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CME ACTIVITY

Management and Treatment of Diabetic Macular Edema After Protocol T

Participants:
Rishi P. Singh, MD, moderator
Mandeep Brar, MD
Mark Dunbar, OD
John W. Kitchens, MD

A CME activity jointly provided by Evolve Medical Education LLC, *New Retina MD, Retina Today,* and *Advanced Ocular Care.*
Supported through an unrestricted educational grant by Regeneron Pharmaceuticals.

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a Live CME Webinar held on March 7, 2016.

TARGET AUDIENCE

This certified CME activity is designed 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:

- Assess clinical studies involving new approaches to treat DME, with particular attention to the DRCR.net's Protocol T
- Differentiate existing DME intravitreal therapy options from recent primary and secondary treatments
- Evaluate treatment options and develop criterion/criteria on when to initiate or alter therapy
- Discuss case scenarios and apply data from recent clinical studies to better manage patients with DME

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Management and Treatment of Diabetic Macular Edema After Protocol T

A discussion that explores the clinical applications of treating diabetic macular edema based on findings from Protocol T.

Despite the existence of credible intravitreal options for diabetic macular edema (DME), the problem of detecting eye disease early to preserve and improve patients' vision remains a challenge. While the prevalence of diabetes in the general population has increased,[1] the rate of annual dilated eye exams for patients with diabetes remains subpar.[2] It is likely that patient loads will continue to expand; however, effective treatment supported by studies such as Protocol T is available and can slow the progress of disease. Screening, follow-up care, maintaining glycemic control, and therapeutic options are but a few of the topics discussed in this webinar.

—Rishi P. Singh, MD, moderator

EPIDEMIOLOGY OF DIABETIC RETINOPATHY

Rishi P. Singh, MD: By 2050, it is expected that as many as 1 in 3 US adults will have diabetes.[3] Why are we seeing such a large increase in the rate of diabetic patients?

Mandeep Brar, MD: I think there is a strong correlation between obesity and the incidence and prevalence of diabetes, specifically type 2 diabetes. This is a function of both decreased levels of activity and poor nutrition. High caloric intake at one time leads to an overwhelming burden on the pancreas. Unfortunately, the incidence of type 1 diabetes among adults is also on the rise. We are not sure why.

Dr. Singh: The parameters for diabetes have changed over the past few years. What changes might account for this sudden increase in the number of patients?

Dr. Brar: One of the most significant changes is not incorporating insulin use as part of the definition. We no longer say noninsulin-dependent or insulin-dependent diabetes, because there is quite an overlap in our treatment choices. We now define them as type 1 and type 2. Type 2 refers to patients whose condition was brought about by obesity and lack of exercise. Such patients may be able to start on oral therapy or single insulin plus oral therapy. A person with type 1 diabetes is defined as someone with 80% beta-cell damage that is acute in onset. These patients risk developing diabetic ketoacidosis and must be treated with insulin from the time of diagnosis.

Dr. Singh: These patients are frequently referred to our retina and optometrist colleagues. What changes have you noted in your clinical practices?

Mark Dunbar, OD: I have not noticed much of a change, because I am at a referral center. Consequently, the number of diabetic patients has always been rather high. I agree, however, with everything Dr. Brar said. We have certainly seen an increase in the obese population, which now includes children. Diet and lack of exercise are the issue. A report from the Centers for Disease Control indicated that 2014 was the first time there was a decline in the numbers, from 1.7 million diabetic patients in the United States in 2008 to 1.4 million in 2014.[4] It seems as though the message is getting through. School lunches are getting better, kids are starting to eat healthier meals. There seems to be an emphasis on getting away from the smartphones and the tablets and the video games and getting children to exercise.

John W. Kitchens, MD: I think we are seeing more diabetic patients at an earlier stage. There are multiple factors for this. I think the Affordable Care Act has been really great at helping some of our lower income patients get insurance, which has led to better screening. The National Committee for Quality Assurance's Healthcare Effectiveness Data and Information Set guidelines are now encouraging primary care doctors to ensure that these patients are being screened for complications associated with diabetes. I also think optometrists and general ophthalmologists are using some new technologies, specifically optical

coherence tomography (OCT), to diagnose these patients sooner and refer them. Also, I think we are doing a better job with awareness. We are not only seeing more of these patients, but we are also seeing them earlier in the course of disease.

TREATING DIABETIC PATIENTS

Dr. Singh: What are some of the systemic comorbidities associated with and treatments for diabetes?

Dr. Brar: The comorbidities are divided into two groups: microvascular and macrovascular events. Diabetic retinopathy (DR), nephropathy, and neuropathy are microvascular events. The most important for patients with diabetes are retinopathy followed by nephropathy, which involves damage to the kidneys mainly from elevated blood glucose levels. Diabetic neuropathy can lead to significant changes in quality of life because of tingling and numbness in the extremities, and it can lead to amputations. The macrovascular disorders—stroke and coronary artery disease—are more than 1.5 times higher in persons with diabetes than people without diabetes.[5] The American Diabetes Association (ADA) provides very clear guidelines on retinopathy prevention, including optimizing glycemic control and blood pressure to slow the progression of disease.[6]

Screening should include a comprehensive eye exam. Based on guidelines from both the ADA and the American Academy of Ophthalmology, we screen within 5 years of a diagnosis for type 1 patients and shortly after diagnosis for type 2 diabetics,[6,7] because these patients might have had prediabetes or undiagnosed diabetes for several years before a formal diagnosis is given. Screening should be repeated yearly, especially in patients with retinopathy or if there is a progression towards worsening retinopathy, or if their systemic disease is uncontrolled. Bear in mind that young type 1 diabetic patients who are going through puberty have additional pressure on the eyes owing to hormonal changes, which leads to wide variance in blood glucose control and may need screening sooner. Pregnancy, too, has a significant impact on baseline retinopathy. Fortunately, none of us is alone on the front lines. We have to approach care as a team. The family doctor, internist, and endocrinologist must make sure the patient sees an ophthalmologist. Optometrists must be comfortable when speaking with ophthalmology colleagues and retina specialists regarding potential treatments and the best options for their patients.

This is a very exciting time with regard to treatment for diabetes. Insulin therapy has been available for quite some time. Basal insulin and the rapid-acting insulin analogs have been implicated in weight gain. The thiazolidinediones (TZDs) have been associated with pedal edema (accumulation of fluid in the feet or lower legs).[8] The TZDs have received quite a bit of bad press owing to negative cardiovascular effects. From a retina viewpoint, higher doses of TZDs (>30 mg/day) have been shown to have a negative impact on retinopathy.[8] Dipeptidyl peptidase-4 (DPP-4) inhibitors are weight neutral. Among the best newer medications indicated for type 2 diabetics are the sodium-glucose cotransporter 2 inhibitors. These drugs decrease the patient's requirement for other medications to improve blood glucose control by lowering the threshold for glucose to pass through the kidneys.[8]

There are two classes of injectable noninsulin agents: the GLP-1 agonists, indicated for type 2 diabetes, which improve blood glucose levels and aid in weight loss; and an amylin analog, indicated for type 1 diabetes.

Basal insulins have also changed. In the past we only had glargine and detemir, but recently glargine U-300, a 24-hour insulin that does not require split dosing as glargine does, was approved. Several weeks ago, there emerged a longer-acting medication similar to detemir, known as insulin degludec. New among the rapid-acting insulin analogs is U-200 for patients who require higher doses of tranditional basal insulins. An inhaled insulin has been evaluated but did not achieve commercial success. There are several insulin pumps in use, and we are now expanding their use to type 2 diabetics.

> "I like to see patients with an A1C of 7.5 or more, as that gives me more room to use oral medications, minimize their use of insulin, and still get them to goal."
> —*Dr. Brar*

STUDY FINDINGS AND REAL-WORLD CLINICAL PRACTICE

Dr. Singh: The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study[9] randomized patients to one of three drugs for the treatment of DME. That study's patient base reflects what we find in clinical practice, where our patients have an average hemoglobin A1C level of 7.7. Dr. Brar, what do you think about those median A1C values? Do they represent patients in your clinical practice?

Dr. Brar: Patients whose A1C is 9 or more are usually referred to an endocrinologist. I like to see patients with an A1C of 7.5 or more, as that gives me more room to use oral medications, minimize their use of insulin, and still get them to goal.

Dr. Singh: When we see A1C values like this in clinical practice, you wonder whether the study findings and recommendations would pertain to your patient population. How do you approach this with patients in your own clinical practices?

Dr. Dunbar: Patients who know their blood sugar levels and A1Cs tend to be better informed, better educated, and seem to do a better job of keeping their numbers down. Patients who do not know or do not check their levels tend to have uncontrolled blood sugar.

I do wonder about access to medications under certain managed

care networks. Do patients have difficulty getting access to and coverage for some of these drugs? Are there any restrictions with regard to getting these drugs for a patient who might do well on them?

Dr. Brar: There is always a way to get medication for patients. The insurance company usually follows step therapy: if your patients fail on an older drug, they can progress to the next drug. Over 3 months, if you choose a DPP-4 that provides a less than 1% drop in A1C, but you need a 2% drop in A1C, you can transition your patient. It is important to remember that in a primary care setting, we delay almost a year in getting patients to the maximum dosage on a new prescription for diabetes before we use a second medication. Guidelines of the ADA[6] and the American Association of Clinical Endocrinologists[10] recommend stepping up the dose every 3 months before you add the next medication.

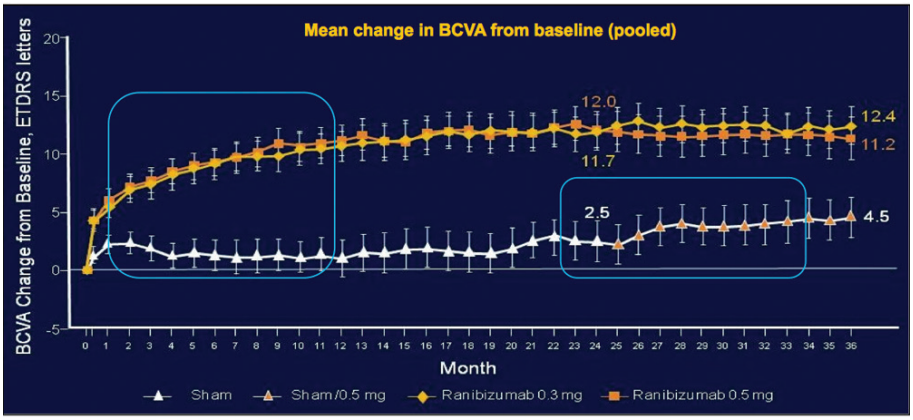

Figure 1. The RISE and RIDE study[15,16] found that treatment delays reduced the magnitude of the visual acuity benefits offered by anti-VEGF therapy.

Dr. Singh: Dr. Kitchens, how would you approach this with your patient?

Dr. Kitchens: If patients do not know their A1C, you should call their compliance into question, and not just with their current medication, but also with their injections or their compliance with future injections. If I see patients with proliferative retinopathy and they have no idea what their A1C or blood sugar levels are, I am more likely to add a panretinal photocoagulation to the initial visit to get their proliferative diabetic retinopathy under control for fear that they will not return for their follow-up appointments. The eyes provide a forum whereby we can talk to our patients about how blood sugars are damaging them. When patients see the OCT and what is happening to their macula, more importantly when they see ultra-widefield imaging results and areas of capillary nonperfusion and neovascularization, it helps them understand what is going on. These tests serve as educational and motivational tools.

Dr. Singh: A post hoc analysis for A1C of the RISE and RIDE trials[11] found that patients' A1C did not change much over a 3-year period (Figure 1). In fact, A1Cs have little impact on the final outcome so far as visual acuity and OCT thickness is concerned.

Let us talk about systemic control and how we can impact both DR and DME. The ACCORD study[12] was conducted on nearly 2,900 subjects who were evaluated over a period of 4 years. Patients were randomized to both intensive and standard glycemic control, dyslipidemia treatment, and intense systolic blood pressure control (targets of <120 or <140 mm Hg). Intensive glycemic control and dyslipidemia control slowed the progression to retinopathy in these patients.

The FIELD study[13] examined the effect of fenofibrate treatment for hyperlipidemia on patients' progression toward DR. Treatment with fenofibrate reduced the need for laser treatment for DR. These three studies contributed to a body of evidence demonstrating that systemic control of A1C and blood pressure is important, and that we should consider this when managing patients with type 2 diabetes. In light of these studies, how do endocrinologists approach such patients?

Dr. Brar: I first examine the basics and how I can help patients understand why blood glucose control is so important. I make sure they know what their A1C is and then prepare a two-step goal for them. Goal No. 1 is to reduce their A1C to 7%. Goal No. 2 is to reduce it as close to 6% as possible, without resulting in low blood sugar. It is important that patients know what the endpoints are and feel as thought they are participating in the process, rather than blindly taking a prescription. There are data showing that TZDs increase the risk of macular edema in patients with type 2 diabetes.[14] If DR has not stabilized with optimization of A1C and blood glucose control then I will look if TZD with dose greater than 30 mg/daily is on the medication list, which can be discontinued, as well as initiation of fenofibrate, if the lipid panel is not at goal. First and foremost, I would spend time discussing these matters with the patient to ensure he or she understood what the ophthalmologist, optometrist, or the retina specialist had said.

Dr. Singh: Does everyone recommend that the primary care physician or the diabetologist stop the TZD drug?

> "If patients do not know their A1C, you should call their compliance into question, and not just with their current medication, but also with their injections or their compliance with future injections."
> —*Dr. Kitchens*

Dr. Dunbar: I have not, mainly because I had not really been aware of the data surrounding it. Electronic health records, however, have made it easier on the physician to know exactly what medications patients are taking.

Dr. Kitchens: We looked at this issue in the RIDE and RISE study;[12,15,16] however, we did not really see an effect of fenofibrate on macular edema.[17] Despite this data, I think the jury is still out. I know I am much more capable of treating DME now that we have the anti-VEGF therapies. I am reluctant to tinker with what is working for these patients from a systemic standpoint. Currently, we have so much control with anti-VEGF therapy that I leave the oral and insulin medications to the primary care doctors and endocrinologists. My primary concern is macular edema.

Dr. Dunbar: Whether you are an optometrist or an ophthalmologist, one of the most important things you do with a diabetic patient is to get a stereoscopic view of the retina at the slit lamp, usually with a 90-D lens or 78-D lens. I look at the optic nerve and try to determine if there is neovascularization of the disc. I scan the retina and try to determine the extent of the retinopathy, whether it is nonproliferative or proliferative. Both optometry and ophthalmology do a good job of classifying the extent of the retinopathy and recommending care accordingly. The vast majority of patients will have varying stages of nonproliferative disease. We typically follow patients with mild to moderate nonproliferative disease yearly and for severe nonproliferative retinopathy every 3 to 4 months according to preferred practice pattern guidelines. For most optometrists, I think the threshold for referring a patient to a retinal specialist really occurs with severe nonproliferative DR because of the increased risk of progression to proliferative disease.

I was recently asked by one of our optometry residents to look at a patient who had proliferative retinopathy. I was not surprised that despite significant retinal neovascularization, the patient still had very good central visual acuity. That said, whether it is nonproliferative disease or proliferative disease, macular edema can present at any stage of disease. With the evolution of OCT and anti-VEGF therapy, it is interesting how our definition of macular edema has evolved. We have become less concerned about "clinically significant macular edema" but more concerned about center-involved macular edema. OCT has been instrumental in helping optometrists and ophthalmologists diagnose with greater accuracy. With the evolution of treatments and refinement of technology, we can do a better job of identifying and diagnosing patients.

The greatest advances have occurred in posterior segment imaging. Fundus photography can capture an incredibly high-resolution fundus photograph that has become almost a standard for baseline exams. This technology allows us to determine the presence of disease and show patients their progress through various stages of disease. Seeing changes in their retina serves as a great teaching tool for patients and helps them understand the severity of their disease. They can see the presence of bleeding or cotton wool spots and ischemia for themselves. Fluorescein angiography has traditionally remained in the hands of the ophthalmologist. The development of widefield angiography allows us to diagnose capillary nonperfusion and ischemia better than ever.

It will be interesting to see how OCT angiography does in the primary care optometric office. The idea is to diagnose retinopathy patients at an early stage of the disease and help both the patient and doctor understand what is happening on a microvascular level. More and more, OCT is being incorporated as part of the basic screening exam. This might warrant a higher fee, but it is more than offset by detecting early macular edema and getting patients to see a retina specialist in a timely manner.

The dilated fundus exam is the standard of care even in the optometric practice. Most state laws mandate or require that a patient, especially diabetic patients, have a dilated fundus exam. The importance of a dilated fundus exam cannot be overstated. It allows the ability to recognize subtle retinopathy that cannot be seen through an undilated pupil. Even utilizing high-resolution fundus photography can be invaluable, and may help to identify high-risk patients earlier.

Before we had OCTs, you had to rely more on your clinical skills and abilities to detect DME. This required a clear view and excellent stereoptics. In the OCT era, the ability to diagnose and capture DME in patients has become easier. Add the anti-VEGF agents to treat DME and there is really no reason why these patients should be falling through the cracks.

Dr. Singh: Outside of the eye care field, what do clinicians do to determine if patients have had their retinopathy examinations?

Dr. Brar: We use a three-step process in all of our diabetes clinics. The first step occurs when they check in. We ask them for their meter or pump, and at the same time we also ask them if they have had an eye exam and, if so, when. If it was done within the last 12 months, we have them sign a records release and fax it in to the optometrist or the ophthalmologist. The second step involves confirmation by the medical assistant that they have an eye exam within 12 months. If not, we provide a referral for a diabetic eye exam. We have learned the importance of specifying

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> —*Dr. Singh*

a diabetic eye exam because patients do not always divulge that information when they go in for their eye exam and then wind up not having their eyes dilated. The third step involves having the endocrinologist review orders, prescriptions, labs, and referrals with the patient, in this case the need for a diabetic eye exam referral. We explain to the patient that dilation of the pupil is very important for getting the best and most complete view of the retina. We sometimes add a fourth step, and that is having a quality team hunt patient's records down for us if the requested records are not provided.

Dr. Singh: Dr. Dunbar, you gave us some really great examples of all the modalities we have. In clinical practice, what do you use to screen and identify patients with diabetic eye disease who need treatment?

Dr. Dunbar: First and foremost, we dilate all of our patients. I use my 90-D lens at the slit lamp to evaluate the nerve, posterior pole, and macula. I also use indirect ophthalmoscope with my 20-D lens to look at the peripheral retina. If a patient has DME or I suspect DME, I order an OCT to help make or confirm a diagnosis.

There is an interesting debate on whether to use the OCT, and/or ultra-widefield angiography imaging or fundus imaging to screen patients. Some eye care providers do and build the cost for imaging into their exam fee. Without a doubt, we have many imaging modalities at our disposal. The question is whether it is appropriate to use them as screening devices for all patients.

Dr. Singh: Dr. Kitchens, which of these modalities or combination of modalities offers the greatest sensitivity for identifying a patient with treatable disease?

Dr. Kitchens: I would say the highest sensitivity of any test for DME is offered by the OCT. It has great sensitivity and specificity, particularly for determining whether there is center-involved DME. When you are talking about sensitivity and specificity for looking at vision-threatening retinopathy, particularly proliferative retinopathy, I think nothing exceeds ultra-widefield angiography with an Optos or a Heidelberg Engineering device. These devices provide more than most of our patients need. As retina specialists, we see the highest risk patients, the patients who obviously have disease. If I were in a primary care eye clinic, the first test I would conduct is the dilated fundus examination. Any signs of retinopathy could then be confirmed on the OCT. In those patients with DME or severe nonproliferative diabetic retinopathy, I would refer them to a retina specialist for evaluation. Having used ultra-widefield angiography for 8 years, I can tell you that the clinical exam alone is not always indicative of the level of disease present—specifically nonperfusion and areas of "occult" neovascularization of the retina.

PREVENTING DIABETIC EYE DISEASE

Dr. Singh: The major issue for most of us right now is that the majority of patients do not get a dilated eye exam. In fact, 40% of patients think there is no need for one.[18] We also need to address patients' concerns with cost or lack of insurance. They do not understand the importance of dilation and consequently become prey to treatment delays.

The RISE and RIDE study[15,16] found that treatment delays reduced the magnitude of the visual acuity benefits offered by anti-VEGF therapy. Patients who were introduced to anti-VEGF therapy 2 years after their initial diagnosis did not achieve the same improvement in visual acuity as those patients who were treated initially with anti-VEGF and followed for a period of time. Early anti-VEGF injections, especially within that first year or even second year, are very important for optimizing outcomes. What strategies have you employed to improve the screening mechanisms we have in place?

Dr. Brar: We must first make sure that we communicate with the patient and see that they have a referral. We are never going to be in the front lines. We also need to provide a service for our primary care associates by training their medical assistants to recognize patients with diabetes and make sure the eye exam referral is in place. The patients need to know why we are doing this and why it is important.

Dr. Dunbar: We have the Diabetic Research Institute as part of the University Miami Health system, and I always viewed that clinic as the front line. Ideally, all their patients should have some form of nonmydriatic fundus photography. With that information we would be able to identify every patient who walks in the door with potential retinopathy. Those with retinopathy or even visual threatening retinopathy could be seen for a comprehensive eye exam. Instead, many patients fall through the cracks.

Either way, I think all our diabetic patients need to hear about the importance of blood sugar control, maintaining appropriate A1Cs, good blood pressure control, whether from their endocrinologist or their eye care provider, as often as possible.

Dr. Kitchens: I agree. We are on the back end of things when it comes to screening. One thing that does improve screening is to dictate letters back to the endocrinologist or the primary care doctor, even if they did not refer the patient to you. If they know what is going on in their patient's eyes, it will improve management. I think knowing that the patient has been taken to the next level of care encourages the endocrinologist and the primary care doctor to do the same. They now know their patient has end-organ disease. It gives them insight into how the years of high glucose levels has affected their patient.

We do need to educate patients about the importance of imaging. I think we also need to give these patients a message of hope. Many times, diabetic patients are told time and time again that they are only going to get worse and that their kidneys will eventually fail. We can make a huge difference and prevent increased vision loss. The Protocol T data[9] show that we can restore their vision, we can reverse their retinopathy, and we can do some really miraculous things with these drugs.

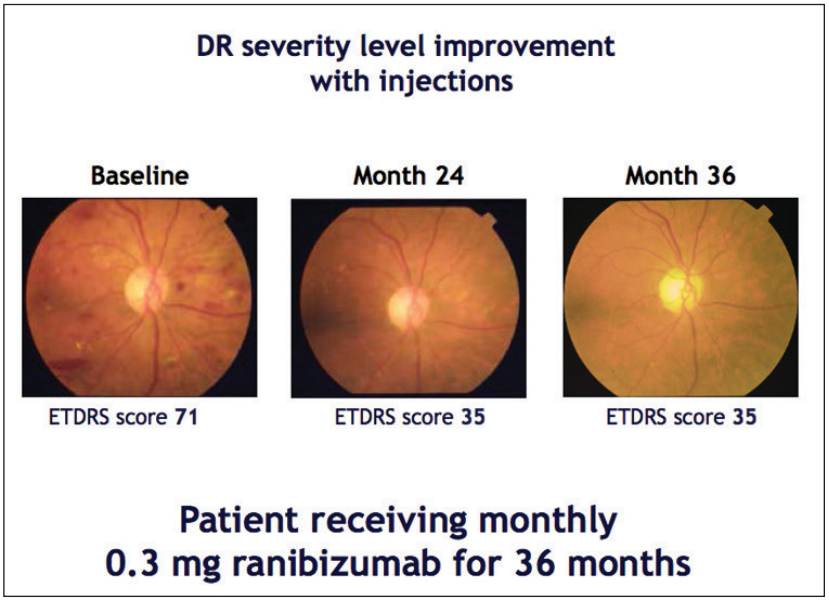

Figure 2. The retina looks fairly normal at month 36 with no signs of retinal hemorrhage.

Dr. Singh: We currently have many different treatment options for DR and DME, including anti-VEGF drugs, steroids, laser treatments, and vitrectomy in end-stage cases. Anti-VEGF can be given as an approved therapy, such as ranibizumab and aflibercept, or as an off-label treatment bevacizumab, which has been widely used. Although it is less expensive than the other two drugs, bevacizumab requires preparation through compounding pharmacies.

Widefield imaging has allowed us to view an entire nonperfused area of the retina. We have found a VEGF drive in diabetic patients that is causing them to develop proliferative disease. If you give rhesus monkeys with normal retinas intravitreal VEGF injections, they develop a state of retinopathy and DME.[19] That is how we were able to implicate VEGF in clinical studies and show that we can reduce the progression of retinopathy over time. RISE and RIDE trials looked at two different doses of anti-VEGF and showed that the rate of progression to proliferative disease was significantly lower in patients who received anti-VEGF monthly for a period of 24 months versus the sham-treated patients, who had a much higher rate of progression of retinopathy over time.[15,16,20] Continued ranibizumab therapy offered impressive improvements in a patient's Early Treatment Diabetic Retinopathy Study (ETDRS) scores over 36 months.[15,20] In Figure 2, the retina looks fairly normal at month 36 with no signs of retinal hemorrhage. These are breakthrough therapies for the treatment of DR and DME.

TWO-YEAR FINDINGS OF PROTOCOL T

Dr. Kitchens: The reversal of retinopathy has been critical with these drugs. The DRCR.net's Protocol S study actually showed that anti-VEGF therapy with ranibizumab was noninferior to the panretinal photocoagulation laser for proliferative disease,[21] which is a remarkable feat. Thus, the DRCR.net has been instrumental in answering questions such as whether intravitreal steroids or anti-VEGF therapies are more effective and whether we should combine laser treatment with anti-VEGF therapy, or whether cataract surgery worsens macular edema. We need some predictive measures to determine how our patients will fare. One of the most critical questions Protocol S answered was to identify which anti-VEGF therapy would be most effective for patients with center-involved DME.[21] The DRCR.net designed the Protocol T study with this in mind.[9]

Protocol T provides the first head-to-head comparison of all three commonly used anti-VEGF agents—aflibercept, bevacizumab, and ranibizumab—for the treatment of DME.[9] Change in visual acuity at 1 and 2 years was the primary outcome. In year 2, we examined patients every 4 to 16 weeks, depending on how they were doing and what treatment they were receiving.[22] These patients were allowed rescue laser treatment 6 months into year 1. After publication of the 1-year primary results, physicians and patients were unmasked to the treatments. Close to 90% of patients completed year 2, allowing us to answer many critical questions. The comparisons between year 1 and year 2 are quite interesting.

Keep in mind that we used US Food and Drug Administration-approved doses for the United States: aflibercept 2.0 mg; bevacizumab 1.25 mg, which is used off-label for the treatment of DME both in the United States and internationally; and ranibizumab, 0.3 mg, which is lower than the usual non-US dose of 0.5 mg.

At the end of year 1, all of the anti-VEGF therapies worked very well. On average, patients randomized to aflibercept gained 13 letters of visual acuity, ranibizumab 11 letters, and bevacizumab 10 letters.[9]

These findings confirmed once again that anti-VEGF therapy was the gold standard for treatment and should be used as first-line therapy. We knew this from Protocol I,[23-25] from RISE and RIDE,[15,16] and VIVID and VISTA.[26]

The only statistically significant difference occurred between aflibercept and bevacizumab. Bevacizumab and ranibizumab were very close. All patients did rather well if they had 20/40 vision or better, which is the ETDRS best corrected vision. They all gained 7.5 to 8 letters at the end of year 1. In patients who actually had visual acuity of 20/50 or worse, we saw a striking difference between aflibercept, ranibizumab, and bevacizumab at the end of year 1: the aflibercept group gained almost 4 lines, the ranibizumab group gained 3 lines, and the bevacizumab group gained 2.5 lines of visual acuity.

By year 2, the gap narrowed, particularly between aflibercept and ranibizumab.[22] At the end of year 2, patients treated with aflibercept gained 12.8 letters, ranibizumab 12.3 letters, and bevacizumab 10 letters of visual acuity (Figure 3). It was reassuring to learn that the aflibercept groups maintained their excellent visual acuity gains. Patients treated with ranibizumab and bevacizumab continued to improve. No drop off occurred in year 2.

Patients in the aflibercept and ranibizumab groups were given five injections, and patients in the bevacizumab group were given six injections. Patients did generally well with the decreased dosing frequency. They received a few more injections in year 2 than what we saw in DRCR.net Protocol I, where patients were given an average of three injections in the second year.[9,22,25]

Patients with good visual acuity (20/40 or better) gained about 7 to 8 letters on average across the board. There were no major differences between drugs with regard to statistically significant gains in visual acuity. Part of the reason we do not see greater gains in vision is due to a ceiling effect. The treatments afford only so much gain.

In patients with the poorest vision (20/50), we saw a sizable difference in year 1 between those treated with aflibercept and those treated with ranibizumab; however, this gap narrowed in year 2. Patients treated with ranibizumab gained a few more letters in year 2. Patients in the aflibercept group maintained their gains over the 2 years. Patients treated with bevacizumab started to improve by the end of year 2 (Figure 4). There was a difference between both ranibizumab and aflibercept over bevacizumab; however, in year 2, it was not statistically significant.

In the clinic, we see patients who were switched from bevacizumab to aflibercept or ranibizumab become drier. So our clinical experience tells us that these numbers are probably correct.

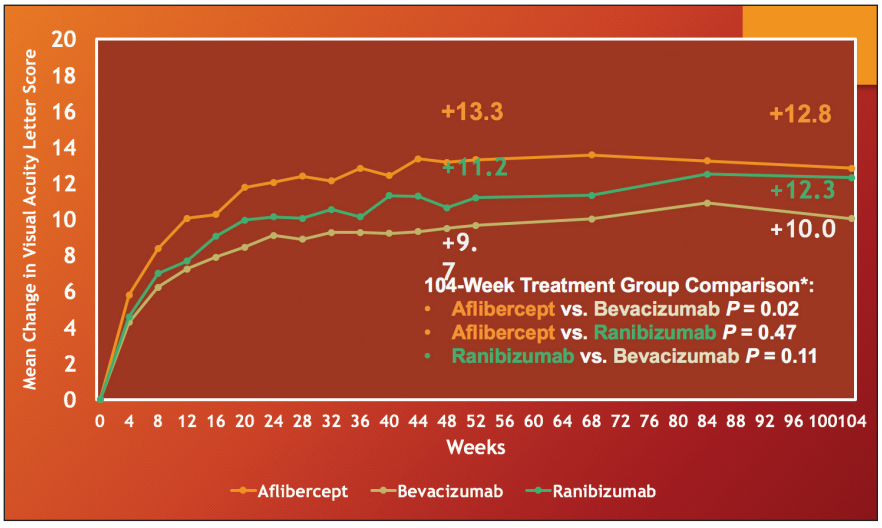

Figure 3. At the end of year 2, patients treated with aflibercept gained 12.8 letters, ranibizumab 12.3 letters, and bevacizumab 10 letters of visual acuity.

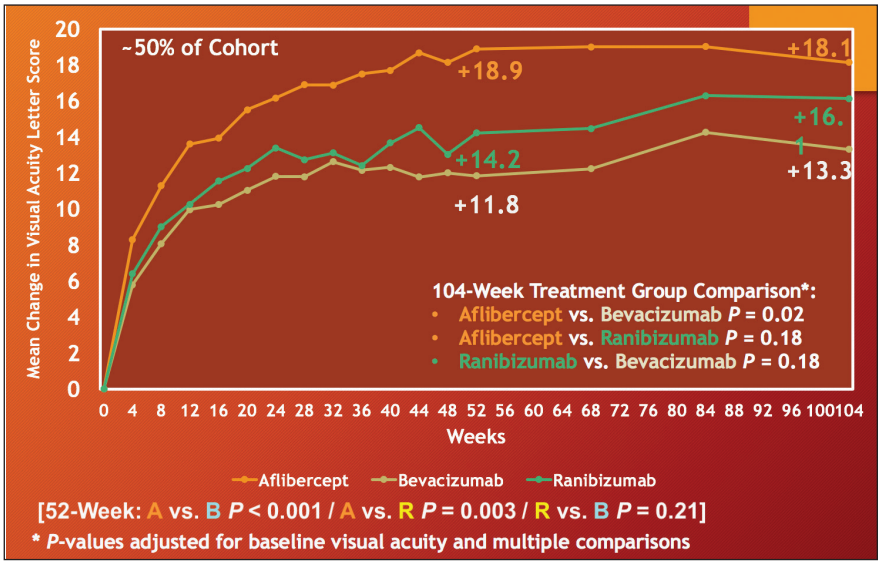

Figure 4. Patients treated with bevacizumab start to improve by the end of year 2.

Dr. Singh: How did Protocol T impact your management of patients, Dr. Kitchens?

Dr. Kitchens: I find it reassuring that all three of these medicines work very well. This helps our decision-making. Our practice now uses more aflibercept owing to the year-1 findings. We will probably find it useful to treat more patients with ranibizumab, since the year-2 findings evened the playing field, and bevacizumab is less costly than aflibercept and ranibizumab. Nonetheless, ranibizumab

is about 60% the cost of aflibercept per injection. So for patients who want an on-label therapy, ranibizumab represents a greater cost savings.

Dr. Singh: I also was impressed with how the gap between aflibercept or ranibizumab narrowed in the second year, and the results were achieved without any ill effects. In the year-2 data, you saw almost no difference in the number of injections, where the gap tightened as well. There was also no difference in visual acuity between those two groups. I think this actually is closer to what we see in clinical practice. I also agree that the on-label drugs appear to do a better job than the off-label drug. I found these data a validation, especially in patients with worse visual acuity.

I would like to put this into context, however. These are ETDRS protocol visual acuity measurements. So they are actually 20/50 on ETDRS, but 20/70 or 20/80 by Snellen acuity.[27] There were no concerns with safety during the study. Can you comment on some of the safety issues in the study?

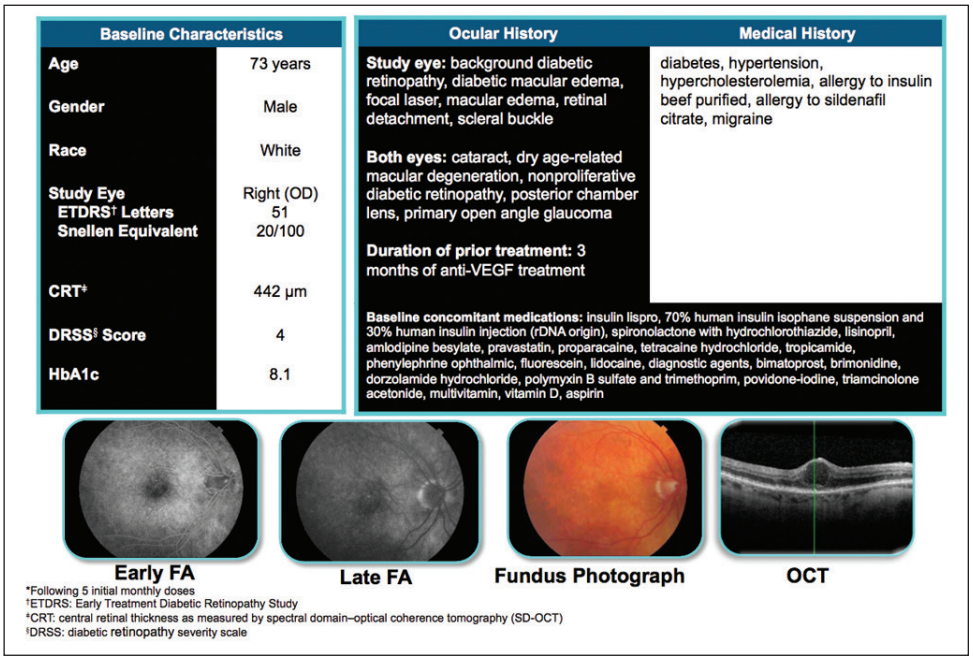

Figure 5. Baseline characteristics of a 73-year-old man with 20/100 visual acuity (Snellen equivalent), central retinal thickness of 442 µm, and an A1C of 8.1 on entry.

Dr. Kitchens: In the Antiplatelet Trialists' Collaboration endpoints (eg, arteriothrombotic events, stroke, and heart attack), we did see a difference in the three different anti-VEGFs. There was a 5% rate for aflibercept, 8% for bevacizumab, and 12% for ranibizumab.[9,22] None was clinically significant. I think it is really important to put this into context. It makes no scientific sense that ranibizumab would cause more systemic side effects. As I said, the occurrences were not statistically significant, but it does not make scientific sense that an agent with a shorter half-life would cause these events. We have great data from Robert Avery, MD, who has shown the effects of anti-VEGF therapy on systemic VEGF levels.[28] Ranibizumab is safe and clears very quickly from the system. The differences we saw in the 2-year data appear, in my opinion, to be an anomaly.

Dr. Singh: Was there consistent concordance between OCT and visual acuity or did some DME patients have a great OCT but poor visual acuity?

Dr. Dunbar: I think there was generally good concordance. In DME, the visual acuity will often be reduced. There are very rare instances where you can have retinal thickening or DME and still have good acuity, unless it is obviously outside the center of the fovea. I think that is why OCT is such a great diagnostic tool. It has the ability to recognize early thickening that is often correlated with patients' visual acuity.

"...OCT is such a great diagnostic tool. It has the ability to recognize early thickening that is often correlated with patients' visual acuity."
—Dr. Dunbar

Dr. Singh: Figure 5 shows the baseline characteristics of a 73-year-old man with 20/100 visual acuity (Snellen equivalent), central retinal thickness of 442 µm, and an A1C of 8.1 on entry. Figure 6 shows his status at week 52 of treatment. This patient's study eye had been previously treated and his fellow eye had a detached retina. The patient is currently on 70/30 insulin suspension spironolactone hydrochlorothiazide, lisinopril, amlodipine, and pravastatin for cholesterol. Comments on this patient's overall medical history and the treatment regimen? Are there any significant concerns or suggestions you might have in managing this patient better?

Dr. Brar: In an older patient, we would have an A1C goal of 7% or less, or as close to 6% as possible. We also know that as patients age, we do not want them to become hypoglycemic and might aim for an A1C of 7% to 7.5%.

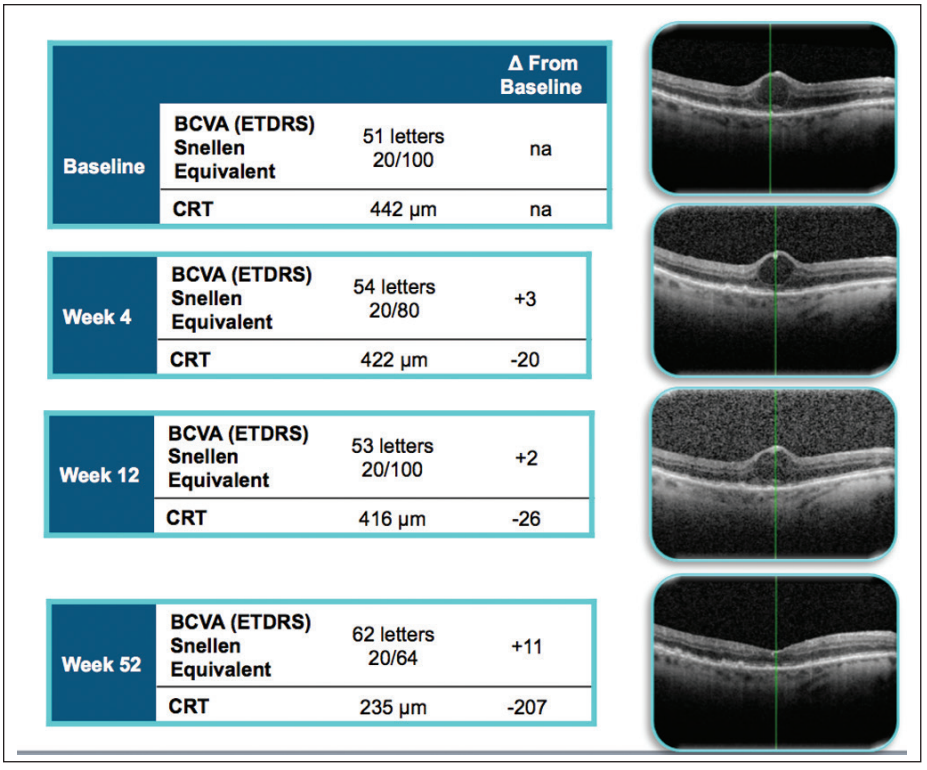

Figure 6. At week 52, there was a huge improvement in retinal thickness and an equally huge gain in visual acuity.

From a medication standpoint, the fixed, split-mixed insulins are not necessarily ideal. The prescribed insulin contains a 70% intermediate-acting insulin, plus 30% of a rapid-acting insulin administered with a single injection. Though this decreases the number of injections required, we cannot adjust the dose of one specific insulin—intermediate or rapid acting—without adjusting the dose of the other component as well, which leads to either inability to attain goal blood glucose control or a higher risk of hypoglycemic events. We all know that hypoglycemia does not benefit the eye and the lowest possible A1C is also preferred. I would definitely consider using technology, such as insulin pump therapy, to administer basal-bolus insulin without increasing the number of injections required.

Dr. Singh: Dr. Dunbar, you look at the patient's OCT and you see a large central cyst. There is not much leakage, but certainly enough leakage to cause the OCT edema. Do we still rely on OCTs to diagnose DME these days?

Dr. Dunbar: It is an interesting case, because you look at the fundus photograph and you do not see a lot of retinopathy. This patient might even have some cataract formation that makes it difficult to get a good view of the retina. The challenge is determining if the level of acuity at 20/100 is from DME or cataracts. The OCT in this case really nails it. This patient would be sent immediately to the retina practice for an anti-VEGF injection.

Dr. Singh: This patient was given an anti-VEGF injection. The first three injections after the first 3 months did not really change things. In fact, retinal thickness was reduced only by 26 µm, and the cystic change remained on the retina. At week 52, however, there was a huge improvement in retinal thickness and an equally huge gain in visual acuity. Is this a common occurrence in clinical practice? And what do you do when you see something like this?

Dr. Kitchens: I usually tell our fellows to look for some improvement after the first injection or second injection to see if a patient is responding. You cannot discern where the leakage is in patients whose angiogram does not show significant leakage. The angiogram also made clear that the focal laser would not prove useful in this case. Usually a very large central cyst can take months, if not years, to respond. The message here is that you should not give up on a patient like this. It took 52 weeks for this patient to show a decent anatomic response.

Dr. Dunbar: Would you vary treatment between anti-VEGF drugs, and if so, how often?

Dr. Kitchens: I would do three injections in a row and keep my eyes on the monthly OCT results. If by week 12 there was no anatomical improvement, I would talk to the patient and tell him or her that if I did not see any improvement by the next visit, it might be time to switch to another class of medicaiton, such as an intravitreal steroid injection.

Dr. Singh: Can we apply the findings of Protocol T to our clinical practices? Is the patient who walks into your clinic the same who was treated in the Protocol T study? Do the study findings apply to the typical patient?

Dr. Kitchens: Generally speaking, I think we can apply these findings. We do have some center-involved patients with good visual acuity. Most of my patients are 20/50 or worse. I do not think the treatment protocols and the particular patient populations of any of the major studies—Protocol T[9] and even Protocol I,[23,24] RISE and RIDE,[15] or VIVID and VISTA[26]—exemplify patients and practices in the real world. Frankly, I think we undertreat our patients. Retina specialists need to ask themselves how frequently they are treating their patients. They need to ask themselves if they are undertreating them. I believe most retina specialists are only treating similar patients 5 to 6 times a year versus nine treatments in the first year and six treatments in the second year as demonstrated successfully by Protocol T.[22]

Dr. Singh: In the patient featured in Figures 5 and 6, there was an 11-letter improvement from baseline and a 207-µm improvement in retinal thickness at 52 weeks. These data illustrate continual improvements with anti-VEGF therapy.

We have been able to show that intensive glycemic control and control of blood pressure and dyslipidemia all affect DR. Fortunately, we have highly effective treatments that can significantly reduce vision loss and improve visual outcomes. It is important that optometrists, endocrinologists, and retina specialists work together to make sure our patients have the best possible results.

Dr. Brar: I would emphasize your point on interprovider communication and include patients in that conversation. Communicate with patients and their families, keep us all talking with each other. Engagement is essential to helping patients buy into the treatment plan and goals.

Dr. Dunbar: The more voices our patients hear, the more they know that we care about them and want the best for them. The interprofessional relationship becomes the key. Optometrists in particular want to comanage with the ophthalmologist and the endocrinologist.

Dr. Kitchens: Anti-VEGF therapy has proved a game changer, not just for DME, but also for proliferative disease. These treatments only work, however, when patients comes to our offices and are treated appropriately. Our responsibility in the medical profession, is to do a better job with screening. We have got to make sure these patients have dilated funduscopic examinations. We must make sure that, at the first sign of vision-threatening disease, patients see a retina specialist and receive treatment.

Dr. Singh: Protocol T demonstrates yet again what fantastic treatments we have for patients. While they differ from each other, aflibercept or ranibizumab have proven superior over bevacizumab for DME. We are going to learn a great deal more from this rich data set, particularly after the substudies have been conducted and when more of our questions have been answered. Does A1C matter? Do baseline factors matter? Which patients will most likely respond to therapy? Are there vision cutoffs for treatment? Is it 20/100 or worse, 20/200 or worse? I look forward to having continued data from Protocol T guide us in managing our patients. ■

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MANAGEMENT AND TREATMENT OF DIABETIC MACULAR EDEMA AFTER PROTOCOL T
CME QUESTIONS

1 *AMA PRA Category 1 Credit™* Expires June 2017

1. **A report from the CDC indicated that 2014 was the first time:**
   a. The number of new cases of type 1 diabetes eclipsed the number of new cases of type 2 diabetes
   b. The number of new cases of type 2 diabetes eclipsed the number of new cases of type 1 diabetes
   c. There was an equal number of new cases identified between type 1 and type 2 diabetes
   d. There was a decline in the number of new cases of diabetes

2. **Based on guidelines from the ADA and the AAO, how often should a person with diabetes be screened?**
   a. Immediately after diagnosis for type 1 patients
   b. Shortly after diagnosis for type 2 patients
   c. Within 2 years for type 1 patients
   d. Within 2 years for type 2 patients

3. **Which of the following treatments for diabetes has been associated with a negative impact on DR?**
   a. Basal insulins
   b. Glargine
   c. Thiazolidinediones
   d. Detemir

4. **In RISE and RIDE, a post hoc analysis found:**
   a. Patients' A1C did not change much over a 3-year period
   b. Patients' A1C levels have a substantial impact on visual acuity over a 3-year period
   c. Patients' A1C levels have a substantial impact on OCT thickness over a 3-year period
   d. Using intravitreal anti-VEGF agents reduced A1C levels over a 3-year period

5. **Which of the following is recommended during eye exams on diabetic patients?**
   a. Slit lamp view of the retina
   b. Optical coherence tomography
   c. Fluorescein angiography
   d. Fundus photography
   e. All of the above
   f. None of the above, unless requested by referring physician

6. **The DRCR.net's Protocol S found:**
   a. Ranibizumab was superior to focal laser for the treatment of DME
   b. Ranibizumab was noninferior to the PRP laser for proliferative disease
   c. Aflibercept and bevacizumab were noninferior to ranibizumab for the treatment of DME
   d. Aflibercept was noninferior to the PRP laser for proliferative disease

7. **According to the results from Year 1 of Protocol T, what was the average letters of vision improvement?**
   a. Aflibercept, 10 letters; ranibizumab, 11 letters; and bevacizumab, 13 letters
   b. Aflibercept, 10 letters; ranibizumab, 13 letters; and bevacizumab, 11 letters
   c. Aflibercept, 11 letters; ranibizumab, 13 letters; and bevacizumab, 10 letters
   d. Aflibercept, 13 letters; ranibizumab, 11 letters; and bevacizumab, 10 letters

8. **What were the visual acuity results from Protocol T, year 2?**
   a. Unchanged from the year 1 results
   b. All three anti-VEGF drugs improved vision by the same number of letters
   c. Aflibercept and ranibizumab improved vision by about the same number of letters
   d. Ranibizumab and bevacizumab improved vision by about the same number of letters

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Assess clinical studies involving new approaches to treat DME, with particular attention to the DRCR.net's Protocol T	_____	_____	_____
Differentiate existing DME intravitreal therapy options from recent primary and secondary treatments	_____	_____	_____
Evaluate treatment options and develop criterion/criteria on when to initiate or alter therapy	_____	_____	_____
Discuss case scenarios and apply data from recent clinical studies to better manage patients with DME	_____	_____	_____

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Name and email _____

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_____

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Rate your knowledge/skill level prior to participating in this course: **5 = High, 1 = Low** _____

Rate your knowledge/skill level after participating in this course: **5 = High, 1 = Low** _____

Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.

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