nitrogen.

Dr. Clark: The big problem with compounding is not what has happened in the past, it is what may or may not happen in the future. If it happens to be your patient who has a bad outcome, at the end of the day it was your decision as the physician to use the drug. You are on your own. But, there are other options available. It is hypothetical, but it is also real. Fortunately, it looks like we have had a significant improvement in that industry, and that is great for when we need to use it. But I think it is the "what ifs" that are very concerning.

Dr. Kitchens: Dr. Kaiser, is the compounding issue the same for you in the large health care system where you practice?

Dr. Kaiser: We do not have the same issue with compounding at my practice. The Cleveland Clinic's pharmacy compounds or fractionates the drug. We do not use an outside compounding pharmacy. They send a syringe or two to microbiology and the entire batch is cleared before we can even use that lot number. We throw out anything that is not used at the end of the week. Thankfully, we have not had an issue with compounding. The bevacizumab used in the DRCR or even in Comparison of AMD Treatments Trials, also known as CATT, is not the bevacizumab most retina specialists can obtain. So the safety issue with bevacizumab is definitely due to fractionation because of sterility and other issues.

Dr. Clark: This affects you, Dr. Kaiser, a little differently than private practitioners because your institution shares in the liability if anything happens. As private practitioners, we have to deal some independent pharmacies, for which we have some knowledge but certainly no vested interest in the work they do. I think it is a particular challenge for private practices.

Dr. Kaiser: Sure, that is fair to say.

PROTOCOL I VERSUS PROTOCOL T

Dr. Kitchens: Dr. Kaiser, do you think we are going to see a difference between Protocol I and T in year 2?

Dr. Kaiser: The positive finding that came out of Protocol I was the dramatic reduction in the number of injections in years 2 and 3, which is great. I hope we will see a similar reduction in injections irrespective of drug in the second year of Protocol T. The bigger question is whether the delta between drugs will remain the same in the second year; my guess is yes. But I am hoping that year 2 at least shows visual stability and no drop off like we saw in AMD studies.

Dr. Kitchens: Are we more or less likely to see a difference between the drugs in the year 2 results of Protocol T?

Dr. Kaiser: I think in year 2 it is going to be consistent. I do not think it is going to be a greater difference [between aflibercept and the other drugs]. I think it is just going to be consistent, and my prediction is that the number of injections will likely be very similar.

Dr. Kitchens: Dr. Brown, what do you think we will see in year 2 of the Protocol T study?

Dr. Brown: Aflibercept did better in this trial than it is ever done. So it is possible there might be some regression to the mean where the three drugs come a little closer together. In terms of the anatomic response, which was really weak with bevacizumab in the better seeing eyes, that is the wild card. Will it continue to be stable or will you get drop off? Because you certainly know that if you do not treat diabetic patients for a while, you get worse vision. Is removing half of the edema that they had essentially enough? I do not know.

Dr. Clark: If I had to guess, I think that the aflibercept results will be fairly stable. We have seen good results historically with ranibizumab for DME, therefore I would predict stabilization or a slow and steady improvement in year 2 with ranibizumab. It may not approach the difference in the poorly seeing eyes. I think the biggest concern is what year 2 is going to look like with bevacizumab. In terms of the practice patterns, I think that is going to be the biggest question that needs to be answered. What does the bevacizumab group look like in year 2?

Dr. Kitchens: Do you think we will see the same thing with retinopathy regression?

Dr. Clark: I think anecdotally as well as in clinical trials, we have seen regression with systematic, consistent anti-VEGF therapy for DME. In many of these patients, the switch does not turn back on and the retinopathy and DME does not worsen. So I think it is very likely that we will see retinopathy regression, assuming the switch is turned off. The big difference in terms of our clinical practice and protocol patients in VIVID and VISTA[1] or RISE and RIDE[6] is that those patients were treated very aggressively for an extended period of time. It is unclear to me if they are going to be different than patients who are treated more in a clinical protocol. It is unclear if we can actually turn the switch off.

Dr. Kitchens: Dr. Brown, do you discuss with your patients early on about the number of injections required in years 2 through year 5 results? In other words, do you tell them that more injections are needed in the beginning of treatment, but that the number will likely decrease as time goes by?

Dr. Brown: Yes, I do discuss these details with my patients. It is encouraging for patients to hear that they will need fewer injections over time. I also tell them that it will partially depend on their lifestyle changes, including controlling their blood sugar. And, for blood pressure, I remind patients that they should be regularly taking their lisinopril instead of forgetting it two-thirds of the time. And lastly, diagnosing things like sleep apnea and other comorbidities that we see so often that can help the edema, with or without our expensive injections.

PCP AND SPECIALIST RELATIONSHIPS

Dr. Kitchens: Let us talk for a minute about the interaction between primary care physicians (PCPs) and specialists like ophthalmologists and retina specialists. Dr. Clark, how important is this in your practice?

Dr. Clark: It is critical on a number of levels. It is critical in terms of patient care, as it always has been. We have to be a part of a multidisciplinary team taking care of these patients. As health care reform matures, there are real tangible reasons why we need to be more engaged with our colleagues in primary care, endocrinology, and the allied health professions. We share a vested interest in communicating quality measures. In order for their practices to perform at an efficient level in terms of reimbursement, we have to communicate with them. It is a much more complex interaction now than merely just sending letters to your friends in internal medicine. It is really part of the framework of modern health care.

Dr. Kitchens: Dr. Brown, any pearls for enhancing that communication between generalist and specialist?

Dr. Brown: There was a paper out of Wills Eye Hospital that was presented at the Retina Society Meeting. It was a multivariable analysis of who really got diabetic retinopathy screening. It turns out that the letter between the PCP and the ophthalmologist was essentially the highest correlated variable on whether patients were getting an eye exam.

I think the pearl is most of these PCPs are the guys in the trenches who are seeing a bunch of patients. You need as quick of a communication as you can get without over detailing it. In other words, they really want to know: Does the patient have diabetic retinopathy? How bad is it? And do they need to do anything? They may or may not look at my optical coherence tomography (OCT), but we insert them in those with electronic

When to Switch Anti-VEGF Agents in DME

Presented by John W. Kitchens, MD

A 68-year-old woman at the time of her original presentation had a history of proliferative diabetic retinopathy involving both eyes. She had undergone previous pan retinal photocoagulation therapy in both eyes and cataract surgery with intraocular lens placement in her left eye 1 year prior to her presentation.

When she originally presented in 2012, she had center-involving diabetic macular edema in her left eye with a visual acuity of 20/80. She was started on a series of bevacizumab injections every 1 to 2 months in the left eye. Six months after presenting, she developed center-involving diabetic macular edema in her right eye and was started on injections of ranibizumab monthly in both eyes (switched from bevacizumab to ranibizumab in her left eye; Figure 1). With monthly injections, her visual acuity improved to 20/25 in her left eye. We gradually extended her treatment interval to 2 months using a treat-and-extend approach. Unfortunately, her edema recurred at this interval and her vision dropped to 20/80 in her left eye (Figure 2). We switched her therapy to aflibercept and were able to treat her every 2 months, with an improvement in her vision (20/30) and no recurrence of her edema (Figure 3).

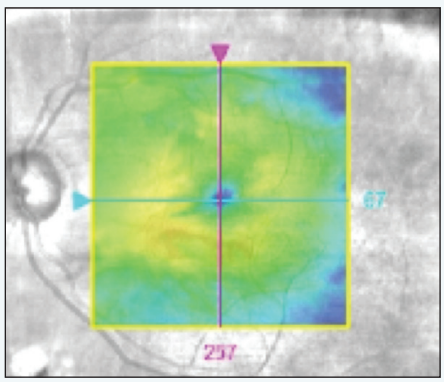

Figure 1. The patient's visual acuity improved to 20/25 in her left eye with monthly ranbizumab injections.

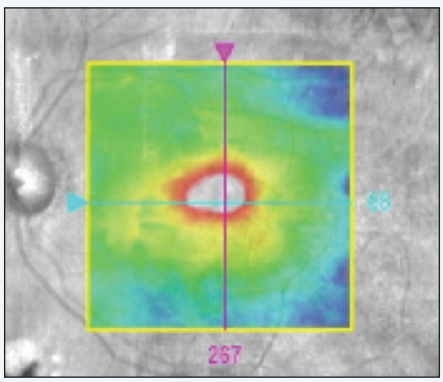

Figure 2. The patient's edema recurred and vision dropped to 20/80 in her left eye with ranibizumab dosing every 2 months.

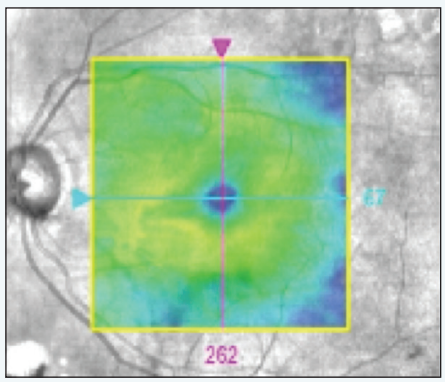

Figure 3. The patient was switched to aflibercept every 2 months. Vision improved to 20/30, with no recurrence of edema.

medical records. We send a rapid fax or a rapid email back with a HIPAA compliance. It just says that the patient was seen in our office. For example, "Ms. Jones had retinopathy, mild; plan is work on her blood pressure and cholesterol and consider sleep apnea studies with Dr. Smith; follow-up 6 months or a year." Another example is "severe diabetic retinopathy; patient counseled on need for much better blood sugar control."

We always ask about their A1C levels. We always explain to them what it means. An A1C of 5 means that 5% of your hemoglobin has sugar stuck to it and 7 means 7% percent, which sounds like only 2% but that is 40%. I always advise them that if they do not know their A1C number, to make sure they know it at the next visit. Then we talk about whether they had a better or worse number and either give them credit for hard work or tell them to work harder.

Dr. Kitchens: You mentioned that the PCP wants to know if he or she needs to do anything different. Can you influence the PCP by the things you say?

Dr. Brown: Absolutely. Most PCPs are pretty good about doing what we ask. They trust us, especially in terms of blood pressure control. With some of these patients, the blood pressure control is almost epidemic. With DME patients, it is rare that the blood pressure is normal. I tell all the patients: "If you have a leaky water hose and you turn up the water pressure, it leaks more. Diabetes makes your blood vessels leak, and hypertension makes them leak more. If you can work on that blood pressure, you can potentially get less shots in your eyes."

Dr. Kitchens: Dr. Kaiser, as noted earlier, you are in a large health care system that is very organized. How has Cleveland Clinic tried to address this tie between PCPs and ophthalmologists?

Dr. Kaiser: We have taken a proactive approach to this problem. Across the enterprise, we are connected through the EPIC electronic medical record system. Thus, interactions between the endocrinologist/PCP and ophthalmology are tracked very closely. When the patient has a PCP visit, a pop-up appears that says either, "yes, green light, they had a visit to the ophthalmologist" or "no, they did not." They can then press a button to make sure that visit is scheduled. This system has dramatically improved our ability to get patients from our own system into the ophthalmologist's office.

But I think the flip side is what Dr. Brown said. If the patient comes from outside the Cleveland Clinic Health System, sending a short note is more powerful than this big long printout from our electronic medical record that they do not want to know or read. They want one line. Patient showed up for a visit? Yes? No? Trouble? No trouble? What is their diabetic retinopathy level? Are they getting treatment? That is all they need to know. My consult letters have come down to a quick one- or two-line summary.

RETINA SOCIETY HIGHLIGHTS

Dr. Kitchens: Dr. Kaiser, here at Retina Society, what is one interesting thing you have seen with regard to diabetic retinopathy?

Dr. Kaiser: It would have to be the VIVID and VISTA data. Today, we saw that in the VISTA study the visual outcomes and the slopes of those visual outcomes of almost 40% of patients who had previous anti-VEGF therapy were the same as in the patients who were treatment naive. In other words, there were very dramatic improvements in vision and reductions in retinal thickness in patients receiving aflibercept, irrespective of whether they had previous DME treatment. This was not a switching study, but you can draw some conclusions that switching a patient from another drug to aflibercept offers a chance for an improvement in vision and further reduction in retinal thickness.

Dr. Kitchens: And that was a washout of 3 months?

Dr. Kaiser: Yes, 3-month washout before the study.

Dr. Kitchens: Dr. Clark, same question to you.

Dr. Clark: The big issue here is that we are increasing our body of evidence with VISTA 3-year data. There is an increasing body of evidence that if we are aggressive with the treatment of DME early in the course of the disease that the improvements we get are sustainable over a long period of time. And that is critical to the management of patients in clinical practice. We are seeing that what we are doing on the front end has a real lasting effect.

Dr. Kitchens: And Dr. Brown, something interesting you have seen here?

Dr. Brown: I think David Boyer's presentation about patients who initially do not respond anatomically but who often with time come around with better visual acuity and better anatomy. We used to do two or three shots, and if the patient did not respond, we moved onto to something else in our armamentarium. It looks like we need to have a little more persistence. It took them years to get DME, and it may take a while to get rid of it and/or to improve it.

Dr. Kitchens: And was that a VIVID and VISTA study?

Dr. Brown: It was. It was an analysis of a VIVID and VISTA with aflibercept[1] looking at the small percentage of patients who do show much improvement on OCT. In other words, they still have a lot of edema after three to five injections, but over the course of the year, the average patient in that group continued to improve visual acuity. One case improved an impressive 15 letters over 3 years.

Dr. Kitchens: Even in the monthly (2q4) arm?

Dr. Brown: Actually, this was a combined group just to get more numbers. He even had some 2q8 (2 mg every 8 weeks) patients who did come around even after a year or so. That is a patient that many of us would have switched to steroids at that point. A lot of us would pull the trigger on a steroid after 5 months and no changes on the OCT. The VISTA and VIVID data show that patients might come around without that added potential risk of cataract and glaucoma.[1]

CONCLUSION

Dr. Kitchens: To close this discussion, I would like each of you to provide one pearl for retina specialists managing diabetic patients. What should they be thinking about? What should they do?

Dr. Clark: I think the key is early aggressive therapy, particularly in the first 6 months of therapy. The goal is to get the retina as dry as possible. I think you need to be very cognizant of finding the best agent for your patient as rapidly as possible and getting the retina dried out as much as possible. We know from multiple clinical trials that the longer you wait to treat these patients, the less improvement you are going to see. So treat early, treat often.

Dr. Brown: Similar to Dr. Clark, I think it is important to look at the risk-benefit ratio in everything. Your chance of causing harm to a patient with an injection literally comes down to the rate of infection, which is somewhere between 1:3000 and 1:5000. Your chance of helping a patient with a DME with an injection is well north of 90%. When in doubt, inject. Inject early and inject often.

Dr. Kaiser: I agree. One of the papers at the Retina Society Meeting talked about real-world treatment rates versus clinical study treatment rates. Real-world treatment rates in the United States are higher than in Europe and other countries, where it is remarkably low. To acheive the visual acuity gains seen in Protocol T, RISE and RIDE, or VIVID and VISTA, you have to treat a lot, especially in that first year. In the second and third years, it is a lot less, but I think most people are undertreating. If there is one take-home message, it is to understand that undertreatment means leaving vision on the table and that is not what anyone wants.

1. Boyer D, Brown D, Kaiser P. One hundred forty-eight week results and outcomes in patients from the VISTA and VIVID clinical studies. Presented at: Retina Society; Oct. 7-11, 2015; Paris, France.
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APPLYING RESEARCH TO PRACTICE FOR PATIENTS WITH DIABETES

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1. **In the VIVID and VISTA 3-year data presented at Retina Society 2015, the visual acuity gains and retinopathy regression in the 2q8 arm _____?**
   a. Decreased
   b. Increased
   c. Were maintained

2. **According to Dr. Brown, the key take-home from VIVID and VISTA 3-year data is:**
   a. Prior focal laser aided in reduction of edema
   b. Aflibercept proved more effective than ranibizumab and bevacizumab
   c. Ranibizumab proved more effective than aflibercept and bevacizumab
   d. Providers should not wait to start anti-VEGF therapy

3. **DRCR.net Protocol T is considered a landmark study in eye for what reason?**
   a. It compared anti-VEGF therapy to steroids
   b. It is the first study to compare head-to-head the three anti-agents most commonly used to treat diabetic retinopathy and diabetic macular edema
   c. It compared steroids to focal laser treatment
   d. It compared steroids, anti-VEGF agents, and focal laser treatment

4. **DRCR.net Protocol T showed:**
   a. Aflibercept with statistically significant visual acuity gains versus ranibizumab and bevacizumab
   b. Bevacizumab with statistically significant visual acuity gains versus aflibercept and ranibizumab
   c. Ranibizumab with statistically significant visual acuity gains versus aflibercept and bevacizumab
   d. All three anti-VEGF agents were essentially equal

5. **A letter between the ophthalmologist and _____ has been shown as the highest correlated variable toward ensuring the patient gets properly screened for diabetic retinopathy.**
   a. Endocrinologist
   b. Diabetes educator
   c. Primary care physician
   d. Cardiologist