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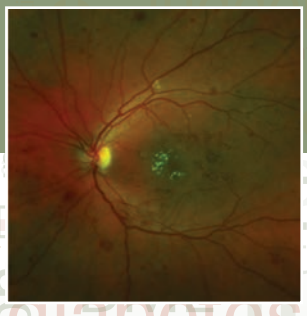

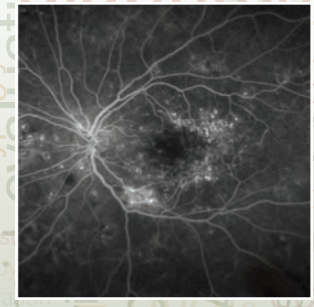

Expert Insights in Today's Multidisciplinary Management of

Diabetic Retinopathy and Diabetic Macular Edema

Proceedings from an Expert Roundtable Discussion

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Purpose and Target Audience

Retina specialists have a number of treatments from which to choose for the management of diabetic eye disease. New data on these modalities continue to emerge, and it is imperative for clinicians to keep up-to-date with the latest evidence. The purpose of this activity is to clarify clinical applications of recent data and to inform retina specialists about current recommendations on glycemic control, diet, and other lifestyle issues for patients with diabetes so that they can reinforce important education messages.

This educational activity is designed for retina specialists and other ophthalmologists treating patients with diabetic retinopathy and diabetic macular edema.

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Learning Objectives

Upon completing this educational activity, participants should be able to:

- Describe the efficacy and safety results from recent clinical trials in DR and DME
- Formulate appropriate long-term treatment strategies for DME based on individual patient characteristics
- Discuss glycemic control targets and dietary control of blood sugar for patients with diabetes

Hardware & Software Requirements

High speed Internet connection (Broadband, Cable or DSL)
Windows 2000 or higher
256 MBs or more of RAM
Internet Explorer 6.0 or higher
Windows Media Player 10.0 or higher
Adobe Acrobat 7.0 or higher
Course content compatible with Mac OS

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Introduction

Retina specialists have a number of treatments from which to choose for the management of diabetic eye disease. New data on these modalities continue to emerge, and it is imperative for clinicians to keep up-to-date with the latest evidence. In addition, retina specialists need to stay informed about current recommendations on glycemic control, diet, and other lifestyle issues for patients with diabetes so that they can reinforce important education messages.

With these needs in mind, a panel comprising 4 retina specialists, an endocrinologist, and a dietitian convened to review the multidisciplinary management of patients with diabetic retinopathy (DR) and diabetic macular edema (DME). The information discussed is summarized in this program, and we hope retina specialists in the United States and throughout the world will find it helpful to them in their daily practice.

—Quan Dong Nguyen, MD, MSc

What Ophthalmologists Need To Know About Diabetes Management

Glycemic control and lipid management are fundamental to diabetes management, and healthy eating and exercise are part of the framework for helping patients achieve their goals. By understanding current standards of care as they pertain to this framework, ophthalmologists can provide the support that will help patients be successful in maintaining better ocular and overall health.

Glycemic Control and Lipid Management

—Andjela Drincic, MD, *Endocrinologist*

Glycemic targets for patients with diabetes are now individualized, taking into account multiple factors (Table 1).[1,2]

Whereas very tight glucose control with an HbA_{1C} (glycated hemoglobin) of 6.0% to 6.5% may be targeted for highly motivated patients who are able to take care of themselves, who have a low risk for hyperglycemia, short disease duration, long life expectancy, no significant comorbidities, and a good support system, an HbA_{1C} of 8% or higher would be appropriate for older patients who have a history of heart disease and a high risk for hypoglycemia.

"Whereas very tight glucose control with an HbA_{1C} of 6.0% to 6.5% may be targeted for highly motivated patients who are able to take care of themselves, who have a low risk for hyperglycemia, short disease duration, long life expectancy, no significant comorbidities, and a good support system, an HbA_{1C} of 8% or higher would be appropriate for older patients who have a history of heart disease and a high risk for hypoglycemia."

—Andjela Drincic, MD

The effect of glycemic control on cardiovascular disease (CVD) risk is a key issue in choosing an HbA_{1C} target because CVD is the major cause of morbidity and mortality among patients with diabetes. Results of studies investigating the effect of intensive glycemic control on cardiovascular outcomes vary, depending on the population studied. Intensive glycemic control significantly reduced cardiovascular complications when it was initiated in patients with newly diagnosed type 1 or type 2 diabetes.[3,4] Studies enrolling older patients who had more long-standing type 2 diabetes and a history of or multiple cardiovascular risk factors, however, found intensive glycemic control had no effect on CVD outcomes.[5-7]

Table 1. Individualizing Glycemic Control[1,2]

	Glycemic Control	
	More Stringent	Less Stringent
HbA_{1c}	6%	8%
Disease Characteristics		
Duration of type 2 diabetes	Short	Long
Risk for hypoglycemia	Low	High
Life expectancy	Long	Short
Microvascular disease	None	Advanced
Cardiovascular disease	None	Established
Comorbid conditions	None	Multiple, severe, or both
Patient Characteristics		
Psychosocial considerations	Highly motivated Adherent Knowledgeable Strong self-care capability	Less motivated Nonadherent Less knowledgeable Weak self-care capability
Resources or support systems	Adequate	Inadequate

Notably, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was terminated early because patients in the intensive glycemic control arm (HbA_{1C} target <6%) had a significantly increased risk for all-cause mortality compared with their counterparts assigned to standard glycemic therapy (HbA_{1C} target 7.0%–7.9%).[7] While the reasons for the excessive mortality in the arm with intensive glycemic control are not known, the deaths were driven mainly by cardiovascular events.

The effect of intensive glycemic control on progression of DR was investigated in the ACCORD Eye Study, which included data from a subset of nearly 3000 patients followed for 4 years.[8] Although intensive glycemic control significantly decreased the odds for progression of DR compared with standard treatment, further subgroup analyses showed the benefit was statistically significant only among patients with mild retinopathy at baseline. There was no benefit among patients

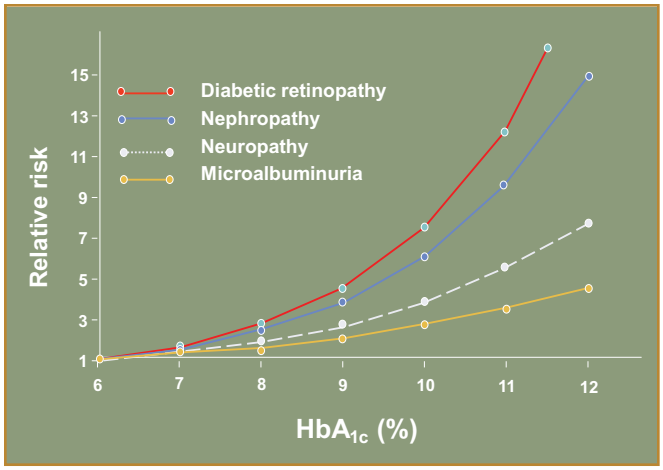

Figure 1. Relative risks for microvascular complications by mean HbA_{1C} level during follow-up in the Diabetes Control and Complications Trial.[11]

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who had no retinopathy or moderate to severe retinopathy at baseline. Earlier studies showed intensive glycemic control reduced DR risk in patients with newly diagnosed type 1 or type 2 diabetes.[9,10]

It is useful for ophthalmologists to know that for patients in whom it may not be appropriate to reach an HbA_{1C} of 7% or 8%, there is still substantial benefit for reducing DR progression by lowering HbA_{1C} from very high levels to fair control (ie, 8%–9%). This is because the relationship between chronic hyperglycemia and the risk for DR is curvilinear **(Figure 1)**.[11]

Lipid management also is critical for controlling CVD risk in patients with diabetes. In the ACCORD Eye Study, adding fenofibrate to simvastatin did not reduce cardiovascular events compared with statin treatment alone. Subgroup analyses, however, identified a benefit of combination treatment in men, but a trend toward increased risk for cardiovascular events in women.[7] In addition to cardiovascular benefits, lipid management with the combination treatment significantly slowed DR progression.[8] Similarly, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study that enrolled patients with type 2 diabetes, fenofibrate had a beneficial effect in terms of reducing the need for laser treatment for DR.[12]

However, statins are considered to be first-line therapy for hyperlipidemia in patients with diabetes, given the impressive cardiovascular benefits of these agents.[13] Combination therapy with a statin plus fenofibrate has not provided additional cardiovascular benefit compared with use of a statin alone; and any combination therapy introduces the risk for side effects and decreased compliance due to complexity of treatment.

Diet and Exercise Update

—Joni Pagenkemper, MS, RD CDE, *Diabetes Educator*

Nutrition therapy is an integral component in the overall management of patients with diabetes. According to the American Diabetes Association (ADA) Standards of Medical Care in Diabetes, all individuals with diabetes should receive individualized medical nutrition therapy, preferably provided by a registered dietitian who is knowledgeable about diabetes medical nutrition therapy[13]

There is no evidence suggesting any ideal distribution of carbohydrates, fat, and protein in an eating plan for patients with diabetes. Rather, the plan should take into account an individual's eating patterns, preferences, and weight management goals to establish total daily calorie intake and percentages derived from each of the macronutrients.

Nevertheless, it is important for patients with diabetes to pay attention to their carbohydrate intake in terms of how much they consume and when they eat relative to use of their glycemia-lowering medications, so that they may reach their HbA_{1C} target and reduce glycemic variability. There is not sufficient evidence to support recommendations for a low glycemic index meal plan, but patients should be educated about the carbohydrate content of foods in order to avoid derangements of glycemia. Portion size of carbohydrates is more important than the source, although patients are encouraged to stay away from sugar-containing beverages and to limit other foods with high simple-sugar content. In addition, the guidelines recommend limiting alcohol to 2 drinks per day for men and 1 drink per day for women. Any alcohol should be consumed with food to minimize the risk for hypoglycemia.

In order to determine appropriate serving sizes and to make healthier choices, patients need to know how to read the nutrition labels on packaged foods. Patients who are concerned that eating healthy is too expensive can be counseled that there are many ways to eat healthy "on a budget" **(Table 2)**.

Table 2. Healthy Eating on a Lean Budget

Top 10 Saving Strategies for People With Diabetes
• Limit impulse purchases—go to store with shopping list, and stick to it!
• Buy in-season—consider growing your own!
• Use coupons
• Purchase sale items in bulk—and freeze if able
• Buy generic
• Think whole (unprocessed) foods—processed = higher price
• Prepare it from scratch—you pay more for convenience
• Shift to smaller portion sizes
• Load up on beans
• Shop at wholesale food stores—Costco, Sam's Club, BJ's

Physical activity is another important element in diabetes management, and the current ADA standards encourage adults to engage in at least 2.5 hours a week of moderate-intensity aerobic physical activity, spreading the total over at least 3 days and without going more than 2 days without exercising.[13] The Standards also recommends reducing sedentary time, especially avoiding sitting more than 90 minutes, and incorporating resistance training at least twice a week for adults with type 2 diabetes, if there are no contraindications.[13]

Dr Nguyen: Dr Eliott, how many of your patients with diabetes have a dietitian who helps them with their daily diet and food intake?

Dr Eliott: The majority of my patients with diabetes work with a dietitian, given that the socioeconomic status of many patients in my practice is average or high. Previously, I practiced in an area where almost all my patients were of low socioeconomic status, and very few worked with a dietitian.

Ms Pagenkemper: Medicare and private insurers provide good coverage for diabetes education and medical nutrition therapy. Access to care may be more limited in lower socioeconomic areas, but services are available through local Cooperative Extension Services, and they can be easily found via an Internet search. Additionally, ophthalmologists and patients can find information about local resources on various Web sites, including those of the American Association of Diabetes Educators (www.diabeteseducator.org), the National Diabetes Education Program (www.ndep.nih.gov), and the Academy of Nutrition and Dietetics (www.eatright.org).

Dr Drincic: The focus of nutrition education for people with diabetes is on moderation, not restriction, and that is surprising to some patients. There is not an ADA diabetic diet *per se*. Instead, what is considered a good diet for a person without diabetes is also a good diet for someone with diabetes.

Dr Do: This information on diet and lifestyle modifications is an excellent reminder to retina specialists to be mindful about overall systemic health in patients with diabetes. I think there is a tendency to overlook nonocular issues in the setting of a busy clinical practice. In addition, intravitreal anti-vascular endothelial growth factor (VEGF) therapies are so effective for reducing DME, regardless of an individual's glycemic control, that we retina specialists probably do not spend as much time on lifestyle modifications as we used to.

Updates on Treatment for Diabetic Retinopahty/Diabetic Macular Edema

Dr Nguyen: The 1-year results from the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T that compared aflibercept, bevacizumab, and ranibizumab for the treatment of DME were published online in February 2015.[14] Dr Do, how have those data affected your approach to treating patients with DME?

Dr Do: Prespecified subgroup analyses in Protocol T found that in patients with baseline vision of 20/32 to 20/40, mean gains in visual acuity (VA) at 1 year were similar in the aflibercept, bevacizumab, and ranibizumab groups, ranging between 7.5 and 8.3 letters.[14] Among eyes with baseline vision of 20/50 or worse, the mean VA improvement was greatest with aflibercept, 18.9 letters, and significantly better compared with both bevacizumab, 11.8 letters, and ranibizumab, 14.5 letters.

On the basis of these results, I am reassured that any of the 3 anti-VEGF agents are effective and safe for the treatment of center-involved DME, and so I am confident in choosing any of the available anti-VEGF agents to treat DME , especially in patients with very good VA at presentation. The results, however, have shifted my recommendations for patients who present with worse levels of vision. In those eyes, aflibercept is now my first choice.

Dr Eliott: I am following those same strategies and not only because of the efficacy outcomes in Protocol T, but also considering that no new safety issues emerged that would affect my decision to use any particular medication. In Protocol T, there were no statistically significant differences between the 3 anti-VEGF treatment groups in rates of serious adverse events—hospitalization, death, major cardiovascular events.[14]

Dr Nguyen: How many of your patients with DME who are candidates for anti-VEGF therapy present with VA 20/50 or worse?

Dr Singh: Probably approximately half my patients fit into that category. However, I think there are some limitations in trying to apply the subgroup results from Protocol T into clinical practice because the VA measurements in Protocol T were done according to the DRCR.net Visual Acuity-Refraction Testing Procedures Manual. In clinical practice, I evaluate VA with pinhole correction and only occasionally get a manifest refraction.

So, I agree that it was reassuring to see all 3 drugs could be effective for treating DME, but I think we need more data to help us refine treatment selection for individual patients. Perhaps we might look for guidance to optical coherence tomography (OCT) characteristics or HbA_{1C} values, and particularly for patients whose VA is 20/40 or 20/50.

Dr Do: I think the vast majority of retina specialists do not use manual refraction. I use the patient's current VA and eye examination findings to make my recommendation for the anti-VEGF agent.

Dr Eliott: The majority of patients needing treatment for DME do not have VA in that borderline range of 20/40 to 20/50, and so the treatment decision for most will be clear cut. Our Retina Service has its own optometrist, so most of our patients have a recent refraction test, and then they have a pinhole vision determined at each visit.

Dr Nguyen: We now have 5-year data from RISE and RIDE, the ranibizumab pivotal trials, showing continued improvement in retinopathy severity over time and maintenance of good vision, although after being switched at the end of 3 years from monthly injections to as-needed treatment, three-fourths of patients still required treatment for stability.[15] Are those findings consistent with your clinical experience?

Dr Do: Per protocol, patients in RISE and RIDE received monthly injections for the first 3 years, and so their experience is significantly different from that of our clinical practice patients. The good long-term outcomes with a low burden of injections in later years among RISE and RIDE patients may be the result of having kept their edema well controlled for a relatively long time using a fixed treatment schedule. In the ranibizumab arm of DRCR.net Protocol I, patients were treated as needed with strict re-treatment protocols. Fewer injections were needed during the second and third years of the study than during the first year, and patients were still able to maintain excellent VA outcomes.[16,17]

Dr Singh: I was impressed by the 5-year results from Protocol I showing the low number of ranibizumab injections given during years 4 and 5—the maximum was just 3 or 4, but about half of the patients received no injections.[18] Those data suggest that anti-VEGF treatment is disease modifying. My clinical experience mimics what was seen in Protocol I in terms of a decreasing need for injections over time, particularly beginning in the fourth year of treatment.

"Those data suggest that anti-VEGF treatment is disease modifying."
—Rishi P. Singh, MD

Dr Nguyen: Data from the ranibizumab and aflibercept pivotal trials have also been analyzed with patients stratified by HbA_{1C} level. Before

Table 3. Effect of HbA_{1C} Levels on DME Treatment Outcomes

	HbA_{1C} Level (%)				
	<6.7	6.7–<7.4	7.4–<8.6	≥8.6	*P* Value
Aflibercept at 1 year[21]					
Increase in ETDRS Letters	11.7	11.9	11.7	11.1	
Decrease in CRT (µm)	-201	-196	-195	-188	NS
Laser at 1 year					
Increase in ETDRS Letters	4.1	1.9	0.8	-0.3	
Decrease in CRT (µm)	-102	-83	-69	-43	<.05
Ranibizumab at 3 years[20]					
Increase in ETDRS Letters	13	12	11	12	
Decrease in CRT (µm)	-301	-278	-248	-244	NS

CRT=central retinal thickness; ETDRS=Early Treatment Diabetic Retinopathy Study.

we talk about the findings, however, I want to say that I was surprised to see that HbA_{1C} did not improve over time in most patients.

Dr Singh: Even after 1 year in DRCR.net Protocol M, in which patients received more frequent subject-specific diabetes education during their retina examination, mean HbA_{1C} remained unchanged from baseline.[19]

Dr Nguyen: Post hoc analyses from RISE and RIDE showed improvements in VA, edema, and DR severity score, with similar outcomes in patients with baseline HbA1C ≥7.0% and those with better glycemic control[20] **(Table 3)**.

In the aflibercept pivotal trials, visual outcomes and anatomic outcomes for patients in the laser group worsened with increasing baseline HbA_{1C}, and patients in the laser group with the lowest baseline HbA_{1C} were also least likely to receive rescue treatment[21,22] **(Table 3)**. Among aflibercept-treated patients, however, there were no significant associations between baseline HbA_{1C} and changes in vision or retinal thickness outcomes.[21] In addition, the need for rescue treatment was low overall and not dependent on baseline HbA_{1C}.

I am not aware of any analyses like this for bevacizumab, although I expect we would see the same lack of dependency on HbA_{1C}. Therefore, I believe we can conclude that it is worth initiating anti-VEGF therapy for patients with DME regardless of their level of glycemic control.

Dr Drincic: Because a low HbA_{1C} target is not appropriate for all patients, these data are also reassuring for endocrinologists.

Dr Singh: The finding that improvement in retinal thickness decreased significantly as HbA_{1C} increased in the laser arm of the aflibercept trials (Table 3) has significantly changed how I practice. Previously I would choose laser instead of anti-VEGF therapy for any patient who I expected might not return for monthly visits. Now, I prefer to treat those patients with an anti-VEGF agent if their HbA_{1C} is high.

"I believe we can conclude that it is worth initiating anti-VEGF therapy for patients with DME regardless of their level of glycemic control."

—Quan Dong Nguyen, MD, MSc

Dr Nguyen: Data from the aflibercept pivotal trials were also analyzed to determine if the benefit of aflibercept for improving VA was affected by baseline demographic or systemic characteristics, including body mass index or the presence of renal impairment, ischemic heart disease, CVD, or hypertension—and it was not.[22] Those findings are interesting in the context of what Dr Do mentioned previously in terms of anti-VEGF treatment being so good that it might override the negative influence of systemic issues on DME.

Corticosteroid Implants

Dr Nguyen: We also have 2 intravitreal corticosteroid implants that are approved for treatment of DME.[23,24] Dr Do, when would you use one of these products?

Dr Do: I consider an intravitreal corticosteroid implant as second-line treatment after a patient has a suboptimal response to intravitreal anti-VEGF therapy. If I am going to use steroid implants, I choose the dexamethasone implant first because the safety profile is more desirable than that for the fluocinolone implant. There may be a minority of cases in which the fluocinolone implant may be a reasonable choice, but adverse events such as elevated intraocular pressure (IOP) must be carefully monitored.

Dr Eliott: I consider adding a corticosteroid implant if a patient has no response or an incomplete response at approximately 6 months after starting anti-VEGF therapy, and I also start with the dexamethasone implant. Patients who do well with the dexamethasone implant can then be considered for the fluocinolone implant because they will have satisfied any insurance requirement for having a steroid challenge.

Dr Nguyen: Dr Singh, do you think there is a need to assess patients for a steroid IOP response before using the dexamethasone implant?

Dr Singh: Any increase in IOP occurring with the dexamethasone implant is usually manageable with short-term topical therapy, and so I do not perform any type of challenge.

Although I consider anti-VEGF therapy as my first-line therapy for DME management, there are situations in which I would use the dexamethasone implant sooner rather than later. One such scenario is that involving a vitrectomized eye. Although I would still start with an anti-VEGF agent, I would use the dexamethasone implant if the patient did not have a sufficient response after just a few injections.

Dr Nguyen: There are data showing the response to the dexamethasone implant for treatment of DME is the same in vitrectomized and nonvitrectomized eyes.[25] I am not aware of any studies investigating if vitrectomy affects the efficacy of the fluocinolone implant. Are there data regarding the anti-VEGF agents?

Dr Do: A post hoc analysis from DRCR Protocol I suggested that ranibizumab had similar efficacy in vitrectomized and nonvitrectomized eyes.[26] I think that information has to be considered cautiously, however, because it is from a post hoc analysis that included only approximately 25 vitrectomized eyes.

Dr Eliott: The results were surprising, and of course it would be nice to see a large prospective study designed to specifically investigate this question. Nevertheless, I think the data on ranibizumab were encouraging in suggesting the benefit of ranibizumab is not different in vitrectomized eyes.

Case —*From the files of Dean Eliott, MD*

A 77-year-old gentleman who is a retired chemist presents 2 months after noticing decreased vision in his right eye. He was diagnosed with type 2 diabetes 13 years earlier, and 3 years ago he had a myocardial infarction followed by placement of a coronary artery stent. His most recent HbA_{1C} is 7.7%. His medications include glimepiride, valsartan, metformin, atorvastatin, metoprolol, and aspirin. The patient is very compliant, and his blood pressure, cholesterol, and weight are normal.

On ocular examination, his VA is 20/60 OD and 20/25 OS. He has very minimal cataract OU. Retinal imaging reveals macular cysts OD **(Figure 2)**, *a small amount of lipid, and a microaneurysm that is too close to the center to treat with laser.*

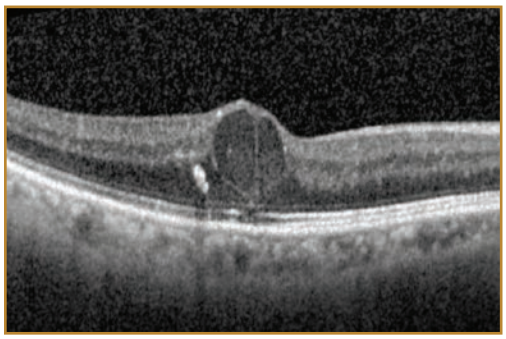

Figure 2. OCT showing large central cysts and adjacent outer retinal hyperreflective foci.

Image Courtesy of Dean Eliott, MD

The patient was started on monthly ranibizumab treatment OD, and after 3 months, his OCT and VA are unchanged.

Dr Nguyen: This is a large intraretinal cytoid space. The cyst appears to have well-defined walls around it.[27] Do you think that makes the DME more difficult to treat?

Dr Eliott: The size of the cyst is atypical, and the edema is localized to the foveal and perifoveal areas. I do think it may be a little more difficult to treat because of its large size.[27]

Since there is no improvement after 3 ranibizumab injections, how would you proceed with treatment?

Dr Nguyen: I would continue with monthly injections and try to get complete DME regression.

Dr Do: Because this patient had a VA of 20/60 at presentation, and given that is not a protocol refraction vision, if I saw him today I would start him on aflibercept instead of ranibizumab.

Monthly ranibizumab was continued. After 6 injections, VA remains 20/60, the cyst is a little smaller, and there is an increase in the adjacent lipid deposition.

Dr Eliott: Dr Singh, what would you do now?

Dr Singh: I might give another anti-VEGF injection and have the patient return in 14 days. If retinal thickness is unchanged at that time, I would switch treatments.

Dr Eliott: We considered having the patient return sooner, but he lives far away, and although he is very cooperative, we thought it would be asking too much. We continued with the monthly ranibizumab injections.

After 9 injections, VA remains 20/60, but the DME shows definite improvement. Continuing with monthly injections, VA at 12 months is 20/50 and the DME is further improved.

Dr Eliott: Dr Nguyen, would you keep him on monthly ranibizumab injections?

Dr Nguyen: I would, considering he is continuing to improve but still has residual DME.

Monthly ranibizumab injections are continued. At 15 months, VA is still 20/50, but there is further substantial improvement in the OCT. At 18 months, VA is 20/30; and after 21 injections, VA is 20/25, the DME is resolved, and the patient is very happy.

Dr Nguyen: We have to remember that DME is a chronic disease. When treating it, we need to be patient and persistent and not change treatment agent or plan too quickly. Some retina specialists talk about re-assessing their treatment plan after 3 anti-VEGF injections. This is an excellent case to demonstrate the importance of persistence and following the approach outlined by the clinical trials.

"We have to remember that DME is a chronic disease. When treating it, we need to be patient and persistent and not change treatment agent or plan too quickly."

—Quan Dong Nguyen, MD, MSc

Case —*From the files of Rishi P. Singh, MD*

A 64-year-old man with type 1 diabetes presents to his general ophthalmologist in May 2010 with a complaint of slightly blurry vision in his right eye for the past 3 days. He has hypertension that is controlled on medication, and he has been advised to speak to his primary care doctor about better lipid and glycemic control because he has elevated triglycerides, a low HDL, and an HbA_{1C} of 10.3%. He is on metformin and rapid- and long-acting insulin.

On examination he has moderate nonproliferative DR (NPDR) OU, mild cataract OU, and clinically significant macular edema (CSME) OD. Visual acuity with correction is 20/20-1 OD and 20/25 OS. He is treated with focal laser OD.

Two years later he presents because of decreased vision in his left eye, beginning 3 months earlier. Visual acuity with correction is 20/25 OD and 20/50 OS. He still has mild cataract OU and moderate NPDR OU, but he now has CSME OU and is treated bilaterally with focal laser **(Figure 3A, next page)**. *Visual acuity is stabilized at 20/25 OD, but worsens OS. He undergoes another laser treatment that results in improvement on OCT and only slight improvement in VA.*

He is referred to the retina service in September 2014 for evaluation of clinically significant DME (CSDME) OS **(Figure 3B, next page)**. *Visual acuity without correction (VA sc) is 20/60+2 and 20/30— with pinhole. He is started on bevacizumab.*

Dr Singh: Dr Do, how would you treat this patient?

Dr Do: Because his VA improves from 20/60 without correction to 20/30 with pinhole testing, it seems reasonable to assume his VA would be 2 lines better than 20/60 using manual refraction testing

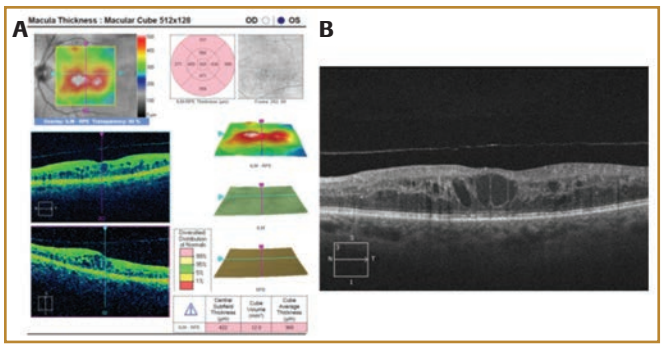

Figure 3. Optical coherence tomography showing increased retinal thickness (A) and the presence of cystoid macular edema on the horizontal raster scan (B).

Images Courtesy of Rishi P. Singh, MD

per protocol. Using the DRCR Protocol T results as a guide, I would start him on anti-VEGF therapy, and I think bevacizumab, ranibizumab, or aflibercept are all great options. With his good vision at baseline, I would recommend bevacizumab.

Dr Singh: The pinhole VA measurement is with a Snellen chart, and VA can improve by 1 line or more using an ETDRS (Early Treatment Diabetic Retinopathy Study) chart. Therefore, he may have 20/25 or even 20/20 ETDRS best corrected VA.

After 3 injections, VA sc is improved to 20/50 -2/+2, but unchanged on pinhole, and CSDME persists. The patient is treated again with bevacizumab. **(Figure 4A)** *At his next visit, the patient states his vision is improved, but VA sc is 20/50 -1/+1 and 20/40-1 on pinhole.*

Optical coherence tomography images are shown in **Figure 4**.

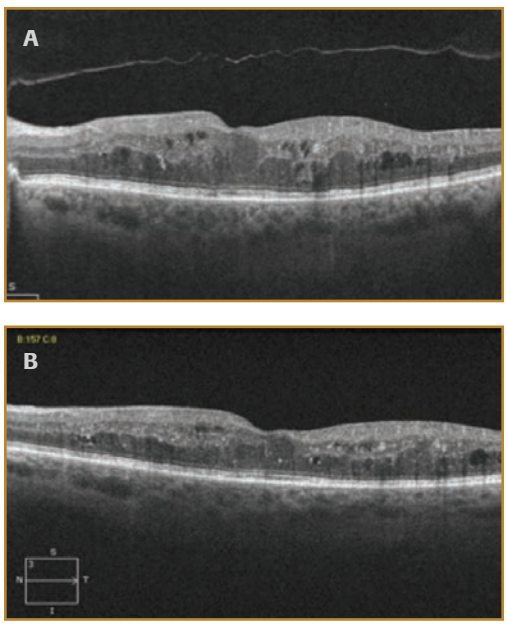

Figure 4. A) Patient has received 4 injections of intravitreal bevacizumab without significant improvement in either OCT or VA. **B)** Persistent fluid is noted in patient's OCT although the retinal thickness and volume of the retina has improved.

Images Courtesy of Rishi P. Singh, MD

Dr Singh: What would you do now?

Dr Nguyen: A reduction in intraretinal fluid seems to have occurred between the 2 visits, but a lot of cystic changes remain. I would continue the bevacizumab.

Dr Eliott: His VA may be a bit worse, but his anatomy looks a bit better. I think bevacizumab was a good choice for the initial treatment, and I also would continue it.

Dr Singh: In looking at the OCT for signs of DME activity, I have learned to rely more on changes in retinal thickness and volume and less on the line scans. In this patient, volume was improving with each injection even though the appearance on the line scans was not necessarily better.

Bevacizumab is continued, and 3 months later, VA remains stable, although there is persistent center-involved DME on OCT **(Figure 4B)**.

Dr Singh: At this last visit, pinhole VA is 20/40+1, and the retinal volume and subfield thickness are at their lowest values since the patient started anti-VEGF treatment.

Dr Nguyen: This case is another reminder about the need to be patient and persistent when treating DME and to not change course too quickly.

Case *—From the files of Rishi P. Singh, MD*

A 49-year-old woman diagnosed 1 year earlier with type 2 diabetes presents complaining of an 8-month history of decreased vision affecting both eyes, worse in the left eye. She also notes flashes, floaters, and photophobia. She has controlled hypertension and is on metformin. Her HbA_{1C} is 10% and average glucose is 167 mg/dL; she has elevated triglycerides (243 mg/dL) and her LDL cholesterol is 135 mg/dL.

Visual acuity is 20/125 OD and 20/100 OS, and she has senile nuclear sclerotic cataract OU. Ultra-wide field imaging shows possible macular ischemia. She has diffuse microaneurysms, increased retinal thickness, and lipid exudates **(Figure 5)**. *She is diagnosed with severe to very severe NPDR and severe CSDME OU.*

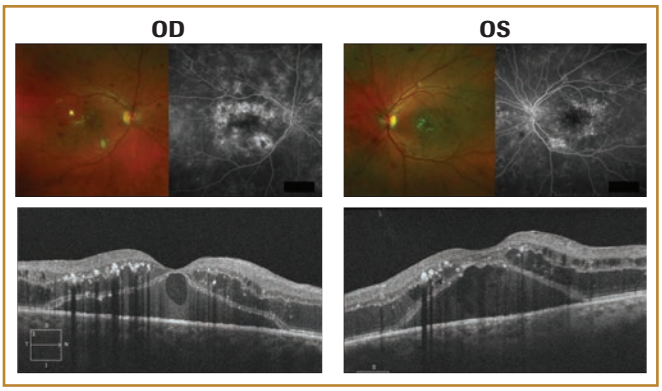

Figure 5. Images from baseline evaluation of a patient with CSDME: fundus photos (upper panels) show diffuse retinal hemorrhages without proliferative changes; fluorescein angiogram shows a slightly widened foveal avascular zone with leakage from microaneurysms; OCTs (lower panels) show intraretinal fluid, subretinal fluid, and lipid exudation.

Images Courtesy of Rishi P. Singh, MD

Dr Nquyen: This patient has poor glycemic control and dyslipidemia, both of which are risk factors for diabetic eye disease and other complications. What can be done to improve her systemic disease?

Dr Drincic: The glycemic treatment for this patient is inadequate and can be intensified. She may be a candidate for insulin, depending on her risk for hypoglycemia and ability to pay for medications, or she can start on a sulfonylurea in addition to the metformin. In addition, she should be started on a statin for her dyslipidemia.

Ms Pagenkemper: Lifestyle management is always foundational for glycemic control. The ophthalmologist should support positive lifestyle changes and encourage patients to contact their primary care physician (PCP) for a referral to a registered dietitian or certified diabetes educator. On the Web site of the Academy of Nutrition and Dietetics (www.eatright.org/find-an-expert), users can search for diabetes educators with a particular expertise (pediatric, cardiovascular, and so forth) by ZIP Code. The American Association of Diabetes Educators Web site (https://www.diabeteseducator.org/patient-resources/find-a-diabetes-educator) also features a search function, by ZIP Code or other criteria, and it provides a referral form for a PCP to sign.

Dr Nguyen: Dr Eliott, what would be your initial treatment for this patient's center-involved DME?

Dr Eliott: On the basis of her VA and the results of Protocol T, I would use aflibercept. I would treat both eyes simultaneously, but using a different lot number of the medication for each eye.

Dr Nguyen: Dr Do, would you do bilateral injections on the same day?

Dr Do: Yes, I am comfortable with that.

Dr Singh: This patient presented to me in 2014 before the Protocol T results were available, and I treated both eyes with bevacizumab.

VA improved to 20/80 OU and to 20/50-2 OU after another injection. Edema was still present and she was treated with focal laser OU.

Dr Nguyen: Do you still use laser in combination with anti-VEGF therapy?

Dr Singh: I do. The protocols for all the anti-VEGF studies included prompt laser or allowed for deferred laser as rescue. In fact, the results from Protocol T showed that, on average, 35% to 55% of patients received laser, depending on their anti-VEGF treatment assignment.[13] Many patients in my practice cannot return for monthly follow-up, and so I will combine laser with anti-VEGF treatment to try to achieve stability.

Dr Do: I agree that the majority of the study protocols allowed for some type of laser. However, the ranibizumab and aflibercept pivotal trials were more like pure anti-VEGF studies because only a minority of eyes assigned to the anti-VEGF treatment group needed rescue with laser.

I do not often use laser in combination with anti-VEGF therapy. When I do, I tend to follow the DRCR.net Protocol I for deferred laser treatment and wait for 6 months after after the start of anti-VEGF therapy, considering that study found prompt laser treatment may have a detrimental effect.[16,17]

Dr Eliott: I use laser very rarely. I generally treat for at least 6 months with an anti-VEGF agent, and then I may use focal laser if there is some circinate lipid with thickening around a microaneurysm, so long as the microaneurysm is not too close to the fovea.

Dr Nguyen: Some retina specialists believe that there is a benefit for using the micropulse laser, such as the yellow (577-nm) laser, as it may have efficacy in the treatment of DME and does not result in retinal damage. More information is needed, however, to determine its role—safety and efficacy of this treatment—in the management of DME.[28]

After focal laser, VA improved in the right eye to 20/40+1 and worsened in the left eye to 20/70-1. After 2 months with no anti-VEGF injection, vision and DME are worse in both eyes and there are significant hard lipid exudates. The patient received bevacizumab OU, which resulted in significant improvement. Bevacizumab is continued in the left eye only, in which VA sc was 20/70-1, and the right eye is observed (VA sc 20/25-3). The right eye did well, but VA in the left eye worsened to 20/300 when the patient was seen in March 2015. Because results from Protocol T were known, treatment for the left eye was switched to aflibercept, and 1 month later, VA was 20/60-2.

Dr Nguyen: This case illustrates the point that there are patients whose vision will improve despite long-standing DME. Others, however, may have permanent loss of vision.

Dr Singh: It also shows that lipid exudates can limit final VA, and we do not have a good way to treat that.

Dr Eliott: Regrettably, lipid tends to precipitate at the fovea or close to it. It would be nice to have something to prevent that.

Summary

Since the introduction of anti-VEGF agents for the treatment of DME, there has been a paradigm shift in the management of this chronic disease. Anti-VEGF agents demonstrate an excellent safety and efficacy profile and have thus become first-line therapy in the management of DME. However, clinical response to anti-VEGF therapy may be highly variable. Laser photocoagulation, including micropulse laser which may cause less retinal damage, may be considered in selected cases. Sustained-release steroid devices also may be a very appropriate second- or even first-line therapeutic choice for selected patients with DME. The importance of proper control of diabetes, hypertension, weight, and lipidemia, along with a well-balanced diet, cannot be overemphasized, because it may help to preserve a patient's vision and prolong his or her life.

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Following are the questions that will be asked.

1. Dietary strategies that are recommended to patients with diabetes for maintaining glycemic control and reducing glycemic variability include:
   A. Avoiding alcohol
   B. Following a low glycemic index meal plan
   C. Limiting intake of foods with a high simple sugar content
   D. A and C

2. Factors favoring intensive glycemic control include all the following, except:
   A. Newly diagnosed type 2 diabetes
   B. Absence of cardiovascular disease
   C. Proliferative DR
   D. Young age with no medical comorbidities

3. In the ACCORD/ACCORD Eye study, which of the following outcomes did patients treated with combination fenofibrate/simvastatin have compared with patients treated with simvastatin alone?
   A. Increased mortality in men, but reduced DR progression
   B. Less vision loss from DME, but more cardiovascular events
   C. Fewer cardiovascular events and DR progression in the overall population
   D. Lower risk for DR progression, but not for cardiovascular events

4. The 1-year results from DRCR.net Protocol T found a benefit of aflibercept compared with both bevacizumab and ranibizumab in patients with _____.
   A. HbA_{1c} >7.0%
   B. Central retinal thickness >375 microns
   C. VA 20/32 to 20/40
   D. VA 20/50 or worse

5. Safety results from DRCR.net Protocol T showed rates of serious adverse events, hospitalization, death, and major cardiovascular events were:
   A. Not significantly different among the 3 treatment groups
   B. Significantly lower with aflibercept vs bevacizumab and ranibizumab
   C. Significantly lower with bevacizumab vs aflibercept and ranibizumab
   D. Significantly lower with ranibizumab vs aflibercept and bevacizumab

6. Data from follow-up to 5 years in DRCR.net Protocol I show:
   A. Initial gains in VA achieved at 3 months with monthly anti-VEGF injections were sustained with an every-3-month injection schedule
   B. Patients maintained on a fixed monthly injection schedule achieved the best long-term VA outcomes
   C. Switching to another anti-VEGF agent was beneficial even after years of treatment
   D. The number of injections was reduced for many patients after ≥1 year of monthly treatment

7. After the first 3 years of monthly ranibizumab, what percentage of patients on the RISE and RIDE trials needed no further treatment for DME?
   A. 25%
   B. 33%
   C. 50%
   D. 75%

8. In the analyses of 1-year data from the trials comparing aflibercept with laser therapy in patients stratified by baseline HbA_{1c} levels, which treatment group had improved VA?
   A. Aflibercept-treated patients with lower baseline HbA_{1c}
   B. Aflibercept-treated patients regardless of baseline HbA_{1c} level
   C. Laser-treated patients with lower baseline HbA_{1c}
   D. Laser-treated patients regardless of baseline HbA_{1c} level

9. Which of the following treatment strategies does results from DRCR.net Protocol I comparing prompt to deferred laser support?
   A. Deferred focal/grid laser + ranibizumab for treatment of DME
   B. Focal/grid laser treatment alone for treatment of DME
   C. Prompt focal/grid laser + ranibizumab for treatment of DME
   D. Use of a 577-nm micropulse laser to treat microaneurysms close to the fovea

10. Available clinical trial data support consideration of _____ when selecting an anti-VEGF agent to treat symptomatic DME.
    A. HbA_{1c} level
    B. VA
    C. History of vitrectomy
    D. A and B

Expert Insights in Today's Multidisciplinary Management of

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Proceedings from an Expert Roundtable Discussion