CME Monograph

Protocol T and More for DR/DME

IMPLICATIONS FOR PRACTICE

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New York Eye and Ear Infirmary of **Mount Sinai**

MedEdicus LLC

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LEARNING METHOD AND MEDIUM

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from an expert roundtable discussion held on December 21, 2016.

ACTIVITY DESCRIPTION

Diabetic eye disease is a leading cause of preventable blindness, which is a growing concern due to the increasing prevalence of diabetes in the United States. Recent clinical trials in diabetic retinopathy (DR) and diabetic macular edema (DME) have indicated that new management plans are needed. These studies demonstrated that various antiangiogenic therapies that target vascular endothelial growth factor (VEGF) are effective in restoring visual acuity in most patients. Nevertheless, patient response may vary, and it is important for the physician to evaluate if patients are candidates for anti-VEGFs. Furthermore, physicians need to decide whether they should switch VEGF agents, consider injectable sustained-release steroid implants, or initiate laser therapy when individuals fail to respond to first-line treatment. Lastly, the method used to detect eye disease will be important for therapeutic assessment. Optical coherence tomography and wide-field angiography have become the modalities of choice for recent clinical trial assessments and should be incorporated into current practice.

The purpose of this activity is to provide an expert interpretation of pivotal clinical trial data, which physicians can incorporate into evidence-based practice strategies when detecting, treating, and monitoring DR/DME.

TARGET AUDIENCE

This educational activity is intended for retina specialists and other ophthalmologists caring for patients with diabetic retinopathy.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Apply key findings from pivotal clinical trials in DR/DME to patient management plans
- Outline individualized treatment plans for patients with DR/DME
- Incorporate imaging modalities into patient management for early detection, treatment, and monitoring

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Protocol T and More for DR/DME
IMPLICATIONS FOR PRACTICE

INTRODUCTION

The therapeutic landscape for the management of diabetic retinopathy (DR) and diabetic macular edema (DME) is evolving as new clinically relevant data emerge. In the decade since the debut of modern agents to inhibit vascular endothelial growth factor (VEGF), many diseases of the posterior segment, including DR and DME, have seen paradigm shifts in management. In this monograph, a panel of leading retina specialists offers insight into the interpretation and application of recent therapeutic studies of DR and DME. In addition, they will share pearls for evidence-based management of challenging cases of patients with DR and DME. The goal of this monograph is to clarify the optimal framework for the evaluation, treatment, and monitoring of DR and DME in 2017.
- Dante J. Pieramici, MD, on behalf of the faculty

DIABETIC MACULAR EDEMA

Importance of Presenting Visual Acuity on Selection of Therapy

Dr Pieramici: Diabetic macular edema is a leading cause of vision loss among working-aged Americans. The prevalence of DME among Americans with diabetes aged 40 years or older has been estimated at nearly 4% or approximately 750,000 cases in the United States.[1] The Diabetic Retinopathy Clinical Research Network (DRCRnet) is a collaborative network assembled to design and conduct impactful multicenter clinical studies of DR, DME, and other related conditions. The DRCRnet Study Group is funded by the National Eye Institute at the National Institutes of Health. Recently, the DRCRnet reported 2-year results of Protocol T, a double-masked comparison of the anti-VEGF agents aflibercept, bevacizumab, and ranibizumab in the management of DME **(see Sidebar: Summary of Protocol T 1- and 2-Year Results).**[2] One important lesson from Protocol T was that when presenting visual acuity (measured in standard fashion using ETDRS [Early Treatment Diabetic Retinopathy Study] visual acuity charts) was good (20/32 to 20/40), the 3 agents provided comparable outcomes at 2 years, but when presenting visual acuity was poor (20/50 to 20/320), there were differences in outcomes among the 3 drugs. In your clinical practice, what effect does presenting visual acuity have on your selection of first-line therapy for significant center-involved DME?

Dr Kim: Prior to Protocol T, we had no guidance on this issue, and I routinely started with bevacizumab by default. Bevacizumab is the least expensive of the 3 anti-VEGF agents, which results in less burden of copay for patients, and preauthorization from insurance companies is not

a concern. Fortunately for me, I have a reliable hospital pharmacy that prepares and supplies it. I also figured I can always switch from bevacizumab to other agents if a patient does not respond to bevacizumab. Because of the release of the Protocol T results, however, we now have an opportunity to practice more evidence-based medicine. In the example you describe—a patient with center-involved DME and a presenting visual acuity of 20/50 or worse—I now tend to start with aflibercept. Protocol T demonstrated that for patients with a baseline visual acuity of 20/50 or worse, the group treated with aflibercept had the greatest visual acuity gain and retinal edema reduction of the 3 agents at the 1-year time point. By the end of year 2 of the study, visual acuity improvements in the aflibercept and ranibizumab groups were comparable, whereas the aflibercept group had a statistically significant visual acuity improvement compared with the bevacizumab group.[2] In eyes with better visual acuity at presentation, I usually start with bevacizumab because of the reasons mentioned previously and because there was no statistically significant difference in visual outcome among the 3 drugs. The only exception would be a patient with good baseline visual acuity but a very thick retina. Bevacizumab was the least effective in reducing retinal thickness.[2] Therefore, in such a patient, I may consider starting with aflibercept.

Dr Baumal: The 1-year data favoring aflibercept became a draw with ranibizumab by the second year.[2] My goal, however, is to achieve a dry macula as quickly as possible, and, in this regard, the study favored aflibercept, so this is often my first-line drug in eyes with poor visual acuity. In patients with better-presenting visual acuity, there was no difference among the drugs,[2] so if cost is a factor, I often start with bevacizumab. In the absence of cost concerns, I would generally start with aflibercept or ranibizumab for patients with DME and better visual acuity who warrant treatment.

Dr Wells: I also use presenting visual acuity as a guide to therapy selection. I should point out, however, that there are always challenges to translating research findings into clinical practice. For instance, I use Snellen visual acuity in my practice, whereas Protocol T used ETDRS visual acuity.[3] Rather than attempting to convert from Snellen to an ETDRS equivalent, I use the Snellen visual acuity we obtain in my office. If it is 20/50 or worse, I tend to use aflibercept. If it is better than 20/50, I tend to use ranibizumab because, in my experience, it costs less than aflibercept, and Protocol T demonstrated that bevacizumab was less effective at reducing edema than both ranibizumab and aflibercept through year 2 of the study.[2] In eyes with better visual acuity at presentation, there was no difference in the 2-year visual outcomes among the 3 drugs, but there was a significant difference in both the rate and magnitude of edema resolution in these eyes, with bevacizumab not performing as well as the other 2 drugs over the course of the study. When we are treating patients, we all want to see the edema go away, and, on average, bevacizumab reduces edema by approximately half compared with the other drugs. Although starting with bevacizumab is reasonable in these better baseline vision eyes, I believe many physicians switch to another anti-VEGF or steroids after a few injections because the reduction in edema is less than desired.

Summary of Protocol T 1- and 2-Year Results

Objective: To evaluate functional and structural outcomes of eyes with diabetic macular edema (DME) treated with aflibercept, bevacizumab, or ranibizumab.[1,2]

Design: Randomized clinical trial[1,2]

Interventions: Subjects with center-involved DME were randomized to receive treatment with aflibercept, bevacizumab, or ranibizumab.[1,2] Injections were given monthly for 6 months, after which injections were given as needed only if visual acuity or optical coherence tomography central subfield thickness worsened. Focal/grid laser could be applied as needed beginning at month 6.

Primary outcome: Mean change in visual acuity measured in standard fashion using ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity charts.[1,2]

Results: The median number of injections in the aflibercept, bevacizumab, and ranibizumab groups in year 1 was comparable at 15, 16, and 15, respectively; in year 2 , the median number of injections was also comparable at 5, 6, and 6, respectively.[2] Over the 2-year period, 41%, 64%, and 52% of eyes, respectively, received focal/grid laser. Mean visual acuity improvement for all eyes **(see Table)** was 13.3, 9.7, and 11.2 letters, respectively, at 1 year[1] and 12.8, 10.0, and 12.3 letters, respectively, at 2 years.[2] The overall comparison has limited clinical use because there was a strong interaction with baseline visual acuity, which was a preplanned subgroup analysis. In eyes with better baseline visual acuity (20/32 to 20/40), mean improvement was 8.0, 7.5, and 8.3 letters, respectively, at 1 year[1] and 7.8, 6.8, and 8.6 letters, respectively, at 2 years (difference is not statistically significant).[2] In eyes with worse baseline visual acuity (20/50 to 20/320), mean improvement was 18.9, 11.8, and 14.2 letters, respectively, at 1 year ($P < .001$ for aflibercept vs bevacizumab; $P = .003$ for aflibercept vs ranibizumab; $P = .21$ for ranibizumab vs bevacizumab)[1] and 18.3, 13.3, and 16.1 letters, respectively, at 2 years ($P = .02$ for aflibercept vs bevacizumab; other between-group differences were not statistically significant).[2] Central subfield thickness on optical coherence tomography improved in all groups; however, both aflibercept and ranibizumab produced significantly better improvement than did bevacizumab overall and in eyes with better baseline visual acuity.[1,2] Anti-Platelet Trialists' Collaboration events occurred in 5%, 8%, and 12% of eyes, respectively, through 2 years of follow-up ($P = .047$ overall; aflibercept vs ranibizumab, $P = .047$; other between-group comparisons were not statistically significant).[2]

Table. Comparison of Mean Visual Acuity Gains (Letters) at 1 and 2 Years in Protocol T[1,2]

	Mean Visual Acuity Gain, Letters					
	1 Year			2 Years		
	Overall	Better Baseline Acuity	Worse Baseline Acuity	Overall	Better Baseline Acuity	Worse Baseline Acuity
Aflibercept	13.3	8.0	18.9	12.8	7.8	18.3
Bevacuzimab	9.7	7.5	11.8	10.0	6.8	13.3
Ranibizumab	11.2	8.3	14.2	12.3	8.6	16.1
Significance	$P < .001$ for aflibercept vs bevacizumab; $P = .03$ for aflibercept vs ranibizumab	Not significantly different	$P < .001$ for aflibercept vs bevacizumab; $P = .003$ for aflibercept vs ranibizumab; $P = .21$ for ranibizumab vs bevacizumab	$P = .02$ for aflibercept vs bevacizumab; $P = .47$ for aflibercept vs ranibizumab; $P = .11$ for ranibizumab vs bevacizumab	Not significantly different	$P = .02$ for aflibercept vs bevacizumab; $P = .18$ for aflibercept vs ranibizumab; $P = .18$ for ranibizumab vs bevacizumab

References

1. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203.
2. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359.

Dr Pieramici: My clinical practice is similar to what you have described. I agree that resolution of edema is important, and it is the parameter we tend to focus on most when monitoring our patients. The 1- and 2-year results of Protocol T were a little bit different, and ranibizumab seemed to catch up to aflibercept by 2 years, at least in terms of mean change in visual acuity.[2] Are you now more likely to use ranibizumab than you might have been after the 1-year data?

Dr Baumal: I like to get the macula dry and have the visual acuity improve as rapidly as possible, so I tend to use aflibercept for DME, but I have patients who have had an excellent response to ranibizumab. There is substantial variation in response among patients. If I see a good initial response to ranibizumab, I will continue it; if not, I may switch to aflibercept.

Dr Wells: The 1-year data informed my approach to therapy selection, and the 2-year data did not change that. We want our patients to get better as quickly as possible. Aflibercept provided better visual acuity almost immediately in the worse baseline vision group,[2] and I want to provide my patients with this benefit.

Dr Kim: We are fortunate in this era to have highly effective therapy in the anti-VEGF agents. I do not think one should be faulted for selecting any of the anti-VEGF treatment options so long as patients are treated aggressively during the first year to get the macula dry. The problem arises when we *under*treat these patients, and real-world data show that when patients do not get the number of treatments that were applied in the clinical trials, their visual improvement is never as good. One of the lessons that I learned from Protocol T and Protocol I, which has 5-year follow-up data, is to treat monthly during the first 6 months and continue treatment if needed, according to evaluation of the visual acuity and optical coherence tomography (OCT) findings.[2,4] In Protocols T and I, on average, 9 injections were given during the first year.[3,5] Fortunately, with upfront loading of treatments, the number of injections declined in the subsequent years while the visual gains were maintained.

Which Patients Might Be Observed Without Treatment?

Dr Pieramici: Are there any patients with center-involved DME in your practice whom you choose not to treat?

Dr Baumal: These patients are rare in my practice, but they do exist. For instance, I may not treat an asymptomatic patient with excellent vision who has a single cyst in the inner retina and a normal-appearing outer retina on OCT. These patients can remain stable, and many even improve spontaneously over time. Another scenario in which I might observe a patient is if the patient has recently had a considerable improvement in blood glucose control and hemoglobin A1c. In this patient, DME can briefly worsen and then stabilize or improve. It is important to pay attention to the systemic medical status, especially blood pressure, kidney function, and glucose control. I may observe a patient with a recent change in antihypertensive therapy or who recently started insulin or dialysis to see if this leads to improvement in macular edema.

Dr Kim: I agree. A patient with minimal cysts but with good foveal depression seen on OCT, visual acuity of 20/20, and no symptoms would be observed. The clinical trials enrolled patients with center-involved DME and visual acuity of 20/32 or worse, so we do not have any guidance regarding patients with good vision. However, DRCRnet is currently studying patients with very good vision, so we will have some answers in the future. If a patient with good vision has a high hemoglobin A1c level, we encourage better diabetes control, and DME may get better on its own as the blood glucose level is better controlled.

Dr Wells: I tend to follow the dictum "Don't make an asymptomatic patient symptomatic." It makes little sense to incur risk when there are no clear benefits to be obtained. Injections are rarely associated with endophthalmitis, but it can happen. My approach to the patients you have described is to talk to them, show them their OCT, explain the situation, and generally follow them closely. I usually will not treat a 20/20 patient at the first visit, but I will follow the patient closely, say in 4 to 6 weeks rather than 3 to 4 months. I am reasonably comfortable following such a patient for a while. Looking ahead, the DRCRnet is recruiting patients into Protocol V,

which compares observation to treatment with laser or anti-VEGF therapy in patients with DME and a visual acuity of 20/25 or better.[6] The results of this study will provide further insight to guide evidenced-based practice.

Dr Baumal: We have more leeway in terms of starting therapy for DME than we do for macular degeneration, in which rapid treatment is of the essence, so observing mild cases of DME initially is a reasonable approach.

Safety Issues

Dr Pieramici: The 1- and 2-year results of Protocol T revealed some differences in safety outcomes, specifically Anti-Platelet Trialists' Collaboration (APTC) events.[2] The differences were statistically significant, but were they clinically significant, and do these findings affect your selection of therapy?

Dr Kim: The APTC events include nonfatal myocardial infarction, nonfatal stroke, and death due to cardiovascular, hemorrhagic, or unknown causes.[2] In Protocol T, APTC events occurred in 5% of patients receiving aflibercept, 8% of patients receiving bevacizumab, and 12% of patients receiving ranibizumab; the 3-way analysis was significant ($P = .047$), although the only significant pairwise comparison was between aflibercept and ranibizumab ($P = .047$).[2] When controlled for confounding variables, the 3-way analysis became insignificant ($P = .09$). It is important to point out that this study was not designed or powered to evaluate statistically significant differences in safety profiles among these agents, so the findings should be taken with a grain of salt. These results differ from comparisons of these agents in other disease states, such as age-related macular degeneration.[7-9] This may be partially explained by differences in subjects because all the patients in Protocol T had diabetes, so they all had systemic vasculopathy and may have been predisposed to these types of events.[2] Overall, this may be more coincidence than cause-and-effect, and I do not think there are clinically significant safety differences among these agents.

Dr Baumal: The higher rate of safety events with ranibizumab was surprising to me.[2] The ranibizumab molecule was designed to be safer than the parent molecule bevacizumab. It lacks the fragment crystallizable region, so it cannot bind complement or promote complement-mediated immune responses.[10] Overall, the rates of safety events are low and do not affect my selection of therapy.

Dr Wells: These results are difficult to explain. One might assume that these events are mediated by systemic levels of the anti-VEGF agent, in which case the results are counterintuitive because ranibizumab achieves the lowest systemic concentration of the 3 agents and, unlike the other 2 agents, does not accumulate with repeat intravitreal dosing.[11] So these findings are interesting but not consistent with prior findings and are implausible, given what is known about the systemic pharmacokinetics of these agents. As a result, I am not generally convinced that ranibizumab is less safe than the other agents.

Anti-VEGF Treatment Nonresponse

Dr Pieramici: Study results describe average responses, and, as we know, not every patient responds well to any given drug. Once you have selected an anti-VEGF agent and initiated therapy, at what point do you decide the drug is not working?

Dr Wells: In the strictest sense, Protocol T required 6 monthly injections with initial therapy before rescue laser could be applied.[2] It is unlikely that most clinicians adhere to this protocol. However, the outcomes seen in Protocols T and I were obtained using this strategy, so it has been proven effective.[2,4] For this reason, I tend to continue monthly injections of my primary therapy through 6 months, as in the DRCRnet algorithm.

Dr Kim: Although I try to continue with the same agent once I start treatment, if vision or edema worsens after 3 monthly injections, I would switch, especially if I started with bevacizumab. If the patient is the same at 3 months, I will continue for another 3 months before considering a switch.

Role of Laser

Dr Pieramici: Where does laser fit into the modern DME treatment plan?

Dr Baumal: It is important to recognize that in Protocol T, 36% to 39% of subjects in each treatment group had undergone focal/grid laser prior to entry.[3] Additionally, 37% to 56% of eyes underwent additional focal/grid laser during the first year of the study. So in essence, the Protocol T outcomes reflect the combined effect of anti-VEGF therapy in addition to laser therapy when needed. A recent post hoc analysis of the VIVID (VEGF Trap-Eye in Vision Impairment Due to DME)/VISTA (Study of Intravitreal Administration of VEGF Trap-Eye in Patients With Diabetic Macular Edema) trials of aflibercept vs laser for DME shed some additional light on the roles of laser and anti-VEGF therapy.[12] In this analysis, a subset of 109 eyes initially randomized to laser that then received aflibercept injections was analyzed. These eyes had lost significant vision (10-11 letters on average) during the laser-only treatment period and gained 14 to 17 letters on average after starting aflibercept therapy through week 100. This net gain is substantially below the gains observed at week 100 in eyes treated with aflibercept from the beginning of the study.[12,13] In my experience, I rarely use laser as initial treatment for DME. The exception to this is in eyes with localized areas, usually noncenter-involved DME with microaneurysms. In Protocol T, laser could be added when initial anti-VEGF therapy failed,[2] and it is not clear how this affected the efficacy of the anti-VEGF agents. I tend to switch to a different anti-VEGF agent rather than adding laser.

Dr Wells: In Protocol I, the eyes that received initial laser did not do as well in the long term as the eyes that

received initial anti-VEGF therapy,[4] so I tend not to start with laser. I will consider laser if, after 6 months of anti-VEGF injections, there is still center-involved edema and there is no progress in terms of edema resolution. In the days of clinically significant macular edema, we treated with laser when the center of the macula may or may not have been involved. I now feel comfortable tolerating persistent noncentral edema. The exception is the eye with a foveal-threatening lipid or circinate ring with visible microaneurysms, in which case focal laser can be very helpful, with minimal scarring.

Dr Kim: For center-involved edema, I no longer use laser as first-line therapy. For perifoveal or extrafoveal edema with microaneurysms causing lipid exudates that threaten the fovea, I still consider focal/grid laser. We can use low energy to minimize scarring and often can avoid the series of monthly injections in those eyes.

Role of Steroids

Dr Pieramici: Are there any circumstances in which you would consider initial therapy with steroids for DME?

Dr Kim: Steroids would be my first choice for pregnant women in whom I do not feel comfortable deferring treatment until delivery. I might also consider steroid therapy in someone with a recent major stroke in whom I cannot safely defer therapy.

Dr Baumal: I would expand that to women who are trying to conceive. As for breastfeeding, I think the risk is minimal, but I would discuss it with the patient before making any decisions.

Dr Wells: There are always patients who cannot reliably maintain the monthly follow-up schedule necessary for anti-VEGF therapy. In these patients—assuming they are pseudophakic and have no evidence of glaucoma—I might consider steroids to reduce the visit burden. I still tend to see them a month after the injection to check their intraocular pressure, and if it is normal, we can spread the next visits out longer.

Dr Baumal: This might also be the scenario in which I would consider the dexamethasone implant **(see Sidebar: Summary of Protocol S 2-Year Results).** It has a longer effect than anti-VEGF therapy. In a phase 2 study, at 90 days post-injection, eyes treated with the implant had significantly improved visual acuity and edema.[14] Likewise, in the phase 3 MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study, the implant conferred better visual acuity and edema outcomes, with a mean of approximately 4 treatments over 3 years, demonstrating its duration of effect **(see Sidebar: Sustained-Release Steroids for Diabetic Macular Edema).**[15] When I use the implant in a patient, I always make sure the patient's intraocular pressure is checked 4 to 6 weeks later, and this can be done by a provider closer to home for patients who live far away.

Summary of Protocol S 2-Year Results

Objective: To compare visual acuity outcomes in eyes with proliferative diabetic retinopathy (PDR) treated with panretinal photocoagulation (PRP) or intravitreal ranibizumab.

Design: Randomized clinical trial

Interventions: Subjects with PDR were randomized to receive treatment with PRP or ranibizumab 0.5 mg given monthly through 4 injections, then as needed for recurrent or progressive neovascularization.

Primary outcome: Mean change in visual acuity

Results: Eyes with PDR and DME received a median of 9 injections in year 1 and 5 injections in year 2; eyes with PDR without DME received a median of 7 injections in year 1 and 3 injections in year 2. At 2 years, the mean visual acuity letter improvement was +2.8 in the ranibizumab group vs +0.2 in the PRP group. This was a noninferiority trial, and the difference was within the margin of noninferiority, supporting the conclusion that ranibizumab was not worse than PRP. However, in eyes with PDR and baseline center-involved DME, the ranibizumab group gained more vision than did the PRP plus ranibizumab group (+7.9 letters vs +1.9 letters). Eyes treated with PRP had significantly more peripheral visual field loss (−422 dB vs −23 dB; $P < .001$), higher rates of vitrectomy (15% vs 4%; $P < .001$), and higher rates of DME development (28% vs 9%; $P < .001$) than eyes treated with ranibizumab. The rates of major cardiovascular events were comparable between the groups.

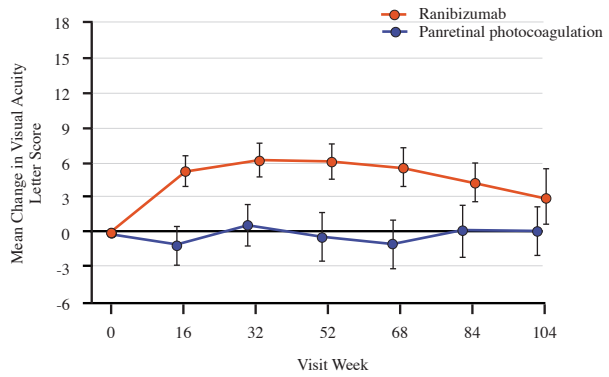

Figure. Changes in visual acuity over time for the overall cohort

Reference

Gross JG, Glassman AR, Jampol LM, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA.* 2015;314(20):2137-2146.

Dr Wells: There is a role for steroids in eyes that achieve an incomplete response to anti-VEGF therapy. I generally continue initial anti-VEGF therapy for 6 to 12 months unless there is significant worsening of vision or edema, in which case I will supplement with laser at the 6-month mark. If the combination of anti-VEGF and laser provides a suboptimal response, I will then consider steroids. I typically use triamcinolone as my initial steroid. In my experience, the dexamethasone implant has a similar duration of response and side effects. Recently, I have used the fluocinolone implant in a couple of patients with severe DME who were worsening with monthly aflibercept. One patient did well, and the other had modest reductions in DME but not much vision improvement. The glaucoma risk is somewhat of a deterrent for me, and I prefer to limit steroid use to pseudophakic eyes to eliminate the cataract risk. We have little evidence-based guidance on the role of steroids combined with anti-VEGF and laser therapy. I look forward to the results of the DRCRnet Protocol U study, in which steroids are given after just 3 anti-VEGF injections.[16]

PROLIFERATIVE DIABETIC RETINOPATHY

Dr Pieramici: Panretinal photocoagulation (PRP) has been the standard of care for the treatment of proliferative diabetic retinopathy (PDR) for 4 decades or more. Recently, the DRCRnet published the results of Protocol S, in which initial ranibizumab treatment (baseline and 3 monthly injections followed by as-needed retreatments) produced visual acuity outcomes that were noninferior to initial PRP.[17] Its approval by the US Food and Drug Administration for PDR was limited to eyes with both PDR and DME.[18] The label was recently updated to include DR with or without DME. Do you use anti-VEGF therapy as primary therapy for eyes with PDR *without* DME?

Dr Baumal: I have treated many patients who have PDR without DME initially with a series of anti-VEGF injections. In my experience, these patients do very well initially, but require close monitoring for recurrent neovascularization, preretinal fibrosis, and traction. Some patients may completely avoid PRP laser. Protocol S corroborated my clinical experience using anti-VEGF therapy for macular edema associated with other conditions, such as retinal vein occlusions; in these eyes, the neovascularization usually resolves rapidly after injection.[17] The challenge in treating PDR with anti-VEGF therapy is that the consequences of being lost to follow-up are more severe than with DME because PDR can lead to hemorrhage, traction detachments, neovascular glaucoma, and loss of the eye. Therefore, it is important to select patients carefully, focusing on those who will be compliant with the treatment burden and be reliable for follow-up; otherwise, PRP can be delivered in 1 or a few sessions.

Dr Wells: This is a situation in which I consult the patient. We discuss the risks—visual field loss with PRP and endophthalmitis with anti-VEGF therapy—and the treatment burden, which will require monthly visits for an extended period. In my experience, most patients prefer a quick definitive treatment and opt for laser. I have had some patients opt for injections. They are motivated initially, but eventually the follow-up becomes burdensome.

Dr Kim: Clinical trial patients are much different than real-world patients in terms of both motivation and tolerance for the burdens of treatment and follow-up. I approach this decision on a case-by-case basis. I share with patients that injections may preserve their visual field and night vision. In Protocol S, there was also less need for vitrectomy surgery and less development of DME in the ranibizumab group than in the PRP group. Despite these benefits, many patients express concerns with monthly follow-up visits. Also, with every injection, there is a risk of endophthalmitis. It is an easier choice when there is also center-involved DME because then you can address both problems with a single therapy.

Dr Baumal: In some cases of severe PDR with vitreous hemorrhage, I treat with PRP laser and anti-VEGF therapy simultaneously or sequentially.

Dr Wells: Anti-VEGF therapy tends to produce rapid, and often complete, regression of the neovascularization, whereas with PRP, the response is slower.[17] So I agree with Dr Baumal. In some cases—particularly the more severe PDR cases—I will give 1 or 2 anti-VEGF injections and then apply PRP. I have taken this approach in a few patients, with satisfactory results.

Dr Kim: It is worth pointing out that more than half of the PRP eyes received rescue ranibizumab, whereas only 6% of the eyes receiving ranibizumab required rescue laser.[17] As Dr Wells pointed out, other potential treatment strategies may include a combination therapy of anti-VEGF injections with laser. The optimal treatment protocol is not yet known. We may find that when combined with PRP, we can give fewer injections, less extensive PRP, or treat for a shorter duration.

Vitreous Hemorrhage

Dr Pieramici: In Protocol S, there was a slightly increased risk of vitreous hemorrhage and a significantly higher risk of vitrectomy in the PRP group.[17] Why do you think this occurred?

Dr Wells: Panretinal photocoagulation is an effective treatment, but as I said, it does not promote rapid and complete regression of the neovascularization. The endurance of neovascularization in the PRP group may explain the increase in vitreous hemorrhage and likely why the PRP group also had a higher vitrectomy rate than the anti-VEGF group in Protocol S.[17]

Dr Kim: Not only was there a higher frequency of vitreous hemorrhage in the PRP group, but the hemorrhages tended to be denser as well. These dense vitreous hemorrhages are more likely to require vitrectomy, so as Dr Wells said, the 2 are likely related.

Altering the Natural History of Proliferative Diabetic Retinopathy

Dr Pieramici: We have already discussed the burden of treatment and follow-up when using anti-VEGF therapy to treat PDR. Protocol S has reported only 2-year data to date, and it remains unclear how long therapy must persist. In Protocol S, the number of injections needed decreased in the second year.[17] This raises an important question, What is the natural history of PDR, and are we altering that course with anti-VEGF therapy?

Dr Kim: The DR severity score improved 2 or more steps over the course of 2 years in approximately half of the eyes in the anti-VEGF group.[17] It appears that not only are these eyes being stabilized, but their retinopathy status is improving. This is a result that will never be matched by laser, which by its nature is a destructive treatment.

Dr Baumal: The DR severity scoring in Protocol S was based on color photographs and not widefield angiography, so it is not clear what might be happening in the peripheral retina. Some of the stimulus for PDR might be coming from peripheral retinal ischemia. I think these patients will always be at risk for PDR and will need to be followed very carefully.

Dr Wells: It has been my impression that PDR has a lifespan and does not always persist indefinitely. We have all seen patients who present with normal visual acuity and no symptoms, but on examination, they have evidence of significant prior PDR that has regressed spontaneously. In some patients, it seems to run its course and burn itself out over time.

Observations from Protocols I and S support this possibility. In Protocol I, with 5 years of follow-up, the number of injections necessary to treat DME decreased every year, with approximately half of the eyes not needing any injections at all in the fourth and fifth years.[4] We saw the same trend in Protocol T,[2] in which the number of injections dropped from the first year to the second year, and in Protocol S as well.[17] So it seems that either the disease—whether it is PDR or DME—burns itself out over time or its natural history is being altered with anti-VEGF therapy.

TAKE-HOME PEARLS

Dr Pieramici: This has been an informative discussion. Before we close, I would like to ask each of you to share your bottom-line take-home message from this activity.

Dr Wells: The most important finding from Protocol T was that anti-VEGF therapy effectively improves vision.[2] In eyes with good baseline vision, outcomes were the same regardless of which agent was used. In eyes with worse baseline vision, aflibercept yielded better vision outcomes than the other 2 agents at the 1-year time point, although by year 2, ranibizumab had closed the gap. Bevacizumab reduces the edema less than the other 2 agents, so I personally tend not to use it for DME. For Protocol S, in eyes with PDR and coexisting DME, anti-VEGF therapy with ranibizumab was superior to laser in terms of improving visual acuity and also in preventing visual field loss, so I think the treatment of choice in these eyes is anti-VEGF therapy.[17]

Sustained-Release Steroids for Diabetic Macular Edema

Two sustained-release steroid devices are available for the management of diabetic macular edema (DME): 1 containing dexamethasone, and the other containing fluocinolone acetonide. In the MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study, 1048 patients with DME received either the dexamethasone implant (0.35 or 0.7 mg) or a sham injection and were followed for 3 years, with retreatment allowed every 6 months.[1] The study end point was ≥ 15-letter improvement in best-corrected visual acuity from baseline to study end. Patients receiving active implants required an average of 4 total treatments over the 3-year study period. Overall, the study end point was met by 22.2% of patients in the 0.7-mg group, by 18.4% in the 0.35-mg group, and by only 12% in the sham group ($P \leq .018$). In a subgroup analysis of patients with previously treated DME, 21.5% of patients in the 0.7-mg group vs 11.1% of sham patients reached the study end point ($P = .002$).[2] Approximately two-thirds of phakic patients receiving an active steroid experienced cataract-related adverse events, and intraocular pressure elevations were generally controlled with observation or topical medical therapy.[1]

In the FAME (Fluocinolone Acetonide in Diabetic Macular Edema) study, 953 patients with DME received either the fluocinolone acetonide implant (0.2 μg/d for the low-dose group and 0.5 μg/d for the high-dose group) or a sham injection and were followed for 3 years, with retreatment allowed after 1 year.[3] As in MEAD, the study end point was a gain of ≥ 15 letters from baseline. Overall, the study end point was met by 28.7% of patients in the low-dose group, by 27.8% in the high-dose group, and by only 18.9% in the sham group ($P = .018$). In a subset of patients with chronic DME (present ≥ 3 years at enrollment), the study end point was met by 34% of patients in the low-dose implant group and only 13.4% of patients in the sham group ($P < .001$).[4] Approximately 80% to 90% of phakic patients required cataract surgery, and 5% to 8% required glaucoma surgery to control intraocular pressure elevations.[3]

Note that the prescribing information for these products specifies that prior to implantation of the fluocinolone acetonide device, a trial of corticosteroids should first be performed to confirm the absence of a steroid-induced elevation of intraocular pressure, whereas no such trial is required with the dexamethasone device.

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Dr Kim: We now have a number of treatment options in our fight against DR and DME to help our patients. These trials show that we are getting visual benefits that were not previously possible with laser alone. It is important for clinicians to be familiar with these trials to practice evidence-based medicine regarding when and how to use these treatment options while keeping in mind that every patient is unique. In addition, we should not forget that the treatment of diabetic retinopathy is a group effort. Successful management of diabetes relies on collaboration and communication among the primary care physician, endocrinologist, ophthalmologist, patient, and patient's family. We all have to work together to achieve the goal of saving vision in our patients, so I see myself as both a coach and a cheerleader, rallying them to victory over diabetes and its complications.

Dr Baumal: As with all good research, Protocols T and S both answered questions and raised new questions. We now have better information to guide our treatment decisions. We also recognize that we have evaluated only specific and limited treatment regimens. It is important to continue to explore the various combinations and sequences of therapy to optimize the outcomes and reduce the treatment burden associated with diabetic eye disease.

Dr Pieramici: We are fortunate to currently have so many options for therapy when managing our patients with the ocular complications of diabetes. Today, we have anti-VEGF therapies, steroids, laser, and surgery. Previous studies have provided extensive data on how populations of patients respond to these therapies. One important lesson from these studies is that there is a significant variability of response among patients. With this in mind, studies provide a framework for helping make management decisions. They are simply guidelines and not a "cookbook" algorithm with which to treat each individual patient. As physicians, we must parse the studies' results and make the best treatment decisions we can for each individual patient according to that patient's unique characteristics, needs, and expectations. The data available to today's clinician concerning the treatment of DME and DR should go a long way in helping us make rational treatment decisions with our patients.

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1. In Protocol T, which was an important factor when selecting initial therapy for DME?

   a. Central subfield thickness on OCT
   b. Hemoglobin A1c
   c. Presenting visual acuity
   d. Phakic status

2. A patient with newly diagnosed center-involved DME requires treatment. His presenting visual acuity is 20/32. Which agent will likely provide the best visual outcome after 12 months of therapy?

   a. Bevacizumab
   b. Ranibizumab
   c. Aflibercept
   d. All provide statistically similar visual outcomes

3. A patient with newly diagnosed center-involved DME presents with visual acuity 20/40. Which agent has had the least effect on retinal edema measured by OCT central subfield thickness?

   a. Aflibercept
   b. Bevacizumab
   c. Ranibizumab
   d. All are equally effective

4. According to Protocol T, the use of supplemental laser—on the basis of lack of improvement of visual acuity and/or edema—was not used until after _____ injections.

   a. 3
   b. 4
   c. 6
   d. 12

5. A patient presents with center-involved DME. Treatment is initiated with the dexamethasone intravitreal implant using the MEAD protocol. What is the probability of gaining ≥ 15 letters of visual acuity after 3 years of therapy?

   a. 10%
   b. 20%
   c. 30%
   d. 40%

6. In which of the following patients with DME would initial steroid therapy be least appropriate?

   a. Pregnant women with severe center DME and poor vision
   b. Patients with extrafoveal or juxtafoveal edema and good visual acuity
   c. Women seeking to conceive with severe center DME and poor vision
   d. Patients who are pseudophakic

7. In Protocol S, eyes with PDR treated with ranibizumab experienced _____ compared with eyes treated with PRP.

   a. More peripheral vision loss
   b. Worse safety outcomes
   c. More vitreous hemorrhages
   d. Similar visual outcomes

8. Which adverse event occurred more often in eyes with PDR treated with PRP than in those treated with ranibizumab?

   a. Visual field loss
   b. Vitrectomy
   c. DME
   d. All the above

9. When initiating anti-VEGF therapy for PDR, DME, or both, the typical treatment burden for year 2 compared with year 1 is best described as:

   a. More injections
   b. Fewer injections
   c. The same number of injections
   d. No further injections

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PROTOCOL T AND MORE FOR DR/DME: IMPLICATIONS FOR PRACTICE

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☐ Yes ☐ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

_____

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

- Apply key findings from pivotal clinical trials in DR/DME to patient management plans 5 4 3 2 1
- Outline individualized treatment plans for patients with DR/DME 5 4 3 2 1
- Incorporate imaging modalities into patient management for early detection, treatment, and monitoring 5 4 3 2 1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.

_____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
   4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes
   1 = definitely will not make any changes 4 3 2 1

Please describe the change(s) you plan to make: _____

_____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?_____
4. Number of patients I see per week with diabetic retinopathy (DR) ☐ 0 ☐ 1–5 ☐ 6–10 ☐ 11–25 ☐ >25 ☐
5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.
   ☐ Patient Care ☐ Practice-Based Learning and Improvement ☐ Professionalism
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6. What other topics would you like to see covered in future CME programs? _____

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1	2	3	4	5	6	7	8	9