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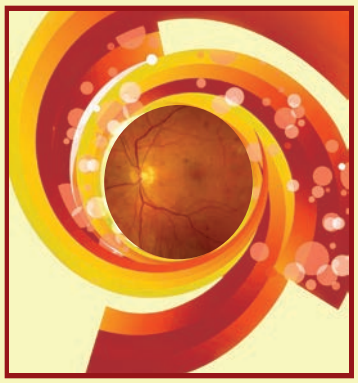

Current Management of Diabetic Macular Edema and Diabetic Retinopathy

A Multidisciplinary Discussion of Clinical Cases

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Target Audience

This activity intends to educate retina specialists, retina fellows, and comprehensive ophthalmologists caring for patients with DR/DME.

Learning Objectives

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

- Recognize the importance of individualized glycemic control in optimizing outcomes for patients with DR/DME
- Discuss the utility of different diagnostic imaging techniques in guiding the management of patients with DR/DME
- Describe the efficacy, dosing, and safety profiles of current and emerging treatment options for DME
- Confidently tailor diagnostic and treatment strategies for various patients with DR/DME
- Communicate effectively with referring physicians regarding the relevant systemic and ophthalmic health issues of their mutual patients with DR/DME

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Introduction

Optimal management strategies for patients with diabetic retinopathy (DR) and diabetic macular edema (DME) continue to evolve at a rapid pace. Careful consideration of numerous patient factors and treatment options is essential to the generation of positive visual outcomes. To that end, we convened a multidisciplinary panel to discuss current approaches to successful management of patients with DR or DME. We have selected several challenging case scenarios that will highlight management options such as laser photocoagulation, anti-vascular endothelial growth factor (VEGF) therapies, intravitreal steroids, and glycemic control.

—Quan Dong Nguyen, MD, MSc

Glycemic Control Strategies

Dr Peters: The recently published position statement of the American Diabetes Association (ADA) for the treatment of type 1 diabetes mellitus addresses this condition across the life span,[1] and although we think of type 1 diabetes as a predominantly pediatric disease, it can develop at any age. In the United States, there are as many as 3 million patients with type 1 diabetes,[2] with approximately 167,000 of them being children or youths.[3] Historically, HbA_{1c} targets for children were higher than those for adults because of the premise that severe, recurrent hypoglycemia in children was associated with neurocognitive compromise,[4] and that childhood was protective with respect to hyperglycemia.[5,6] The concerns pertaining to hypoglycemia and neurocognitive problems have been allayed,[1,7,8] and early hyperglycemia and glucose variability may pose risk to the central nervous system.[9]

On the other hand, people with type 1 diabetes used to die before they reached advanced age because of hypoglycemia and other complications. Now, patients with type 1 diabetes are living longer.[10,11] We have lowered pediatric targets and raised targets for older adults.[1] Our knowledge about type 1 diabetes is ever increasing, and we are doing more type 1-focused research.

Clinical evidence has supported the benefits of glycemic control for patients with type 1 diabetes, with studies such as the Diabetes Control and Complications Trial (DCCT), which showed unequivocally that for the pathognomonic complication for type 1 diabetes, DR,[12] there is tremendous benefit associated with intensive therapy. In the primary-prevention cohort of the DCCT, there was a 76% reduction in the adjusted mean risk for retinopathy development for those patients who received intensive therapy.[12] With respect to the secondary-intervention cohort, the progression of retinopathy was slowed by 54%, and the development of proliferative or severe nonproliferative retinopathy was reduced by 47%.[12] Benefits were greater in those patients who started intensive therapy earlier.

It is extremely difficult to achieve the same level of glycemic control in patients with type 1 diabetes in the world outside of clinical trials, because patients are trying to balance high and low blood sugars often without the assistance of expert diabetes clinicians. When the individuals in the control arm of the DCCT were made aware of the data from the trial, they lowered their HbA_{1c} levels from a median value of 9.1% to 8.2%, where they then remained.[13] The patients who were tightly controlled during the trial found it too difficult to maintain their HbA_{1c} levels at 7%, even with the tools and resources made available to them. Without the active conditions of the trial, the median HbA_{1c} levels of the intensively treated patients went from 7.2% to 7.9%.[13]

From these results, the phenomenon of metabolic memory was noted. If a patient's HbA_{1c} is 9% for 10 years and is subsequently lowered to 7% for the next 10 years, the risk for microvascular and macrovascular complications is much worse than if the HbA_{1c} starts out at 7% for the first 10 years and then increases to 9% for the second 10 years. There is something about that first phase of diabetes during which if tight control is achieved, long-term outcomes are improved. This is what was observed in the sustained follow-up to the DCCT and the Epidemiology of Diabetes Interventions and Complications (EDIC)—the intensive therapy group continues to do better for many years. In a recent study, the risk for further progression of retinopathy, progression to proliferative diabetic retinopathy (PDR), clinically significant macular edema, and the need for intervention (photocoagulation or anti-VEGF) over 18 years of follow-up in the DCCT/EDIC were described.[14] Although the cumulative incidence of these outcomes continues to be lower in the group that initially received intensive treatment, the annual incidence of these outcomes is now comparable between groups, largely because of a reduction in risk in the group that initially received conventional treatment.[14]

There are other instances of metabolic memory found in large studies looking at patients with type 2 diabetes.[15,16] The UK Prospective Diabetes Study (UKPDS) also showed the benefit of early tight glycemic control. These patients had been recently diagnosed with type 2 diabetes and randomized to 1 of 2 arms: an intensive treatment arm (with either a sulfonylurea or insulin) or a conventional diet-controlled arm.[15] The intensively treated patients had a 12% reduction in all diabetes-related end points over 10 years (P=.029) and a 25% reduction in the risk for microvascular end points, largely because of the reduced need for laser photocoagulation.[15] As in DCCT, the patients' HbA_{1c} values tended to drift up over time in the follow-up study, but the benefits of early tight control were demonstrated with a persistent 24% relative reduction in risk for microvascular disease (P=.001).[17] Later tight control may not be as beneficial.

How well are we doing? The Helmsley Charitable Trust has established a registry of more than 26,000 patients from approximately 60 type 1 diabetes clinical centers in the United States, and it has shown that even the best centers are not able to get the average HbA_{1c} of their patients to less than 7%.[18] Adolescence is a particularly difficult time for glycemic control,[3,19] whereas older patients tend to do better. Approximately 27% to 34% of adults are at target.[20] The frequency of severe hypoglycemia increases with age, and this is why the HbA_{1c} targets for older patients with type 1 diabetes are not more aggressive.[1] If a patient is aged 65 years or older and has comorbidities and/or a short life expectancy, the HbA_{1c} target becomes greater than 7.5%.[1] If the patient is particularly complex or in poor health, it becomes extremely difficult to establish a target without increasing risk to the patient.[1,21]

When considering a strategy for glycemic control for patients with type 2 diabetes, the ADA/European Association for the Study of Diabetes (EASD) position

statement advocates a patient-centered approach. The other members of the Writing Group and I thoroughly reviewed the available evidence when we put the statement together, and our recommendations are less algorithmic than previous approaches. Comparative efficacy studies are limited; with respect to pharmacotherapy, metformin should generally be regarded as the optimal first-line drug, unless it is contraindicated.[22] After that, the picture is less clear. The Group spent hours looking at this and we were not able to establish a definitive second-line step because of several variables such as practice setting, individual patient characteristics, financial considerations, and the role of formularies.

Looking at the clinical trials, in addition to UKPDS and DCCT, there also are data from ACCORD,[23,24] ADVANCE,[25] and VADT.[26] These trials were conducted in older patients who had complications, many of whom had had macrovascular events. It was thought that tightening glycemic control would result in improved macrovascular outcomes. In the latter 3 studies, some microvascular end points (pertaining to retinopathy, nephropathy, and neuropathy) showed a degree of improvement with tight control.

In ACCORD, the HbA_{1c} target was below 6%.[23] Trying to reach this target actually increased mortality, and the study was stopped after a mean of 3.5 years of follow-up.[23] Were these deaths due to the development of hypoglycemia among patients? This turned out not to be the case.[27,28] If a person with diabetes develops severe hypoglycemia, whether on intensive therapy or not, it has been shown that the risk for death increases 2- to 4-fold.[27] For patients with long-standing diabetes, pushing their HbA_{1c} values down with drugs that can cause hypoglycemia is potentially dangerous. However, in addition to the finding of the risk for severe hypoglycemia (noted in all studies), in ACCORD the treatment approach designed to lower the HbA_{1c} to less than 6% seemed to increase mortality. It is doubtful an explanation for this will be forthcoming, because all analyses done to date have been negative, but this study has changed current practice approaches and made individualization of A1C targets mandatory.

In the aforementioned ADA/EASD position statement on type 2 diabetes, we focused on several domains when trying to individualize a patient's target HbA_{1c}.[22] These domains are all-encompassing, addressing the risk for complications, patient life expectancy, disease duration, cardiovascular disease, and other factors. The goal is to balance the patient with respect to all these domains, and to arrive at an individualized target.

In the real world, patients exhibit a huge amount of variability with respect to these individual domains. Some patients may be very worried about retinopathy, but severe underlying cardiovascular disease may limit how aggressive clinicians can be with glycemic control. Each patient should have his or her own target. The goal is to get as close to normal blood sugar levels as possible without causing hypoglycemia or other adverse side effects.

In order to minimize the risks of pharmacotherapy, my preference is to use drugs that do not cause hypoglycemia and weight gain, and we have a lot of options to that end. If patients are willing to work with me, I can usually get even those with advanced type 2 diabetes to target using a combination of basal insulin, a glucagon-like peptide-1 receptor agonist, sodium-glucose co-transporter 2 inhibitors, and metformin. Treatment of type 2 diabetes has become much easier to manage given the new (along with some of the old) medications we have available.

Case 1

Dr Do: A 38-year-old gentleman with a history of type 1 diabetes came in for his annual eye examination a few months ago. At the time of presentation, he had been bothered by occasional blurred vision for several months. His HbA_{1c} was 7.0% three months prior to presentation. His visual acuity was 20/30 in the right eye and 20/20 in the left eye. A dilated examination showed some hard exudates and some mild macular edema **(Figure 1)**. Dr Nguyen, when you assess your patients for suspected DME, what imaging test(s) do you routinely obtain?

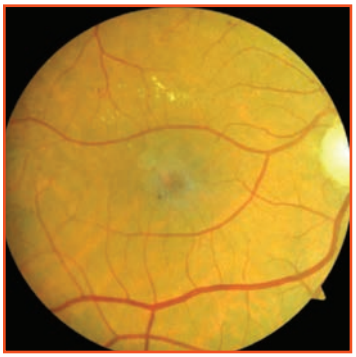


Figure 1: Case 1 dilated examination (OD).

Photo Courtesy of Diana V. Do, MD

Dr Nguyen: In patients with new onset DME, I will obtain fluorescein angiography,[29] as well as spectral domain optical coherence tomography (OCT).[30] If possible, the fluorescein angiogram could be done in a wide-angle system in order to assess the vasculature in the peripheral retina.[31]

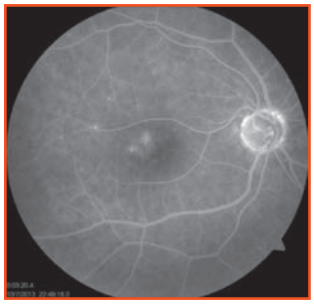
Dr Do: Dr Heier, what are your thoughts on the necessity of angiography, given the sensitivity of OCT and the fact that many of our randomized clinical trials have not really mandated the use of angiography?

Dr Heier: I absolutely think that angiography is necessary. In a straightforward patient like this, the OCT might show edema, and it might be fine for managing this particular patient. There are patients, however, who may have what appears to be relatively subtle disease, and if they have had diabetes for years, you can see gross nonperfusion and unexpected neovascularization.[32] I always obtain a baseline fluorescein angiogram in patients with diabetes and unexplained loss of visual acuity; I may not get another one for years if the patient's disease is easily managed after initial assessment.

Dr Do: With this particular patient, we obtained both a fluorescein angiogram and an OCT **(Figure 2)**. On the angiogram, there is evidence of leakage in the parafoveal region, and the OCT shows center-involved DME.

He had not had any previous treatment. Dr Heier, for this patient who has a visual acuity of 20/30 and complains of occasional blurriness, what treatment option would you choose?

Dr Heier: I am a little hesitant to start this patient on anti-VEGF therapy at this early stage. His HbA_{1c} of 7.0% is fair,



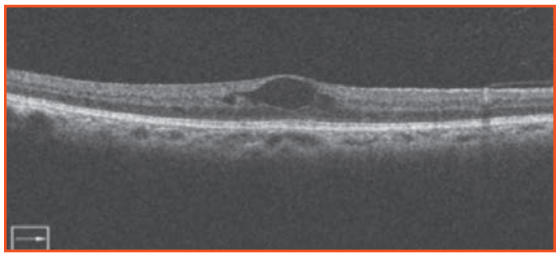


Figure 2: Case 1 fluorescein angiogram and OCT.

Photos Courtesy of Diana V. Do, MD

but I would want to know if it was lower in the previous assessments. I have had patients who averaged 6.0%, lost that level of control for a little bit, and subsequently developed fluid. Unless patients are very symptomatic, I might try a short period of attempting to restore glycemic control (3-6 months often allows an adequate period for improvement) and managing other factors such as poorly controlled hypertension, rather than essentially committing them to a series of injections. If they are very symptomatic, if their control has been excellent, and if their blood pressure is under good control, I will discuss anti-VEGF therapy with them; and then if I am going to treat, anti-VEGF would be my treatment of choice.

Dr Do: Dr Nguyen, if you were going to choose an anti-VEGF agent, which one would you choose for this patient? Let us assume patient insurance coverage and finances are not factors.

Dr Nguyen: In a case such as this, if finances are not a factor, I would choose either ranibizumab or aflibercept because both have been US Food and Drug Administration (FDA) approved for the indication of DME. I am comfortable using either drug, but I may prefer ranibizumab because it has a longer record of safety since it was approved several years before aflibercept.[33,34]

Dr Heier: I think most ophthalmologists would choose bevacizumab as first-line therapy because cost cannot be ignored. I have gone on record a number of times stating that I always use bevacizumab as my first-line therapy. I think that patients do well with it, and almost 90% of my patients get bevacizumab. That being said, if cost was not an issue, I would never use it because of the availability of FDA-approved drugs that may be more efficacious in some patients.[35] Some information has recently been released regarding the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study, which compared the safety and efficacy of 2.0-mg aflibercept, 1.25-mg bevacizumab, and 0.5-mg ranibizumab in the treatment of patients with DME. These data have not been peer reviewed. They indicate that there may be differences among aflibercept, bevacizumab, and ranibizumab with respect to gains in visual acuity and rates of cardiovascular events.[36]

Glycemic Control Questions on the Minds of Practicing Retina Specialists

Dr Heier: Dr Peters, is there a general target for early glycemic control? If a patient presents to an ophthalmologist with an HbA_{1c} of 9%, but no retinopathy, how aggressive should we be in initiating a referral to an endocrinologist?

Dr Peters: Certainly an HbA_{1c} of 9% is always concerning, and that patient should be seen by an endocrinologist. That being said, it is still important to establish what the individual patient's target is. It is also important for the patient and for all the medical providers involved with the patient's care to establish which provider is setting the patient's target.

Dr Nguyen: Do you believe that all patients with diabetes should be managed by an endocrinologist?

Dr Peters: I think that all patients with type 1 diabetes, if possible, should be monitored by an endocrinologist because of the technical complexity of ongoing management. I think that the vast majority of patients with type 2 diabetes have to be managed in a primary care setting. There are relatively few endocrinologists who focus primarily on the management of diabetes. If a patient with type 2 diabetes is complicated or having difficulty getting into a target range, then that patient should be seen by an endocrinologist. Other providers, including Certified Diabetes Educators and dietitians, also have an important role. If you can connect your patients with the diabetes community, that can be very empowering for the patient.

Dr Nguyen: Do you have a morning glucose target in mind for most patients?

Dr Peters: The ADA target is between 70 and 130, but if I have a patient who has difficulties with hypoglycemia, I would increase the fasting target to 100 to 130. I generally aim for between 90 and 130 before meals, but it might be lower or higher, depending on the individual patient.

Dr Nguyen: How does the rate of glycemic reduction potentially worsen retinopathy?

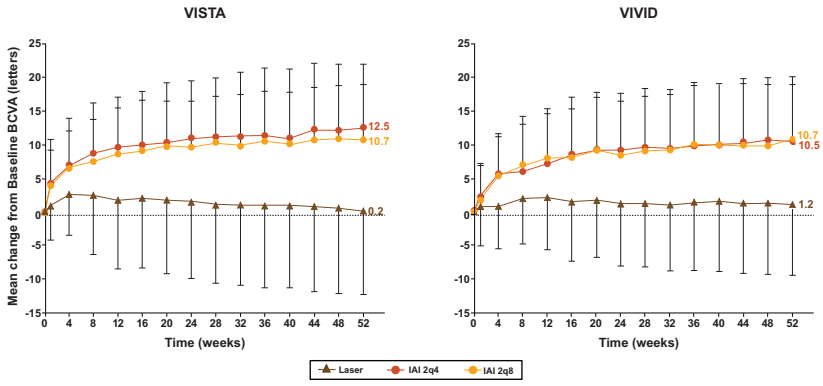
Dr Peters: In the DCCT, 13.1% of patients randomized to the intensive control arm had worsening of retinopathy within the first year of treatment, compared with 7.6% of the patients assigned to conventional treatment.[1] Some of the risk factors for early worsening that were identified included higher HbA_{1c} levels at screening and reduction of these levels within the first 6 months of treatment. The DCCT authors did not find any evidence supporting the concept that more gradual glycemic control might be associated with a lower risk for early worsening. That being said, they did recommend ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for the first 6 to 12 months of treatment.[1] They also recommended delaying the initiation of intensive glycemic treatment until the retinopathy was treated, particularly for patients with poorly controlled diabetes.[1] The outcomes for those patients who were intensively controlled who had early worsening of retinopathy were the same or better than for those in the conventional group who did not have early worsening.

1. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1998;116(7):874-886.

Dr Do: Many ophthalmologists are aware of the clinical trial data showing that center-involved DME is best treated with an intravitreal anti-VEGF agent. One of our first landmark studies was from DRCR.net, which looked at ranibizumab, given with either prompt or deferred laser, and it showed that either dosing regimen of ranibizumab was superior to preservative-free triamcinolone with laser and also superior to focal/grid laser.[37]

Regarding bevacizumab, which is the most popular choice among the American Society of Retina Specialists membership, the BOLT clinical trial that was conducted in the United Kingdom additionally provides us some prospective clinical trial data to suggest that bevacizumab is also an effective option for center-involved DME.[38]

Aflibercept was recently approved by the FDA for the treatment of DME, based on the 1-year data from the phase 3 VISTA and VIVID studies.[39] Aflibercept treatment, whether dosed every 8 weeks or every 4 weeks, was superior to focal/grid laser, and eyes gained an average of 10.5 to 12.5 letters of visual acuity **(Figure 3)**.[39] Both dosing regimens of aflibercept had similar efficacy. We also have some of the 2-year data from VISTA, and both dosing regimens resulted in sustained visual acuity with similar Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events across all groups.[40]

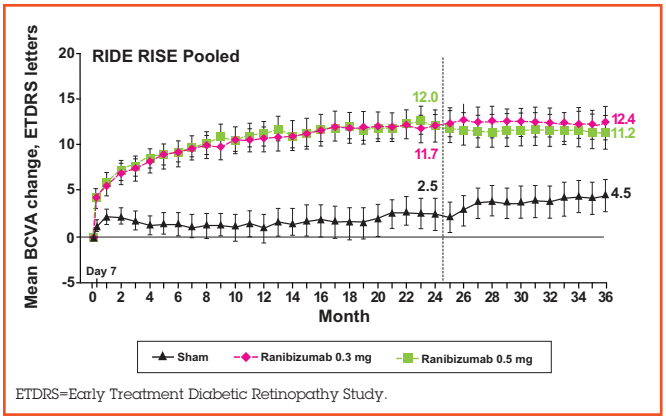


BCVA=best corrected visual acuity; IAI=intravitreal aflibercept injection.

Figure 3: Mean standard deviation change in best corrected visual acuity from baseline through week 52 with censoring of values after additional treatment was given (last observation carried forward).[39]

When we further probe our armamentarium, we see that the RISE and RIDE studies demonstrated the superiority of ranibizumab to sham treatment.[33] Looking at the extension study, patients who were initially randomized to sham treatment and crossed over to treatment with ranibizumab 2 years later never matched the gains in visual acuity seen in patients who were initially treated with ranibizumab **(Figure 4)**.[33]

This suggests that a long delay in beginning anti-VEGF therapy for DME causes some level of irreversible damage to the retina, and those eyes will not catch up to eyes that began anti-VEGF therapy much earlier. Maybe you could delay for a few months, but certainly do not delay for a period of years.



ETDRS=Early Treatment Diabetic Retinopathy Study.

Figure 4: Mean change in best corrected visual acuity over time, RISE and RIDE 3-year pooled data.[33]

Returning to our case, the patient's visual acuity remained stable after a 1-month period of observation, but his edema increased on OCT, so I elected to treat him with the only on-label anti-VEGF treatment available at the time, ranibizumab. I gave him 1 dose, but his visual acuity did not improve significantly, and his edema persisted. I administered a second ranibizumab injection, and his visual acuity improved to 20/25 with some decrease in central retinal thickness. After a third ranibizumab injection, his visual acuity improved to 20/20 and the center-involved edema resolved.

Another FDA-approved treatment option that exists for patients with DME is the dexamethasone delivery device.* The MEAD study looked at the safety and efficacy of this option, and in a recent subanalysis of the study, dexamethasone was found to be more effective than sham therapy in all subgroups, regardless of duration of DME, type of DME, duration of diabetes, patient age, or perfusion status.[41] Patients who were pseudophakic at baseline showed benefit from dexamethasone at each chronological point that was evaluated, while patients who were phakic at baseline did not show continued benefit from dexamethasone after the first year of treatment because of the emergence of cataracts. However, when these patients had their cataracts removed, their visual acuity results were comparable to those patients who were pseudophakic at baseline. We do not know the optimal dosing strategy for this implant; in recent phase 3 clinical trials, dexamethasone was given every 6 months.[42] Most of us would say that it needs to be dosed every 3 to 4 months, according to our clinical experience with the dexamethasone implant for retinal vein occlusion. Dr Nguyen, when would you recommend the dexamethasone implant for DME?

Dr Nguyen: I would tend to select anti-VEGF therapy as an initial treatment based on the clinical outcomes data. If you compare the overall gains in vision and percentage of patients who gained more than 3 lines of vision in RISE/RIDE and VISTA/VIVID against the gains in the recent dexamethasone study, the anti-VEGF therapies had an edge.[33,39,42]

* A fluocinolone delivery device also has been approved by the FDA recently for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. It is expected to be available early 2015.

Dr Do: Dr Heier, if we are concerned about the treatment burden to the patient and the patient's family, then the dexamethasone delivery device may be an attractive treatment option because it can be given every 3 to 4 months. For some patients, this interval might even be stretched out further. What is your perspective on the implant option?

Dr Heier: I am happy that the dexamethasone implant was approved, and I do think that it will help some of our patients. But I still think that anti-VEGF therapy is the best first line of therapy, largely for its safety profile. Although cataracts would not be an issue for the pseudophakic patient, the problem of treatment-induced glaucoma remains,[42] and patients with diabetes are already more likely to have elevations in intraocular pressure than patients without diabetes.[43] As you mentioned, I believe that the number of patients who will be able to get to 6 months with 1 implant will be relatively low. Three to 4 months seems a more likely interval.

Dr Nguyen: Dr Peters, if a patient's HbA_{1c} is between 7% and 7.5%, and he or she continues to have problems with recurrent macular edema, is there any utility to lowering the patient's HbA_{1c} further?

Dr Peters: I think that there is a benefit regarding the retinopathy issue. I am not sure there is always a benefit in terms of the entire person, and that is where we providers have to collaborate. Some patients are quite fragile, and the risks for hypoglycemia are too great.

Case 2

Dr Heier: This case features a 36-year-old woman with a 25-year history of type 1 diabetes who presented with a 5-day history of "black blobs" in the central vision of her right eye. Her most recent HbA_{1c} was 8%. She received panretinal photocoagulation in her right eye and focal treatment in her left eye in 2011 (the laser was performed prior to our care of her). Her visual acuity at the time of presentation was 20/25 in her right eye and 20/20 in the left.

The patient's imaging shows some preretinal hemorrhage inferiorly in the right eye; there is evidence of previous laser. The left eye looks good. Dr Do, how would you suggest this patient be managed?

Dr Do: I would recommend obtaining a fluorescein angiogram to evaluate the retinal vasculature.[29] I suspect that there will be significant capillary nonperfusion and multiple areas of neovascularization in her right eye. She may have more retinopathy problems with her left eye as well. If this patient has poor glycemic control, retinopathy is likely to be fairly symmetric in both eyes.

Dr Heier: You are correct. There are some areas of neovascularization and perhaps some capillary nonperfusion. Her widefield angiogram shows that there are a number of areas of neovascularization and extensive capillary nonperfusion **(Figure 5)**. Dr Nguyen, how would you approach this patient?

Dr Nguyen: This patient has PDR that seems to be laser deficient at the time of this imaging. I would perform additional panretinal photocoagulation, because there is evidence to support its efficacy in controlling the progression of the PDR.[29,44] Because there is no macular edema, I would delay pharmacologic therapy at this time.

Metabolic Parameters and the Response to Pharmacotherapy in DME

Given the prominent role of anti-VEGF therapy and steroid therapy in the armamentarium for the treatment of DME, it is important to assess parameters that may influence their efficacy. Although no double-masked prospective studies have been conducted to assess the relationship between glycemic control and responsiveness to pharmacotherapy for patients with DME, the question has been addressed with other investigations. The limitations of investigation designs and variation in results have hindered the ability to draw any definitive conclusions.

A recent subanalysis of the MEAD data, which looked at the role of intravitreal dexamethasone implant therapy in the treatment of DME, found that there was a trend toward greater influence of dexamethasone in patients who had better control of their diabetes.[1]

A retrospective study conducted by Ozturk and colleagues was designed to assess the effects of glucose regulation on visual outcomes for patients with DME who were treated with ranibizumab. In this study, the patients' HbA_{1c} values negatively correlated with the change in central subfield macular thickness (coefficient = –0.50, $P<.001$).[2]

Another recent retrospective case analysis conducted by Matsuda and colleagues enrolled 124 consecutive patients with DME to determine the role of systemic factors on functional and anatomic outcomes of anti-VEGF therapy (bevacizumab).[3] Patients with a serum HbA_{1c} of ≤7.0% had a more robust response with respect to best corrected visual acuity and central subfield macular thickness than those whose HbA_{1c} values were >7.0%. Patients whose glycemic control improved during the study had lower retinal thickness than patients whose HbA_{1c} was stable or had deteriorated.[3]

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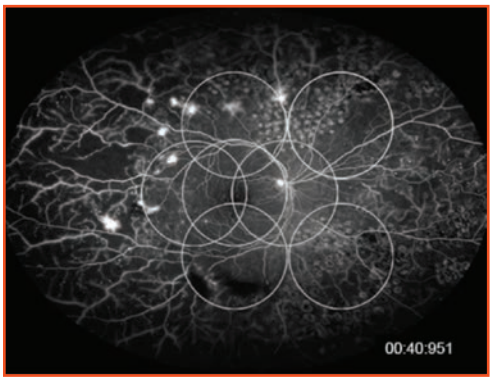

Figure 5: Case 2 widefield angiogram (OD).
Photo Courtesy of Jeffrey S. Heier, MD

Dr Heier: Dr Do, if there was macular edema, would you approach this patient differently?

Dr Do: I would recommend anti-VEGF injection to treat the macular edema, and panretinal photocoagulation laser to control the proliferative aspect.

Dr Heier: Would you administer these 2 treatment modalities at the same time or would you do the anti-VEGF first and then the laser?

Dr Do: I tend to do both procedures at the same visit to avoid the need for the patient to come back multiple times. I also try to do all the panretinal photocoagulation in 1 session.

Dr Peters: This young woman is the perfect example of a patient who should be referred to an endocrinologist, if she is not already under the care of one. Given the fact that she is of reproductive age, any attempts to treat her ophthalmic problems would be significantly complicated by a pregnancy.[45] Contraception should be discussed. You do not want a patient with poor glycemic control or unstable vision becoming pregnant.

Dr Do: Yes, I agree completely. We do not know the effects of anti-VEGF therapy on pregnant women, so we certainly do not advocate using it in patients who *are* pregnant. We always counsel our young female patients to use a reliable birth control method, as you have advised.

If this patient with progressive eye disease was to become pregnant, I would attempt focal/grid laser first for DME, because that is the safest option.[46] If the edema does not respond, and her vision is being further compromised, then an intravitreal steroid injection may be the next best option. The safety of intravitreal anti-VEGF agents in pregnancy is unclear, and we do not recommend anti-VEGF injections in this population.[47] In my opinion, anti-VEGF would be a first-line agent for women of reproductive age who have diabetes and DME, *if* they are able to be reliable with contraception. If not, then laser or intravitreal steroids might be other options to consider.

Dr Heier: Let us move on to the patient's left eye; her OCT shows a few cysts but a nice contour.

There is some evidence of neovascularization on her 7 standard field imaging, and on her widefield imaging **(Figure 6)** gross nonperfusion is evident.

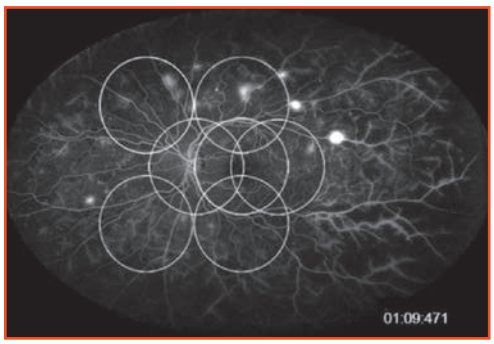

Figure 6: Case 2 widefield angiogram (OS).

Photo Courtesy of Jeffrey S. Heier, MD

Recent studies, such as those conducted at the Joslin Diabetes Center and Weill Cornell Medical Center, have shown that ultra-widefield angiography potentially reveals a much greater extent of disease pathology than does 7 standard field imaging, and may, in fact, alter the classification of DR in as many as 10% of eyes evaluated by the 7 standard field imaging technique.[32,48]

I get baseline widefield imaging on every patient with diabetes, as well as on patients with retinal vein occlusion. For this particular patient, we were amazed by the extent of disease in her left eye.

Dr Do, when treating a patient with DR with anti-VEGF therapy, do you follow the patient with angiography?

Dr Do: I think that when treating DME, an angiogram at baseline is helpful. For routine follow-up and ongoing management decisions, OCT is more practical. In my opinion, you need to repeat the angiogram only if something changes or if the patient does not respond as you would expect.

Dr Heier: We have recently conducted a study looking at just such an issue, and we are currently evaluating the results.[49] We treated patients who had PDR with either 12 monthly injections of aflibercept or 6 monthly injections followed by a period of 6 months during which the injections were given every other month. We then followed the patients with widefield angiography, with the intent of examining the degree of nonperfusion and how the anti-VEGF therapy affected it.[49] I expect to have those results early 2015.

Case 3

Dr Do: We next have a case of a 62-year-old woman with a 5-year history of type 2 diabetes who presented with a complaint of decreased vision in her left eye. Her diabetes was initially treated with oral antiglycemic agents, but she subsequently required insulin. Her most recent HbA_{1c} was 8.5%. At the time of presentation, she was noted to have center-involved DME in her left eye with a visual acuity of 20/80 **(Figure 7)**.

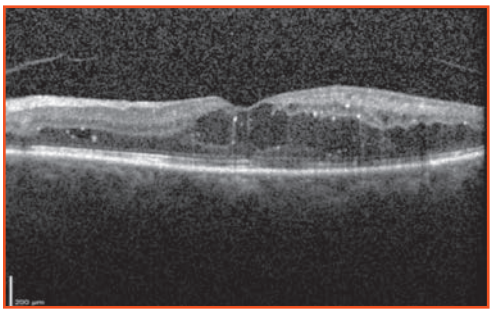

Figure 7: Case 3 baseline OCT OS (20/80–1).

Photo Courtesy of Retina Consultants of Houston

Her retina specialist elected to treat her with ranibizumab, and after 1 injection, her visual acuity improved to 20/60. Her edema was still persistent, and her ophthalmologist administered a second injection. Her vision then was 20/60+2, and her foveal contour returned. Dr Heier, in this patient, would you continue treatment or begin a period of observation at this point?

Dr Heier: I would continue treatment here. As in RISE and RIDE, we often see slow recovery of vision in patients with diabetes.[33] There are still some exudates and fluid temporarily, so I would continue until I was absolutely convinced that she had maximized visual gain.

Dr Do: Dr Nguyen, do you ever consider combining anti-VEGF with laser, and if so, when do you add the laser?

Dr Nguyen: I usually start with anti-VEGF injections alone. If the eye has a suboptimal response to the intravitreal VEGF blockers, I may switch anti-VEGF agents or add focal/grid laser to the injections.

Dr Heier: While I am not yet convinced that subthreshold micropulse diode laser[50] will work, if the problem is recurrent, as it is in this scenario, I would be interested to see if such an approach would help.

Dr Do: I know many of our colleagues like to combine the effects of anti-VEGF therapy with focal/grid laser. Interestingly, the DRCR.net Protocol I demonstrated that in year 3, eyes randomized to ranibizumab with deferred laser (laser given at month 6 or later) had gained almost 3 letters more compared with eyes randomized to ranibizumab with prompt laser. These data suggested that anti-VEGF treatment with deferred laser may be more beneficial than when laser is used at the beginning.[51]

In this case, the patient's retina specialist provided another anti-VEGF treatment, and her vision improved to 20/40. Dr Nguyen, what would you do at this time? Would you observe, or continue the anti-VEGF therapy? When would your end point be?

Dr Nguyen: The patient has continued to show improvement in vision, so I would like to make sure that we have maximized her potential gain in visual acuity. I would continue to treat her at this point, because there may yet be some level of edema that we could eliminate.

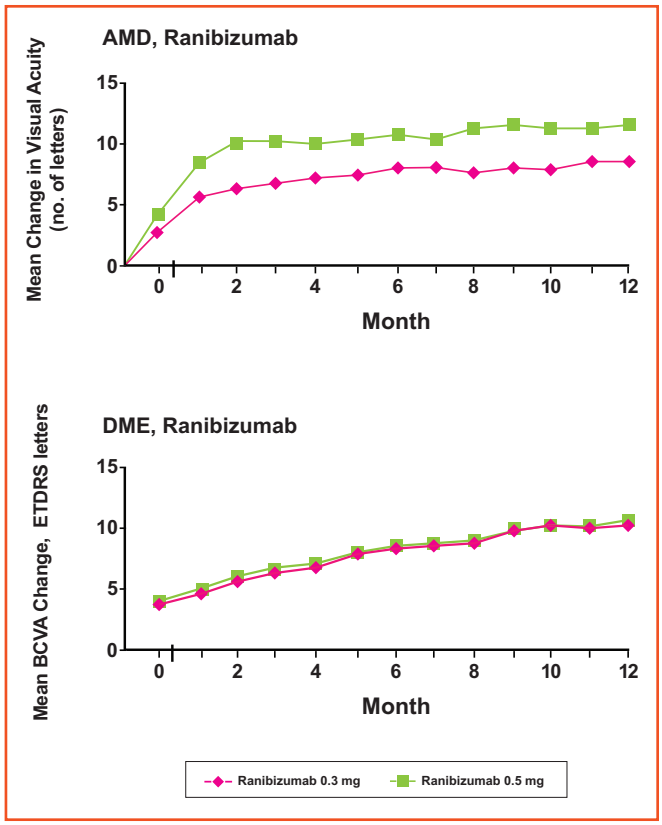

Figure 8: Visual acuity response curves from ANCHOR (AMD)[52] and RISE/RIDE (DME).[33]

Dr Do: That is what her specialist did. He administered another ranibizumab injection. Her macula looked great, with no edema. Her visual acuity improved to 20/40.

Subsequently, her provider decided to administer yet another injection, and her vision improved by 1 line to 20/30. Dr Nguyen, what would you do now? Do you think that the eye will go to 20/20 if you give 1 more injection? Should we continue?

Dr Nguyen: She continues to improve, so I would say to continue monthly therapy.

Dr Do: When you look at the visual acuity response curves from the randomized clinical trials pertaining to the treatment of wet macular degeneration and DME, you can see that visual gains rise quickly in age-related macular degeneration (AMD) and may also plateau more quickly in AMD than they do in DME **(Figure 8)**.[33,52]

We do not know why this slight difference occurs. One study looking at bevacizumab for the treatment of DME found that although anti-VEGF therapy did lower intraocular VEGF levels dramatically, the effect on other cytokines involved in disease progression was not as great as it is in AMD.[53,54]

Conclusion

Dr Nguyen: I think that there are several key messages to highlight. First, we need to be patient with our treatment choices with DME, because it appears that the time to maximal effect of anti-VEGF therapy may be longer for DME than it is for some other retinal vascular diseases. Anti-VEGF therapy does appear to be a therapeutic cornerstone for DME, particularly for those patients with central involvement. Second, an individualized approach to glycemic control may benefit patients with diabetes more than trying to treat to a specific HbA_{1c} goal. Third, DR and DME are quite complex and variable in their presentations, and it may be worthwhile to consider widefield angiography as a means of detecting and assessing the true scope of these diseases.

My appreciation to our panelists for a lively discussion of some essential management strategies for our complex patients with DR and DME. An individualized approach can provide great improvements in glycemic control as well as in visual outcomes.

Trial Abbreviations Used

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
BOLT	A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema
MEAD	Macular Edema: Assessment of Implantable Dexamethasone in Diabetes
RIDE/RISE	A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus
VADT	Veterans Affairs Diabetes Trial
VISTA/VIVID	A study of intravitreal administration of aflibercept in patients with diabetic macular edema

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CME Post Test Questions

To obtain *AMA PRA Category 1 Credit™*, please see detailed instructions on page 2.

1. Which of the following factors would tend to favor more stringent management of hyperglycemia for a patient with type 2 diabetes?
    a. High level of risk potentially associated with hypoglycemia
    b. Low patient motivation
    c. Long-standing duration of disease
    d. Lack of established vascular complications

2. Which of the following statements regarding the management of hyperglycemia in type 1 diabetes is true?
    a. Adult glycemic targets are more stringent now than they have ever been
    b. Early problems with hyperglycemia do not predispose children to complications as adults
    c. Ophthalmologic monitoring should take place before and during the first year of increased glycemic control efforts
    d. Patients with long-standing diabetes should always aim for an HbA_{1c} value of ≤6%

3. The use of ultra-widefield angiography for patients with diabetic macular edema:
    a. Has been mandated as a means of following anatomic outcomes in clinical trials
    b. Has revealed a correlation between the degree of retinal ischemia and macular thickness
    c. Has the potential to change the classification of a patient's ophthalmic disease
    d. Has been shown to be less efficacious than 7 standard field imaging as a means of detecting diabetic pathology

4. Dexamethasone implant use for the treatment of diabetic macular edema:
    a. Is currently FDA approved for pseudophakic adult patients
    b. Provides up to 2 years of medication per implant
    c. Carries no appreciable risk for elevations in intraocular pressure
    d. Is a Pregnancy Category X treatment

5. Anti-VEGF therapy for clinically significant diabetic macular edema:
    a. Is regarded as a first-line choice for this condition when it involves the foveal center
    b. Has worse functional and visual outcomes than laser photocoagulation
    c. Has only 1 FDA-approved option
    d. Typically achieves maximum functional gains by 2 months of treatment

6. Which of the following statements regarding the relationship between type 1 diabetes and patient age is true?
    a. Older patients are less successful with glycemic control than adolescent patients
    b. Approximately 30% of adult patients are at glycemic target
    c. The frequency of severe hypoglycemia decreases with age
    d. Pediatric glycemic goals have been made less stringent because of validated concerns regarding neurocognitive dysfunction

7. A patient with evidence of clinically significant diabetic macular edema should have an HbA_{1c} target value:
    a. ≤7.0%
    b. ≤6.5%
    c. ≤6.0%
    d. That takes into account multiple individual patient factors, including risk for hypoglycemia

8. All the following statements regarding the use of OCT in the management of DME are true, except:
    a. OCT imagery has a high level of correlation with visual acuity
    b. OCT is a highly reproducible method of measuring pathological features of DME
    c. OCT can monitor response to therapies such as surgical intervention and intravitreal pharmacotherapy
    d. OCT may be performed in conjunction with fluorescein angiography

9. All the following factors may adversely influence visual health for patients with diabetes, except:
    a. Pregnancy
    b. Hypertension
    c. Poor glycemic control
    d. Low serum triglyceride levels

10. When assessing the response of patients with DME to anti-VEGF therapy, it is important to consider that:
    a. Visual gains plateau more quickly in DME than they do in AMD
    b. Glycemic control influences the efficacy of all anti-VEGF agents
    c. Prolonged delays in anti-VEGF therapy may limit the magnitude of visual gains for patients who are candidates for it
    d. Anti-VEGF therapy should be combined with laser therapy within the first month of pharmacologic treatment

Activity Evaluation/Credit Request

Original Release: January 2, 2015 ▪ **Last Review:** December 9, 2014 ▪ **Expiration:** January 31, 2016

Current Management of Diabetic Macular Edema and Diabetic Retinopathy: A Multidisciplinary Discussion of Clinical Cases

PARTICIPANT INFORMATION *(Please Print)* ❑ Home ❑ Office

Last Name _____ First Name _____ Birth Month/Day (mm/dd) _____

Specialty _____ Degree ❑ MD ❑ DO ❑ OD ❑ PharmD ❑ RPh ❑ NP ❑ RN ❑ PA ❑ Other _____

Institution _____

Street Address _____

City _____ State _____ ZIP Code _____ Country _____

E-mail _____ Phone _____ Fax _____

LEARNING OBJECTIVES

The objectives were achieved.

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

Recognize the importance of individualized glycemic control in optimizing outcomes for patients with DR/DME ❑ Yes ❑ No

Discuss the utility of different diagnostic imaging techniques in guiding the management of patients with DR/DME ❑ Yes ❑ No

Describe the efficacy, dosing, and safety profiles of current and emerging treatment options for DME ❑ Yes ❑ No

Confidently tailor diagnostic and treatment strategies for various patients with DR/DME ❑ Yes ❑ No

Communicate effectively with referring physicians regarding the relevant systemic and ophthalmic health issues of their mutual patients with DR/DME ❑ Yes ❑ No

FINANCIAL INTEREST AND BIAS

Disclosure of relevant financial interests of presenters and planners was stated. ❑ Yes ❑ No

This educational activity was free of commercial bias. ❑ Yes ❑ No

If no, please explain. _____

_____

IMPLEMENTING INTO PRACTICE

Do you intend to make changes or to apply new knowledge as a result of this educational activity?

I intend to make changes to improve my effectiveness. ❑ Yes ❑ No

This experience will not change my practice, as my current behavior is already consistent with the information provided. ❑ Yes ❑ No

If no, please explain.

_____

_____

What strategies for improvement or changes do you plan to implement following this educational activity?

_____

_____

Please indicate all barriers you perceive in implementing these changes. (check all that apply)

❑ Lack of professional guidelines or consensus
❑ Lack of resources
❑ Further training is needed
❑ Patient compliance issues
❑ Lack of health system support
❑ Cost/Reimbursement/Insurance issues
❑ Opportunity to practice
❑ No barriers
❑ Other, please specify _____

How do you think your changes will affect patient outcomes?

_____

_____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10