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CME ACTIVITY

DRCR.net Protocol Review

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable meeting held in December 2015.

TARGET AUDIENCE

This certified CME activity is for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES

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

- Discuss the ocular and systemic effects of anti-VEGF therapies in patients with diabetes and how to educate patients on appropriate expectations
- Assess clinical studies involving new approaches to treat DME and proliferative diabetic retinopathy
- Use expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules
- Evaluate treatment options and develop a treatment regimen that can reduce patient burden and practice capacity

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DRCR.net Protocol Review

A roundtable discussion focusing on various protocols and how they affect patient and practice management.

As a result of newer treatment options for diabetic macular edema (DME) and diabetic retinopathy (DR), the Diabetic Retinopathy Clinical Research Network (DRCR.net) has undertaken numerous research studies to further define the best treatment options for a variety of patient profiles. (The 2015 American Society of Retina Specialists Preferences and Trends survey indicated most retina specialists overwhelmingly [about 60%] would treat a young patient with both anti-VEGF and laser.[1])

Retina Today convened a panel of leading experts to discuss the ramifications of these studies, what their protocols involve, and what clinicians should consider the most important take-home messages for the various protocols. The objective is to review all the new data and put it in the context of a practical framework for how we approach patients with DR and DME, given all the advances that we have seen in the past couple of years.

—Andrew A. Moshfeghi, MD, MBA

Andrew A. Moshfeghi, MD, MBA: In the past 10 years or so, we have had anti-VEGF agents replacing focal and grid laser for the management of DME. We have always had corticosteroids available to us, but only recently were these available on label.

In the Early Treatment of Diabetic Retinopathy Study (ETDRS),[2] only 3% of enrolled subjects gained 3 lines of vision. About a quarter were able to stall continued vision loss compared to only 12% in the control group. But this was not enough for us to tell our patients that focal grid laser was going to improve vision.

Charles C. Wykoff, MD, PhD: We need to remember that the patient population studied in ETDRS was unique to the patients enrolled in the phase 3 trials that have led to the FDA approval of ranibizumab and aflibercept. In the ETDRS, 85% of the eyes were 20/40 or better and 63% were 20/25 or better at baseline.[2] In the FDA registration trials for ranibizumab and aflibercept all eyes were 20/40 or worse.[3,4]

R.V. Paul Chan, MD: I agree. We do evaluate patients differently today. In the 1980s, we did not have optical coherence tomography (OCT) available for routine clinical practice. Today, OCT drives so much of our treatment decisions.

Dr. Moshfeghi: Today, we are using clinically significant macular edema. This is similar to saying center-involved macular edema, or nearly center-involved macular edema. But we tell our patients that focal grid treatment slowed vision loss. That was really the mainstay of therapy until the early 2000s, when we started using a little bit of off-label triamcinolone, as well as perioperative triamcinolone. Then obviously, we used the anti-VEGF agents that became available in an off-label fashion in 2005. But between 2006 and 2010, how did people manage DME?

Jorge A. Fortun, MD: Before Protocol B,[5] you did not really have any good data to support the use of traditional steroids. It was anecdotal papers. For the most part, people were just using focal laser based on EDTRS.

Dante Pieramici, MD: We were using a lot of off-label bevacizumab, but we were using it with laser in a combination approach.

Geeta A. Lalwani, MD: We were all relying on anecdotal evidence.

Dr. Wykoff: It was the Wild West. There was a lot going on without much solid evidence. Intravitreal steroids were being used, and we learned about their potential effects on intraocular pressure. The whole concept of intravitreal injections was still fresh.

Dr. Fortun: I think the paradigm is interesting. We are very comfortable injecting age-related macular degeneration (AMD) patients monthly. We felt like we were treating DME patients more often—every 3 months or 4 months—that we were doing intravitreal treatment too aggressively.

Dr. Moshfeghi: When I have used bevacizumab and ranibizumab to treat wet AMD (wAMD), I felt they were similar. But when I use them for DME, I do not think bevacizumab is as good as ranibizumab.

Dr. Pieramici: It seemed like we obtained a more consistent response with ranibizumab. When the writing committee for the DRCR.net Protocol T convened we went around the table and asked people what they thought the results were going to be. People felt that ranibizumab and aflibercept were probably similar in efficacy, and bevacizumab was less effective. These conclusions were based in large part on the anatomic response. Protocol T demonstrated that the anatomic response of bevacizumab was inferior to the other agents.[6,7]

Dr. Wykoff: There is no trial that shows that bevacizumab is a better drying agent than either of the other two drugs. It is always the reverse. Before the DME trials, CATT showed clearly that bevacizumab was not as effective a drying agent.[8]

Dr. Fortun: As Dr. Wykoff pointed out, when you consider a disease process where the level of VEGF is exponentially higher, as in retinal vein occlusion or DME, we appreciate a difference in the efficacy of the various agents.

Dr. Pieramici: We found this to be especially true when we compared monthly to prn or treat-and-extend.

Dr. Wykoff: When we started using bevacizumab, many physicians were dosing at 6-week intervals. But it is now obvious the drug clears much more quickly than that in most patients.

We used to think bevacizumab might last longer in the eye because it is a larger molecule than ranibizumab, but intraocular half-life data as well as clinical efficacy endpoints have indicated that is not true. In fact, bevacizumab appears to be a worse retinal drying agent and also has a shorter duration of clinical efficacy than ranibizumab.[7-9]

"When I have used bevacizumab and ranibizumab to treat wet AMD (wAMD), I felt they were similar. But when I use them for DME, I do not think bevacizumab is as good as ranibizumab."

—Dr. Moshfeghi

Dr. Lalwani: DME is often a bilateral disease. We have all seen individual cases where one eye is injected with bevacizumab and the other eye with ranibizumab. Sometimes the difference in response is quite striking, in my opinion.

PRAGMATIC TREATMENT PARADIGMS

Dr. Moshfeghi: We are all familiar with the seminal and pivotal studies on ranibizumab.[10-12] But we also need to remember these studies are not designed in the same way that National Institutes of Health-sponsored studies are designed. For most companies, those pivotal studies are undertaken to get a drug approved, which means frequent dosing right up until the primary endpoint visit (often 24 months) and with change in visual acuity being the key variable. So we have come to expect a rapid improvement in visual acuity as early as 1 week that steadily improves. And as long as patients are dosed regularly they continue to have a steady improvement. Comparatively, the sham group did not have eligibility for laser, and had much poorer visual acuity outcomes.

In RISE and RIDE, at month 24 the ranibizumab group had a 2-line benefit compared to the sham group—11.7 letters of visual acuity gain in the 0.3-mg group compared with a 2.5 letter gain in the sham group.[11] We also know after month 24, the crossover group received treatment and there was a clear benefit to crossing over, but the crossover group never achieved the same visual gains as the original treated arms did.[13] We can see similar outcomes with RISE and RIDE on OCT.[11,13] The sham arm had some drying, but did not dry out as much as the active treatment arms did. But when they crossed over, they were able to achieve some anatomic benefit.

Dr. Fortun: I do not know that you can fully extrapolate some of the key points across disease states. In DME studies, the

control arm does not necessarily lose vision, but in AMD studies, they do. Unlike AMD, where we really want to get patient's retina fluid-free, we can probably tolerate some degree of fluid in diabetics without a direct consequence to vision.

Dr. Chan: These studies using anti-VEGF therapy for DME have good results. But we have to keep in mind that these results are within the context of a study. Patients are coming back every month, and this may be difficult in real-world practice. The diabetic patients in my practice may find it extremely difficult to be compliant with monthly visits.

Dr. Pieramici: Let us not forget the sickest of the sick—those on dialysis or with active proliferative disease—are typically not eligible for these kinds of studies. They are the ones who disappear for 6 months and return with significantly worse disease.

Dr. Wykoff: The issue of the use of "last observation carried forward" is a really interesting point in the analysis of data from RISE and RIDE.[3] If you look at the third year OCT data from the RISE and RIDE trials, when the control arm switched from sham injections to ranibizumab injections, it appears as though the control arm does not dry out as much as the ranibizumab arm.[14] But since more than 40 patients dropped out in the first 2 years in the sham arm, those patients' last recorded data points are carried forward with "last observation carried forward" and inappropriately limit mean anatomic improvements. When only the sham patients who received at least one ranibizumab are included, their mean final retinal thickness is actually slightly thinner than the ranibizumab arms by about 10 µm to 20 µm. This indicates that chronic fluid may cause damage and loss of retinal tissue in some patients, ultimately limiting maximal visual recovery. These patients never reach the same level of visual benefit that they would have if they had been treated earlier.

Dr. Fortun: This also indicates a disease-modifying ability of these drugs, and we should ask what is it doing to profusion status? How does it affect visual acuity in the macula?

Dr. Moshfeghi: That is a clinical trial. Putting these data into perspective, in clinical practice, what is your typical sort of baseline? How do you work that newly referred patient up in your clinic?

Dr. Chan: I always do a full examination at baseline, which includes an OCT and photograph. Also, I will perform fluorescein angiography (FA) on certain cases. The FA is useful for identifying ischemia and leakage, and I will order the FA if I think it is going to change my management.

> "The DRCR.net protocols give some insight regarding the timing of when to treat and not treat. "
>
> *—Dr. Chan*

Dr. Moshfeghi: Most of us are still ordering baseline FAs for wAMD, and not doing regular FA to monitor these patients. But how frequently are we integrating FA in patients who actually have DME or significant nonproliferative DR?

Dr. Fortun: At baseline, I check the macro ischemia and the overall status of global perfusion. I follow those patients with OCT and repeat angiography if my course of treatment is not going the way I want it to go, and I want to change treatment. I exclusively manage some patients with an anti-VEGF monotherapy for their non–high-risk proliferative disease, and then use frequent angiography because it is a good way of following proliferative disease.

Dr. Wykoff: I get a baseline FA in any diabetic who I am going to treat. I like to know the extent of capillary damage and, in particular, how much retinal nonperfusion is present. I prefer to have wide-field imaging, and recent data suggests that peripheral examination and imaging findings are valuable for prognostication. For example, the presence of predominately peripheral lesions in eyes with nonproliferative DR confers a 4.7-fold greater risk of progression to proliferative DR over 4 years.[15] We need more data to further determine how wide-field imaging can inform clinical management and prospective analyses are ongoing.[16]

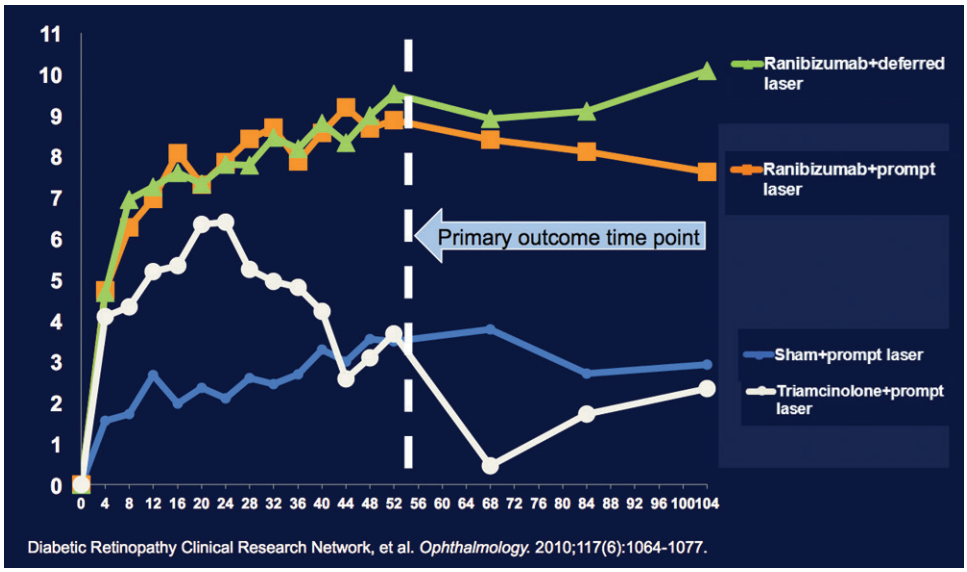
Dr. Pieramici: In patients with moderate to severe nonproliferative DR or greater, I prefer serial angiograms every year. Clinical examinations are just not good enough, particularly in patients with cataracts or poor cooperation. Wide-angle angiograms allow us to better assess the peripheral nonperfusion and notice subtle cases of neovascularization.

Dr. Moshfeghi: I get FAs at baseline. I think we need those. I am starting to get them more regularly on patients whose fellow eye is undergoing anti-VEGF treatment for DME. If the second eye does not have any center-involved DME, the peripheral retinopathy may be dramatically different in that fellow eye.

Dr. Wykoff: I also use angiograms to monitor the fellow eye. At this point, OCT angiography (OCT-A) can show me macular perfusion status but current modalities do not allow peripheral imaging and do not show leakage, both of which are readily available with the use of fluorescein.

Dr. Chan: OCT-A is promising for looking at macular disease, but we should keep in mind that it does not show leakage as a FA would.

Dr. Moshfeghi: I think 2016 is going to be the year of everybody talking about how they are using OCT-A in the various diseases.



Courtesy of Andrew A. Moshfeghi, MD, MBA

Figure 1. Data from Protocol I showing change in visual acuity.[17]

Dr. Wykoff: Noninvasive testing is certainly appealing and as hardware and software improve, hopefully many of the current limitations can be resolved. OCT-A is not easy to use. It can be challenging to get reliable, reproducible, high-quality images.

Dr. Pieramici: That will get better with time, but still, I think that FA is an excellent test for DR. There are downsides, but patients seem to tolerate it quite well, and it has decades of documented experience.

Dr. Moshfeghi: Do you think OCT-A will help in the management of diabetic eye disease?

Dr. Chan: I do think that OCT-A will help guide our management. And at the end of the day, it comes down to the question of how we use these imaging techniques to best care for our patients.

EVIDENCE-BASED MEDICINE: PRACTICAL APPLICATIONS FROM CLINICAL STUDY RESULTS

Dr. Moshfeghi: Both RIDE and RISE and VIVID and VISTA had very similar results in terms of rapid, sustained improvement over time with different dosing regimens.[3,4]

Dr. Pieramici: Some patients need more frequent treatment.

Dr. Moshfeghi: Does anyone have a fixed regimen for aflibercept that is different from bevacizumab or ranibizumab?

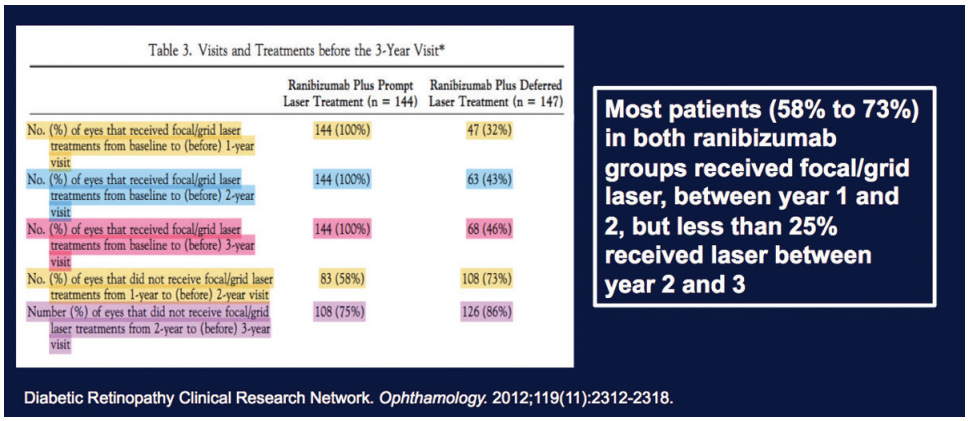
Dr. Lalwani: I most often use aflibercept almost monthly, maybe slightly more than monthly, but it is very consistent. But I rarely extend, because I do not get the results I want if I extend.

Dr. Fortun: DME treatment is usually a gradual improvement. I explain it to patients that blood vessels in their retina have stopped working, and we need to eliminate the fluid like we would with kidney dialysis. Our monthly injections are like retinal dialysis, but they do not have to come in 3 days a week. Protocol I gave us some good evidence that aggressive monthly treatment is often best in the long run.[17] But what are other treatment paradigms for DME? We cannot really fully extrapolate our treatment paradigms that we use for AMD.

Dr. Chan: The DRCR.net protocols[18] give some insight regarding the timing of when to treat and not treat. If the OCT continues to show improvement after injection, then we should consider treating. If there is stability on the OCT, then we may want to observe. Regardless, I think many of us are now encouraging these patients to come in monthly for an examination or treatment.

Dr. Fortun: We are dealing with a younger patient population that has other systemic comorbidities that require other health care visits. Some are still working. Even though monthly follow-up and treatment is a better treatment paradigm, it is very difficult to implement in the real world.

Dr. Wykoff: Fluid in DME may be different than in AMD. In AMD, I go after fluid relentlessly, using monthly treatments as long as intraretinal or subretinal fluid or hemorrhage persists. We do not have the answer yet for DME. The phase 3 trials for ranibizumab and aflibercept used intensive treatment that was given regardless of anatomic and OCT findings.[3,4] The DRCR.net Protocols I and T suggest that visual benefit can be achieved with significantly fewer injections, especially after the first year of treatment (Figure 1).[7,19] To achieve this, Protocol T employed futility criteria in which an eye stopped receiving injections after 6 months when visual acuity and OCT changes stabilized, even if the macula still had DME.[7] For example, an eye with 600 microns of DME that was unresponsive to bevacizumab would have stopped receiving injections if after a prespecified number of injections the amount of fluid did not change. The clinical applicability of this to the real world is limited as very few retina specialists would simply stop injecting this eye—most would either switch anti-VEGF agents or employ a steroid treatment.



Courtesy of Andrew A. Moshfeghi, MD, MBA

Figure 2. Three-year data from Protocol I.[17]

Dr. Fortun: The beauty of the DRCR.net trials is that even if we cannot fully translate the protocols, there are futility measures. We can tolerate a little bit of fluid in our diabetic patients.

Dr. Wykoff: But if you got rid of that fluid, would you get an extra line of vision? We do not know. We really need this data. I am hesitant to assume that persistent fluid is okay even with ongoing treatment without more and longer-term data.

Dr. Pieramici: But I think what the DRCR.net Protocol I has shown us is that you will still get very similar results doing less treatment than the FDA trials.[19] However, even in the VISTA and VIVID and the RISE and RIDE, there were still patients that had edema at the end of the trials.[3,4] One important question is, when do you switch to something else? Is there a group of patients that after three or six injections and less than 10% OCT change, or less than 5-letter improvement, can be considered as failing treatment? We know if we keep injecting for another year or 2, we can get some significant response in vision in many patients. With DME, there is a disconnect between retinal edema and visual acuity response, different from what we experience in the treatment of neovascular AMD.

Dr. Wykoff: That is important. What you are implying is very different than the DRCR.net approach. You are saying if we keep injecting these patients, some will get significantly better.

Dr. Pieramici: The anatomy may still be less than perfect. The anti-VEGFs are first-line treatment. I would probably start with aflibercept.

Dr. Fortun: In VISTA, well over 50% of patients can be considered "not ideal" responders after the first four injections.[4] That is something we can translate to clinical practice. If they do not respond after four injections with your first agent, then either the patient is going to be a late responder, or they may just be suboptimal responders where you need to use something else.

Dr. Lalwani: DME differs quite a bit from wAMD because you do not get the "wow" effect. I counsel patients that they need to expect to see me monthly for the next 3 to 6 months, where we are going to inject almost every month during that time. I counsel patients that the visual improvement will be somewhat lighter.

Dr. Fortun: Protocol I showed us that if we are aggressive with treatment early on, we can drop the number of injections precipitously, even after year 1 and certainly in year 2.[19,20] More than 50% of patients did not need any injections.

Dr. Moshfeghi: For the prompt and deferred laser group in years 1 and 2, it was only eight injections per year. But then, by year 2, they are only getting two or three injections. By year 3, one or two. By year 4 and 5, it is even lower: zero or one injection (Figure 2).[19,20]

Dr. Wykoff: A subtle point with Protocol I that I find fascinating and encouraging for ongoing trials is that median numbers of injections through 5 years was 13 versus 17 in the prompt versus deferred laser groups.[19] Approximately one-third fewer injections were needed in the arm that received prompt macular laser, suggesting that macular laser may be able to be used to reduce treatment burden in some eyes.

Dr. Moshfeghi: I think more of us are doing mandated injections for several more months with DME than we do for wAMD, especially now that we have the benefit of the 5-year results. I do not use focal laser in general for diffuse DME unless I see a patch of leaking microaneurysms. We do for focal but not as much as I should. I am kind of biased towards anti-VEGF monotherapy, because it works well in most patients. I do not like to use a lot of steroids.

Dr. Wykoff: We think of the DRCR.net Protocol T as an anti-VEGF comparison trial, which it was, but it was also a combination therapy trial. Over 2 years, a majority of patients received macular laser, ranging from 41% to 64% of each arm.[7,21]

Dr. Pieramici: If you look at many of the anti-VEGF studies for DME, you find that a significant number of the patients randomized had prior focal laser; this is true of the DRCR studies as well.

Dr. Moshfeghi: I have found that triamcinolone is impressive in the first couple of months, but patients develop cataracts and the vision gains decrease. We know early, frequent treatment can result in long-term visual acuity improvements. If you do eight or nine injections in year 1, you might do zero or one injection in years 4 and 5. I always thought it would be the opposite, that because DME was a systemic disease, we were going to have to keep treating these patients much more frequently than the wAMD patients. This is the most surprising.

Dr. Pieramici: It also gives us some direction. The chronic treatment or extended delivery may not be as necessary as I would have thought initially.

Dr. Wykoff: We need more data. We can look at RISE and RIDE,[3] and we are getting more and more data from VISTA and VIVID,[4] but that trial program started later. We learned a lot from the open-label extension following the completion of RISE and RIDE. After finishing 3 years of monthly anti-VEGF injections, patients went to a prn strategy. Almost 25% did not need a single injection in the following year, but that also means 75% continued to need treatment, with a mean of 3.8 annualized injections per year.[22] While the DR severity score (DRSS) improvements achieved during the core RISE and RIDE trials appeared to be maintained in many patients, some patients did experience worsening of their DRSS when the injection frequency decreased.[3] While the treatment burden is not going to be monthly forever, it may be substantial for a proportion of patients. DRSS itself is becoming a treatment endpoint beyond just DME and this is being considered in multiple ongoing trials, including the DRCR.net's Protocol W, and the PANORAMA study.[23,24]

> "We must remember that clinical trials provide guidelines for treatment and not patient-specific recommendations."
> —*Dr. Pieramici*

Dr. Moshfeghi: One of the major findings of Protocol T is this dichotomous baseline visual acuity grouping, 20/50 or worse, 20/40 or better.[7] Here is a study where we simplify it by saying it is bevacizumab versus ranibizumab versus aflibercept, but it is not. It is bevacizumab versus ranibizumab versus aflibercept patients who may have had bevacizumab, ranibizumab, or aflibercept with a washout for a year. They may have had previous laser and they are eligible to receive laser.

When we look at the overall cohort, there was a statistically significant visual acuity difference between aflibercept versus ranibizumab and aflibercept versus bevacizumab. But it was a small difference, and so was felt to be not clinically meaningful.[7]

Dr. Wykoff: I think that is fascinating. In the second sentence of results in *The New England Journal of Medicine* abstract, the primary endpoint results state that "it was not clinically meaningful.[25]"

Dr. Pieramici: The differences were statistically significant suggesting that a real difference exists between the groups on average.

Dr. Moshfeghi: The problem is, they did not provide an operational definition of "clinically meaningful" a priori. Now if they had said if it was 5 letters or less, or something like that, then we would call it clinically meaningful. But they did not.

Dr. Pieramici: In our daily practice, we consider an individual

patient. Based on the trial, we are now armed with the information that a difference in efficacy between the drugs exists, at least between groups of patients. How the individual patient will respond is variable. We must remember that clinical trials provide guidelines for treatment and not patient-specific recommendations.

Dr. Moshfeghi: The Protocol T investigators did look at a predetermined endpoint, which was looking at visual acuity change on the basis of presenting visual acuity at baseline. The patients with 20/32 or 20/40 at baseline had basically no observable difference in change in visual acuity over time.[7] So what drove the visual acuity? And the 20/50 demarcation is where we started seeing the bigger separation. The editorial did not just throw out the primary outcome, it really did provide a direction on how we should manage patients.

Dr. Fortun: It was a predetermined analysis to look at patients with worse vision. It was showing us what we were already seeing with some of the retinal vein occlusion data, and some of the AMD. Because patients with much higher VEGF or worse disease are probably going to do better anatomically and, consequently, visually from having aflibercept not work.

Dr. Chan: Patients who received aflibercept appeared to require less laser and less retreatment.[7]

Dr. Fortun: The big losers in this are some of our patients that cannot get the drug. Because what it clearly showed is, yes, aflibercept was clearly better than bevacizumab.[7]

Dr. Pieramici: Most importantly, this study demonstrated that all agents were effective at improving vision and improving edema in patients with center-involved DME. [7]

Dr. Chan: That is an interesting point when you are looking at access to care since bevacizumab may be the only option for some patients, especially when you consider practices outside of the United States in developing countries. Also, we again need to keep in mind that Protocol T did not exclude macular laser.[7] This is an important consideration in areas where patients may not be able to easily travel for monthly visits, or there is a lack of access to medications. Macular laser is still a viable option and may ease the burden of requiring frequent follow-up visits and injections. So although the results of these studies are promising, we need to ask ourselves, how all of this is relevant to what happens in our daily practices with patients with DME?

Dr. Wykoff: We need to clearly separate the issues. There is science, and then there is real-world applicability. As retina specialists, I think it is important to consider the details of both. The science may lead us to one conclusion. But once societal and economic issues are considered, a different clinical choice may be made because of these very real issues.

Dr. Fortun: Protocol T may have us saying aflibercept is so much better than bevacizumab. The truth is that bevacizumab is still so much better than nothing. As access to care becomes an issue, we are lucky to have very good agents to treat this disease.

PROTOCOL S AND PROLIFERATIVE DISEASE

Dr. Moshfeghi: In terms of DR severity, we are going to talk a little bit about Protocol S. Basically, Protocol S is looking at laser versus ranibizumab for PDR.[26]

We had seen in RISE and RIDE,[3] and then the VISTA studies,[4] that patients who were getting treated for DME had significant improvements in their DRSS. We all saw this clinically in our patients, where it almost looks like a lot of these patients do not even have DR anymore, because they have been treated so frequently with the anti-VEGFs. That is what got those medications their secondary indication for management of DR—not really independent of DME, but in patients who had DME.

This is PDR. We have all been taught that the mainstay of treatment here is panretinal photocoagulation (PRP). Visual acuity was the main outcome. We knew that some of these patients were going to have some DME and that there would be some improvement attributable to that. There is about a 3-letter gain favoring ranibizumab versus the group that got predominately PRP.[26]

The change in visual acuity in the overall cohort looks more impressive than the 2.3 letters, because you do see early, sustained separation between the two arms.[26] In patients who had baseline DME, that separation is even more impressive. It is interesting that the patients with no DME actually lost a little bit of vision; they might have developed DME. But PRP can constrict the peripheral visual field.

Dr. Wykoff: People are accustomed to thinking about trials as very regimented, like Protocol T,[7] VISTA and VIVID[4] and RISE and RIDE.[3] Protocol S[26] was different. While the trial was large and statistically sound, it involved many factors that were at the discretion of the investigators and therefore potentially subjective. For example, the key inclusion criteria of proliferative DR was defined as, "presence of proliferative DR, which the investigator intends to manage with PRP alone but for which PRP can be deferred for at least 4 weeks in the setting of intravitreal ranibizumab, in the investigator's judgment.[26]" We should be careful

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>
> —*Dr. Wykoff*

in our interpretation of the results, because this trial may not be directly applicable to all proliferative DR patients. Another issue is burden of care. Patients randomized to ranibizumab received greater than a third more clinical visits. We have a disease that we know is potentially blinding in a majority of untreated eyes. It is potentially risky to inject medications and just hope these patients come back indefinitely.[26]

Dr. Fortun: Implementing Protocol S illustrates how, as much as we try to institute evidence-based medicine, we cannot always apply clinical trial results directly to practice. PRP is a more definitive "set it and forget it" treatment. Anti-VEGF for proliferative DR will require frequent and careful follow-up, and failure to follow-up may result in disastrous progression to neovascular glaucoma. There is probably a role of using these treatments in conjunction with laser, to try to minimize the side effects of PRP while providing more lasting effects of PRP.[26]

Dr. Chan: We know that patients who have PRP can develop macular edema and constriction of the visual field. So if there is an alternative to PRP in a compliant patient, in someone who is going to reliably come back for intravitreal injections, you may want to consider that.

Dr. Wykoff: The economics and cost-effectiveness, no matter which anti-VEGF drug you use, are staggeringly in favor of PRP treatment over the long term. There may be medico-legal issues of seeing a patient with proliferative DR and not offering PRP nowadays. Those patients may not come back. It is impossible to predict compliance all of the time.

Dr. Moshfeghi: This validates how we manage some of our proliferative DR patients. If there is no laser available, the anti-VEGFs can buy some time before the patient needs laser.

Dr. Chan: We find similar situations where anti-VEGF monotherapy for retinopathy of prematurity (ROP) may be the treatment of choice, especially if laser is not available.[27] ROP is VEGF-driven. But it is different than DR in that ROP is a developmental condition that occurs in neonates, and active disease generally occurs within a finite period of time. In most patients who we laser for treatment-requiring ROP, laser is very definitive and stops progression of disease. For children who we inject with anti-VEGF agents, recurrence is a real concern, and we still have a lot to learn about the long-term outcomes and potential adverse events for the use of anti-VEGF therapy for ROP.

Dr. Moshfeghi: It is sort of an interesting parallel, because here we are talking about how we are not really going to do anti-VEGF monotherapy for proliferative DR. We are going to still do PRP, maybe integrating anti-VEGF therapy a little bit. But in ROP, do you have certain patients where you just do not do laser?

Dr. Chan: I have a number of patients who I injected with anti-VEGF and never had to do laser. I need to examine these children frequently in the office, and now I will also routinely get a FA to assess their vascular development.

Dr. Moshfeghi: It is interesting to me that that is acceptable, but here in this other disease where we say to ourselves, it is really not acceptable. We should trust the anti-VEGF.

Dr. Chan: I think ultimately anti-VEGF therapy will be acceptable for the treatment of PDR, maybe as monotherapy or in combination with laser. And an important question to answer is which patients are the right candidates for treatment with anti-VEGF agents. Patient selection is incredibly important, and if we can improve drug delivery (eg, sustained release), we may be better equipped to deal with patient compliant issues.

Dr. Lalwani: ROP is a window of disease. If you go through that window, you do vascularization and the disease process is over. Diabetes is different because it is ongoing for life; if anything, the systemic disease continues to get worse. It is very hard to justify this clinically, as Dr. Wykoff spoke to earlier. You have clinical science and you have real-world patients. This is where real world really weighs in heavily, in terms of your patient and monitoring.

Dr. Pieramici: In light of Protocol S,[26] what gives me pause are the visual field results. We used to expect loss of night vision but thought that maybe some of that is just from the non-perfusion, the disease itself. Protocol S, however, confirmed a very significant loss of visual field associated with laser, more than

could be explained by the disease itself. If I am a young person and I have early proliferative disease, do I really want to lose my night vision and side vision?

Dr. Lalwani: This is your young person who has a little bit of proliferative disease, who has really checked in, who is really well-controlled and you are aiming to do a little bit of anti-VEGF. Then they are hoping that they get the disease process together, and it does not recur. But that is a small part of my diabetic population.

Dr. Wykoff: I would make the point that anteriorly applied PRP presumably is going to have a minimal effect on visual field. The one image of PRP shown at the live presentation of the Protocol S data at Retina Subspecialty Day of American Academy of Ophthalmology 2015 documented PRP laser spots placed just outside of the macula, adjacent to the vascular arcades.[28] In many patients, such tight, dense, posterior PRP is unnecessary.

Dr. Pieramici: I believe more PRP will be done, but it will be targeted to areas of nonperfusion. I think we will start seeing the use of these two in combination in an attempt to get the best of both worlds.

Dr. Wykoff: I agree. Like Protocol T, Protocol S is really a combination therapy trial.[26] This was not just PRP versus anti-VEGF. This was in many ways anti-VEGF versus PRP plus anti-VEGF. Also, 45% of the laser arm got additional laser. While we think of laser as permanent, and it is, it may not be sufficient to have just one treatment long term.

Dr. Pieramici: The visual field results really showed me that we are doing a lot more damage in the periphery with the PRP. Maybe we should be thinking a little bit more about where we are putting the laser. A targeted approach guided by wide-field angiography may be a more rational approach.

Dr. Wykoff: The visual field is, in some ways, a safety outcome measure. It is not an efficacy endpoint. We also need to consider other safety measures. PRP has no risk of endophthalmitis or systemic anti-VEGF exposure. Six out of 22 systemic organ systems considered showed statistically significantly more events among the ranibizumab arm compared to the PRP arm.[26] Maybe that can be attributable to ascertainment bias or some other issue, but it needs more study.

Dr. Moshfeghi: Aiello's group published results in 2015 evaluating multiple patients and comparing seven ETDRS photography fields compared to ultra wide-field imaging.[15,29] Those who had predominantly peripheral retinopathy were more likely to have progression to PDR. If they had PRP, the laser was going to make the proliferative DR worse.

> "When the anti-VEGFs are working, I would be hard pressed to change them unless the patient is really complaining."
> — *Dr. Lalwani*

With that in mind, and with everything we said about visual field, and dense versus less dense PRP or incomplete PRP, how do you approach PRP for your new proliferative DR patients in the absence of traction retinal detachments?

Dr. Wykoff: I start anteriorly. I use wide-field guided imaging, whenever possible. I target the ischemic areas, and I start as far anteriorly as possible. I always tell patients up front that we can repeat the laser to get more coverage, but we cannot undo the laser. So I tell them we are going to start anteriorly and if the proliferative DR progresses, we will put in more laser. Unfortunately, there are patients who are going to be noncompliant. It is a frustrating thing to recognize, but it is true, at least in my practice.

Dr. Pieramici: Patients with significant DR likely are, or at least used to be, non-compliant to medical care. I find that this is especially true of patients with diabetic eye disease significant enough to require vitrectomy surgery.

Dr. Fortun: I think it is good to start with peripheral laser, because you are helping the patient with a visual field. If you ever get to do more PRP, it is that peripheral stuff that is going to be hard to do with hemorrhage.

Dr. Chan: I have some patients who are deeply terrified of having laser and, for whatever reason, they are more amenable to injections. They believe laser is a more permanent and destructive procedure, which it is, and they would prefer to avoid this type of treatment. But they are willing to come back monthly for an examination and possible injection.

SUBOPTIMAL RESPONDERS AND WHAT TO DO NEXT

Dr. Moshfeghi: Now we have a few different steroids to choose from for patients who are the suboptimal responders to anti-VEGF monotherapy for DME. We have off-label triamcinolone. We have

on-label dexamethasone and on-label fluocinolone. I have seen a couple of patients that had really unimpressive OCT results in the early months. They had a slow, gradual reduction in the retinal volume and thickness. It was not like what we see when we inject triamcinolone, where we see this rapid deturgescence of the macula.

Dr. Wykoff: I consider steroids when I am not seeing a robust anatomic response to anti-VEGF injections. I have found both dexamethasone and fluocinolone intravitreal implants to be helpful in incomplete responders.

Dr. Pieramici: Steroids have side effects and are not my first-line therapy for DME in most cases. The pressure effect is real, the cataract effect is real. Especially in young people with relatively clear lenses, I am not going to subject them to that without a good reason.

Dr. Moshfeghi: Let us say you get a good response with one of the anti-VEGFs, but the patient has to be seen monthly or every 8 weeks. What is the treatment ladder there? It is a different situation when someone is a suboptimal responder to anti-VEGF monotherapy, and they have been receiving monthly injections? Would you start dexamethasone in a good responder? If so, when?

Dr. Wykoff: It is patient-specific. I have patients who are happy receiving monthly injections and do not want to change. I have other patients who tell me they "hate" the injections and want to have them less frequently—those are patients with whom I discuss steroids very early in the management course.

Dr. Pieramici: It is an easy conversation with the anti-VEGFs, because it is safe for the eyes, besides the risk of endophthalmitis. With steroids, you need to start a whole conversation about the ocular side effects, and that can be a difficult conversation.

Dr. Fortun: I also leave the question of treatment burden on the patient. If they are okay getting monthly injections, I am okay with it, too. Otherwise you can tell them, I have something else.

Dr. Lalwani: I agree that it is very patient-driven. When the anti-VEGFs are working, I would be hard pressed to change them unless the patient is really complaining. It is a patient's decision, especially when anti-VEGFs are working.

Dr. Fortun: I have used quite a bit of dexamethasone for DME as an adjuvants, and that is somewhat driven by me. I do not like seeing a persistent fluid in the back. Sometimes if I am not with a suboptimal responder then I will add steroids because, despite the side effects, nothing works like steroids in DME.

Dr. Pieramici: Fundamentally, our job is to make our patients' quality of life better by improving visual acuity by getting rid of the edema. But sometimes the patients have imperfect vision—perhaps 20/30, 20/40, or 20/50—and have a lot of edema, but they are happy with their visual function and are skeptical about engaging in intravitreal treatments.

Dr. Moshfeghi: I think that patients complain about the injections, but that does not mean that they are not willing to get it, and that they are not willing to come in frequently to get it. As long as it means that their vision is going to be good, they are willing to get injections.

Dr. Fortun: You have got to change your perception about DME. In AMD, the reason I care about that little bit of fluid is because it could cause a drastic loss of vision if patients have a bleed.

Dr. Pieramici: A lot of times, these diseases are more a problem for the physician than the patient. When I see a patient with a small central cyst and excellent vision, the first thing I say is, are you having a problem with your eyes? Most of the time they will say, "No, but my doctor says I have a problem." These are excellent cases to watch. If things worsen, then treatment will be welcomed.

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CME QUESTIONS:
DRCR.NET PROTOCOL REVIEW

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1. In the FDA registration trials for ranibizumab and aflibercept, all enrolled eyes were:

a. 20/25 or better at baseline
b. 20/40 or better at baseline
c. 20/40 or worse at baseline
d. 20/50 or worse at baseline

2. According to the results from Protocol T:

a. the anatomic results were the same between bevacizumab and ranibizumab
b. the anatomic results with aflibercept and ranibizumab were superior to bevacizumab
c. the anatomic results with bevacizumab and ranibizumab were superior to aflibercept
d. the anatomic results were identical among the evaluated agents

3. In the DME and AMD studies:

a. the control arm in AMD is likely to lose vision
b. the anatomic response is the same to all the anti-VEGF drugs
c. the vision improvement with anti-VEGFs occurs rapidly in AMD but not in DME
d. treatment continues monthly until the macula is completely dry

4. The presence of predominantly peripheral lesions in eyes with non-proliferative diabetic retinopathy:

a. confers a 2.3-fold greater risk of progression to PDR over 4 years
b. confers a 4.7-fold greater risk of progression to PDR over 4 years
c. confers a 5.2-fold greater risk of progression to PDR over 4 years
d. confers a 6.6-fold greater risk of progression to PDR over 4 years

5. The use of steroids in the treatment of DME:

a. should be limited to only pseudophakic eyes
b. will likely result in a very rapid reduction in retinal volume and thickness
c. should be considered a first-line therapy as the side effect profile is equal to the anti-VEGFs
d. should be considered in cases where anatomic response to the anti-VEGF agents is suboptimal

6. Protocol S, which compared ranibizumab and PRP in the treatment of PDR, found:

a. comparable vision gains between the two treatments
b. posterior PRP has a minimal effect on the visual field
c. a significant loss of visual field with laser
d. results can be easily applied to all patients with PDR

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the ocular and systemic effects of anti-VEGF therapies in patients with diabetes and how to educate patients on appropriate expectations	_____	_____	_____
Assess clinical studies involving new approaches to treat DME and proliferative diabetic retinopathy	_____	_____	_____
Use expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules	_____	_____	_____
Evaluate treatment options and develop a treatment regimen that can reduce patient burden and practice capacity	_____	_____	_____

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Please identify how you will improve/change:

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_____

_____

____ Create/revise protocols, policies, and/or procedures. Please specify

_____

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If no, please identify the barriers to change.

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_____

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