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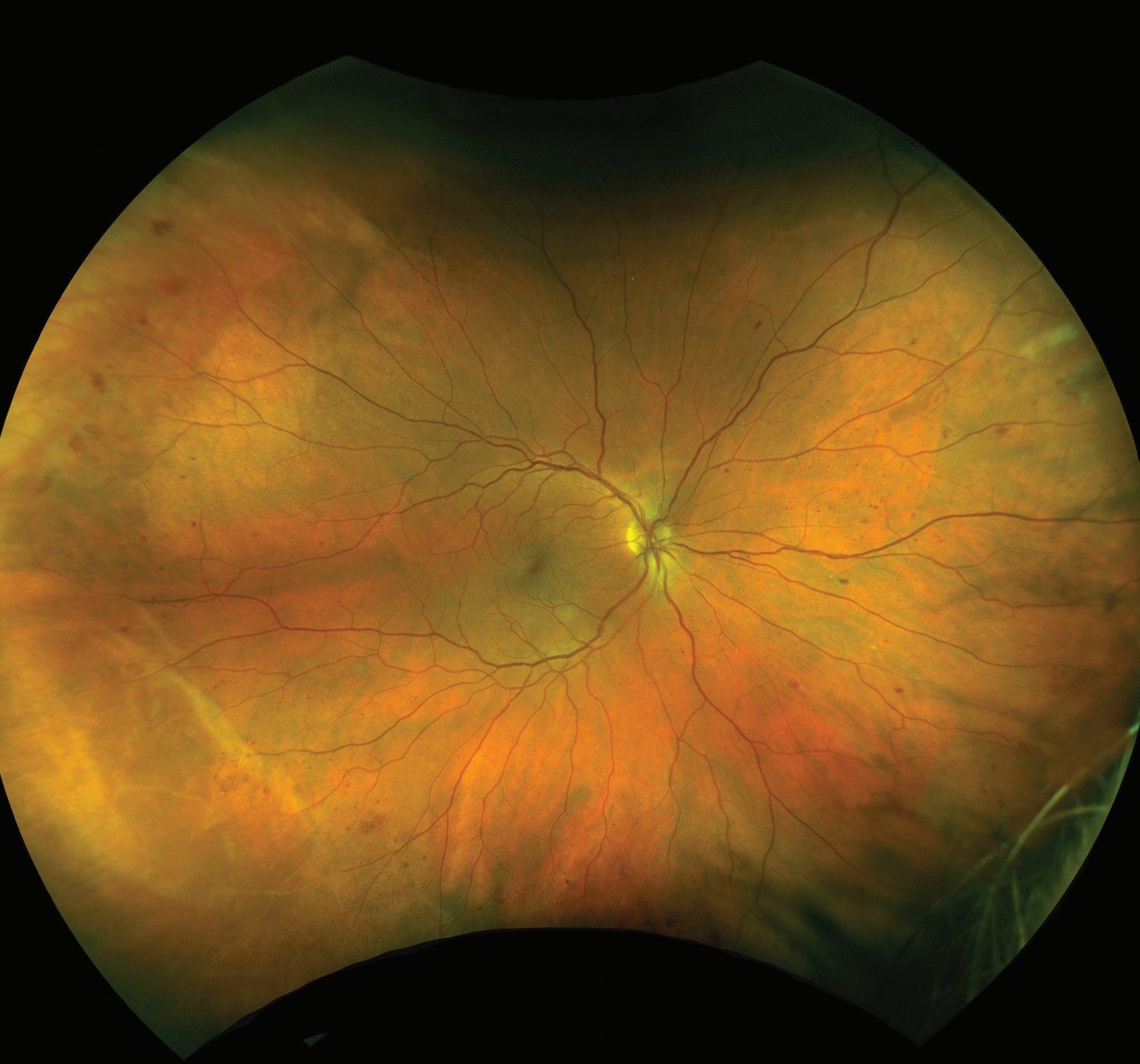
Ophthalmology MANAGEMENT | Retinal PHYSICIAN

Exploring the Diabetes Patient Journey

Experts discuss best practices for the shared care of patients who have diabetes



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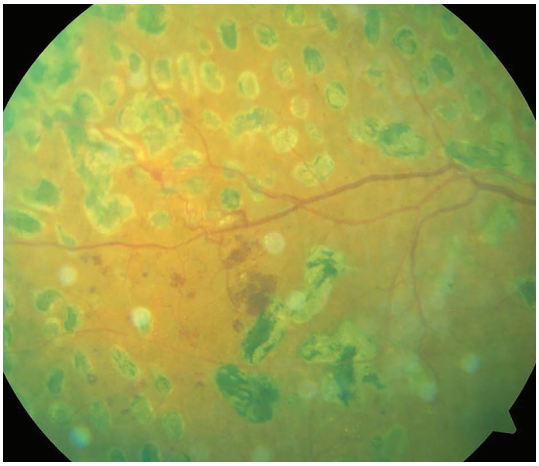
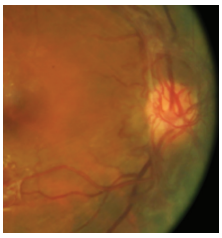
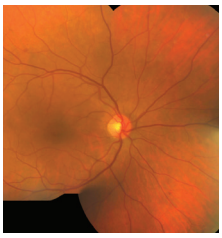
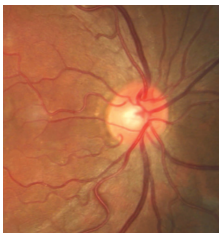
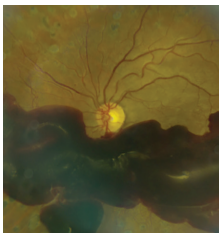
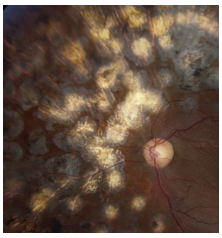


Cover image courtesy of Kirsti Ramirez, OD, and Carolyn Majcher, OD.

Exploring the Diabetes Patient Journey

Experts discuss best practices for the shared care of patients who have diabetes

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A New Road Map for a Diabetes Patient's Journey

With today's therapeutic options, successful outcomes are attainable

BY NANCY M. HOLEKAMP, MD

I never thought I would be able to say that we can reverse diabetic retinopathy during the course of my career. Yet today, we are doing exactly that. Not only are we preventing blindness, but we are improving vision, and that's really remarkable. Despite this good news, however, we are faced with some familiar challenges.

Patients with diabetic retinopathy are about to embark on a journey that demands a huge commitment. It requires impeccable compliance to be successful with the current treatment regimen. It requires very hard work on the part of both patients and physicians, who must be consistent and persistent to achieve the best results. It's not easy, and no one can slack off.

We often hear people talk about the burden of managing diabetic retinopathy, but the burden of vision loss is much greater. If you want to compare burdens, blindness always wins.

What I see helping people on this journey is this: Every medical professional who touches patients who have diabetes — primary eye care providers, primary care physicians, endocrinologists, nephrologists, podiatrists, pharmacists — must emphasize the critical importance of managing this disease. The staff in the retina specialist's office has to be encouraging. Patients' employers have to be understanding about the need for frequent time off. Family members have to be engaged and supportive.

This is not an individual's journey. It's a multifaceted, multi-person journey. But, the journey is worthwhile. The prize at the end? Patients get to keep their vision.

We see the very best results with DME and diabetic retinopathy in clinical trials. What is it about clinical trials that makes them unique and makes the results better?

The hallmarks of a clinical trial include consistency in treatment and follow-up, compliance, good communication, teamwork, and best management practices. It takes motivated patients to participate in clinical trials. They must adhere to a monthly schedule, not only for possible treatments but to be monitored and have data collected. The study team reminds patients to keep their appointments and calls them if they miss appointments. Everything we do to ensure the success of a clinical trial helps to make each patient's journey successful. Thus, I propose that we treat all of our patients as if they're in a clinical trial.

Is this a realistic goal? I believe it is. I have many very compliant patients in my practice who are not in clinical trials, and they achieve equally good results.

"Patients with diabetic retinopathy are about to embark on a journey that demands a huge commitment. It requires very hard work on the part of both patients and physicians, who must be consistent and persistent to achieve the best results. It's not easy, and no one can slack off."

Early in the anti-VEGF era, the clinical trials required monthly injections, and most clinicians predicted that regimen would be unsustainable. Yet, today, many of us administer monthly injections for 3 to 6 months at a time, and even those who follow a treat-and-extend regimen typically administer 10 injections in the first year. So we can do that; there's precedent. Whatever regimen we follow, we — as individuals who take care of patients with diabetes — must be committed to this journey, and so must our patients.

In the articles that follow, clinicians share insights on this journey and the tools and processes they employ to help navigate their patients toward successful outcomes. ■

Managing Diabetic Eye Disease in 2019

A wider range of therapies and indications facilitates individualizing treatment

BY DAVID A. EICHENBAUM, MD

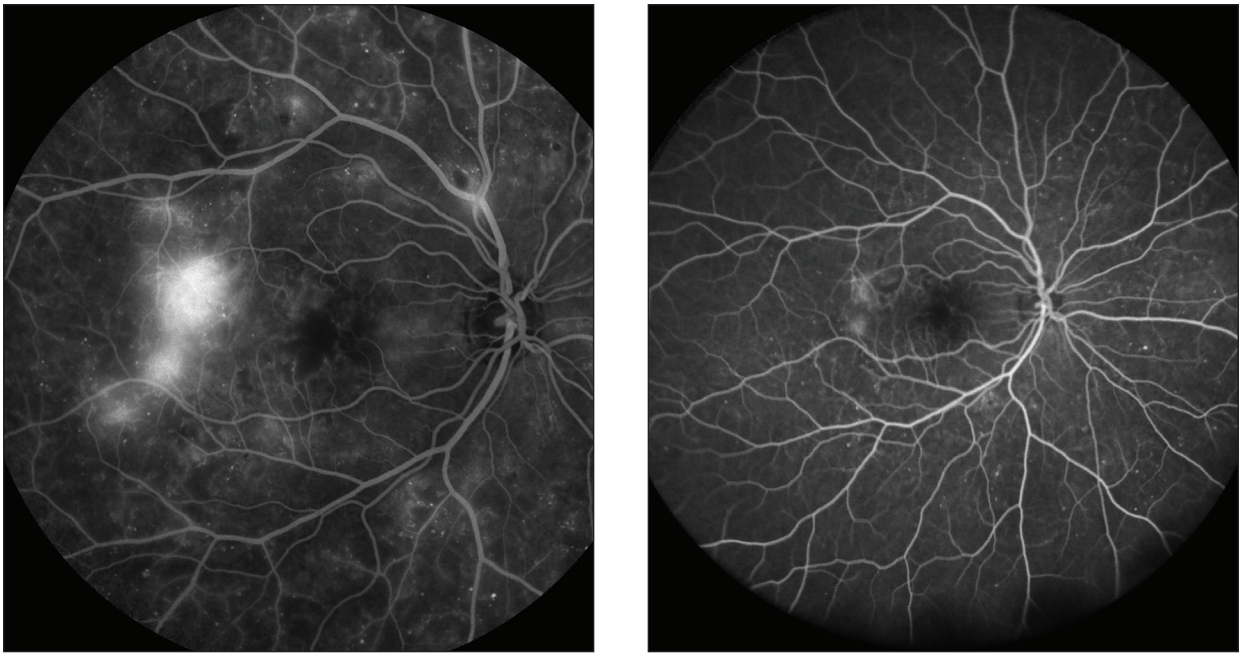
Thanks to advances in therapeutics over the last 10 years, patients with diabetic eye disease now have an excellent prognosis for longstanding good visual function.

Intravitreal anti-VEGF injection remains our preferred first-line treatment, and in 2017, FDA expanded the indications for ranibizumab (Lucentis, Genentech) to include all forms of diabetic retinopathy with or without DME, shifting our treatment paradigm toward earlier intervention.

The severity and urgency of diabetic eye disease increases from very early nonproliferative diabetic retinopathy (NPDR) without diabetic macular edema (DME) to NPDR with DME to proliferative diabetic retinopathy (PDR) without or with DME.

While it may be expedient to group patients according to disease type, no single algorithm drives treatment decisions in each of these categories. Various factors, including a patient's systemic status and ability and willingness to adhere to our recommendations, will determine how we individualize treatment. Even our decisions to treat or not to treat are subject to certain variables.

Not every patient with diabetic retinopathy needs treatment immediately, but when it's time to treat, I believe anti-VEGF therapy should, at the very least, be a core part of the plan. There are many reasons for that, but the most important is that anti-VEGF treatment is the first modality in two generations to have reliable evidence for diabetic retinopathy regression and has reproducibly shown a significant reduction in sight-threatening diabetic disease advancement.



Images courtesy of David Eichenbaum, MD

Figure 1. Photos of a right eye with active, high-risk PDR. Prior to treatment, the patient's visual acuity was 20/25. After 9 months and 5 doses of Lucentis, her visual acuity is 20/20-2.

"I tell all new patients who require treatment that we're about to start a marathon. ... It's important to prepare patients for that commitment, while reassuring them that if they persevere for a year, they will usually require fewer treatments going forward while preserving their vision."

New Diabetes Referrals: The Marathon Begins

A typical urgent case is a patient with poorly controlled type 1 diabetes who presents with bilateral high-risk PDR, a mild, symptomatic sub-hyaloid vitreous hemorrhage, minimal or no macular edema, and no significant premacular traction (Figure 1). In that type of situation, whatever modality I decide to use — anti-VEGF injections or laser or a combination of both — the first year is usually the most intensive period of treatment for patients.

I tell all new patients who require treatment that we're about to start a marathon. We're going to get to know one another well during that first year, because I will want to see them frequently.

Often, I tell a typical treatment-naïve patient, such as the PDR patient without DME described above, that I will see them and treat them every month for 3 months and then likely see them less often. Although I individualize injection and scatter laser in such a situation, I often think about Protocol S data, in which the average patient had seven treatments to control the PDR in the first year.[1]

It's important to prepare patients for that commitment, while reassuring them that if they persevere for a year, they will usually require fewer treatments going forward while preserving their vision.

Update Established Patients

Established patients with longstanding diabetes and advancing or progressive disease may have been treated with a laser in the past. Today, however, we have an opportunity to inform them that if they convert to proliferative disease or reactivate old proliferative disease, we have newer, more elegant modalities than we had in the not-so-distant past, and that we may use them instead of, or in combination with, laser to achieve better results.

An example would be a patient with proliferative disease who had undergone panretinal photocoagulation (PRP) several years ago. The condition worsens, and a vitreous hemorrhage occurs.

Ten or even 5 years ago, the recommendation would have been observation or a vitrectomy. However, today, we may be able to stop progression and foster a quicker recovery with medical therapy.

THE PATIENT COMPLIANCE CONUNDRUM: INTERRUPTIONS IN DIABETES THERAPY

The outlook for patients with diabetic eye disease has improved significantly in the last decade or so, but most predictions of maintaining good visual function come with a caveat: "... if patients come in for treatment."

A recent report found that unintentional interruptions in anti-VEGF therapy may result in potentially devastating visual consequences in patients with diabetic retinopathy.[1]

Lapses in follow-up are not uncommon in this patient population, and this study underscores how important it is for us to be vigilant when caring for patients with diabetes. What's more, we need to have a plan in place for when a lapse occurs.

WHO IS AT RISK?

We never know which patients with diabetes are going to interrupt treatment or follow-up, but with experience, I think most of us have a sense of who is at risk. Unfortunately, the patients who are at the highest risk for lapses are those who are the sickest.

They may have nephropathy and need dialysis, or they may need wound care for lower extremity ulcers. Any number of systemic issues may interfere with their ability to keep

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Still a Role for Laser

Although anti-VEGF injections have a huge role in diabetic retinopathy care, they're not the end-all be-all therapy. If fact, when patients, particularly patients with PDR, show poor tolerance to injections, poor compliance, poor response to anti-VEGF therapy, or rapid recurrence of proliferation, it's imperative that we be knowledgeable, confident, and ready to use the laser.

I consider anti-VEGF therapy and PRP complementary therapies that contribute to a tailored treatment approach. While the Protocol S trial evidence was constructed in an either/or fashion, we can extract pearls from the evidence and use both modalities in a combined fashion in our clinics.[1]

My "pearl" for scatter laser is that it is reasonable to have a relatively low threshold for adding some PRP, and, in combination with anti-VEGF therapy, scatter laser is more benign than it has been in the past, particularly with regard to inducing DME.

Complementary Intravitreal Steroids

Intravitreal corticosteroids are often a complementary therapy for patients with DME. Protocols I and T taught us that not every patient achieves a dry macula with anti-VEGF therapy, and we should not become complacent in the minority of patients who retain significant intraretinal fluid despite optimal anti-VEGF therapy.[2,3]

Steroids also have shown some regression of diabetic retinopathy,[4,5] but we need to remember that the regression effect from corticosteroids has never been shown to be as robust as the regression achieved from intravitreal anti-VEGF therapy.

"Established patients with longstanding diabetes and advancing or progressive disease may have been treated with a laser in the past. Today, we have an opportunity to inform them that if they convert to proliferative disease or reactivate old proliferative disease, we have newer, more elegant modalities than we had in the not-so-distant past."

Conundrum, continued from page 7

appointments. They are at a high risk for vision loss from worse diabetic disease and at a high risk for treatment interruption because of systemic complications.

Patients who have access problems, such as high-deductible insurance coverage or difficulty making their copays, are also at risk for missing appointments. These are situations in which our ability to individualize treatment becomes important.

HAVE A PLAN

I use anti-VEGF therapy to treat almost all of my patients who have diabetes, but I have something of a hair trigger for performing panretinal laser in addition to the injections if I believe a patient is likely to become systemically sick or be hospitalized.

Similarly, if I sense a patient is going to interrupt treatment for a personal or financial reason, I consider panretinal photocoagulation for proliferative disease or focal laser for DME. These are well-established, durable treatments, even if they're not necessarily as beneficial as regular anti-VEGF injections.

COMBINE THERAPY

Most patients are somewhere between the very sick with severe diabetes and poor access and the perfect patient with better-controlled diabetes, good access, a good attitude, and good follow-up. That's why some form of combination therapy with anti-VEGF and laser can be exceedingly effective in many patients.

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A New Dialogue With NPDR Patients

Typically, we monitor patients who have nonproliferative disease, seeing them periodically to detect and document changes. This is a patient population I rarely treat at the first — and maybe not even the second — visit, but I start a dialogue with patients who have severe NPDR without DME.

These patients have good visual acuity, often 20/20, and they don't have symptoms of vision loss, but we know they have a high risk for conversion to proliferative disease or DME. We also have recent post-hoc data from RISE/RIDE and VIVID/VISTA that show anti-VEGF therapy can induce the most profound regression of retinopathy in eyes with severe nonproliferative disease, so I discuss the option of anti-VEGF injections.[6,7]

Depending on how well I know a patient, the status of the second eye, and the patient's engagement and understanding of the risks and benefits of treatment, I will treat with intravitreal injections of ranibizumab for NPDR without DME.

"With all of the tools we have — multimodal imaging to monitor their status and multiple highly effective treatment options — we can tell our patients that, as long as they continue to see us, it's likely they'll preserve good vision and see well for a very long time."

We are building a fairly robust database for this indication, with data from the RISE/RIDE trials,[6] and Protocol S,[1] as well as data from the VIVID/VISTA trials[7] and the Panorama study of aflibercept (Eylea, Regeneron),[8] showing profound regression in eyes with severe NPDR without DME, and that these eyes do not require monthly injections, as best we can tell.

Once patients have DME, we know they require frequent treatments to do well, but patients who have diabetic retinopathy without DME don't seem to require as many treatments as those with DME, if the endpoint of therapy is disease regression.

CLARIFYING THE RETINA SPECIALIST'S ROLE FOR PATIENTS

Patients with diabetes are often juggling appointments with multiple medical professionals. Adding yet another specialist, particularly another eye specialist, may be confusing for them. We need to make sure patients understand the role of the retina specialist versus the role of a primary eye care provider.

It is important to emphasize to patients with diabetes that even though they may be seeing a retina specialist frequently for treatment of their diabetic eye disease, the primary eye care provider will continue to have a critical role in their care for specific needs, such eyeglasses or contact lenses, cataract evaluation and management, or glaucoma management.

Long-term Management

The most important point we must make to patients after successfully regressing retinopathy, whether we reduce the frequency of treatments or stop treating altogether, is that we must monitor them for life. We also must encourage them at every visit to maintain their systemic control.

With all of the tools we have — multimodal imaging to monitor their status and multiple highly effective treatment options — we can tell our patients that, as long as they continue to see us, it's likely they'll preserve good vision and see well for a very long time. Regardless of the modalities one chooses to employ, achieving a patient's buy-in for regular, ongoing follow-up is probably the most important goal. ■

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Helping Patients Adhere to Lifelong Diabetes Management

Education and encouragement, reinforced at every visit, helps motivate patients

BY JOSEPH J. PIZZIMENTI, OD, AND SHANNON LEON, OD

Primary eyecare physicians often see patients early in the diabetes journey. Patients may be newly diagnosed with diabetes and referred to us for a comprehensive eye exam (including dilated retinal evaluation), or they may already have diabetic retinopathy that we are monitoring. These patients may still be processing the implications of their diagnosis when we see them.

As members of their care team, we are responsible for their ocular health, but we are also in a position to emphasize and expand upon the reasons why they should commit to managing their disease as prescribed.

In this article, we discuss the obstacles to adherence and how we can help patients overcome them.

Obstacles to Self-care

A patient's adherence to care and therapy has a profound effect not only on retinopathy but also on his or her overall well-being. Patients' attitudes, beliefs, and knowledge about diabetes may adversely affect self-management.

Patients are instructed and encouraged to adhere to the medical treatment regimen for their diabetes and to address modifiable risk factors and concomitant conditions, such as hypertension, dyslipidemia, obesity, sleep apnea, and smoking. For many patients, the recommended lifestyle changes may seem daunting. Keeping them engaged and motivated at every visit is important.

We use positive reinforcement of productive behaviors — for example, if they lower their HbA1c by even 0.5% or reduce their weight by even 2 pounds — to help motivate patients. We use a sensitive, caring approach to discuss setbacks, explaining that poor adherence to their diabetes care program may result in suboptimal glycemic control, potentially leading to microvascular complications. We emphasize that severe vision loss from diabetes is often preventable with timely detection and treatment.

Ongoing Challenge: Missed Appointments

One of the most challenging aspects of caring for patients with diabetes is that many of them have a tendency to not

EDUCATIONAL ASSETS FOR PATIENTS WITH DIABETES

Enhanced knowledge may lead to improved adherence, and patients can consult various trusted sources to educate themselves.

Eye on Diabetes was a program developed by an interprofessional provider team that uses a structured curriculum of interactive classes to enhance patients' knowledge of diabetes and its ocular implications.[1]

The National Eye Institute (NEI) has developed numerous educational brochures and videos to help patients better understand diabetic eye disease (nei.nih.gov/diabetes).

The NEI offers the following easy-to-remember acronym to help people with diabetes keep their health on TRACK:

- Take your medications as prescribed by your doctor
- Reach and maintain a healthy weight
- Add physical activity to your daily routine
- Control your ABCs — A1c, blood pressure, and cholesterol
- Kick the smoking habit

In addition, patients can reduce their risk of developing severe vision-related complications by having regular comprehensive eye examinations with dilated retinal evaluation.

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Practical Use of Posterior Segment Imaging in Diabetic Retinopathy

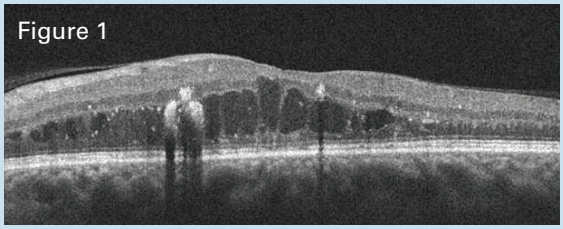
BY JOSEPH J. PIZZIMENTI, OD,
AND SHANNON LEON, OD

In patients with diabetes, certain factors should alert clinicians to look more intently, perhaps using more sophisticated methods to identify a particular finding or group of related signs. The case history and patient demographic information should drive this purposeful examination process.

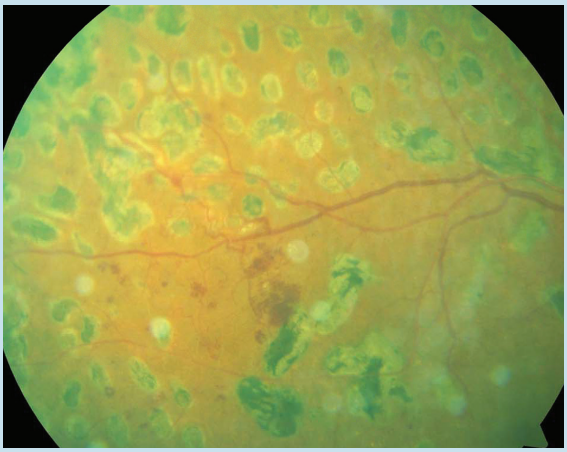
When properly implemented, posterior segment imaging technologies, such as OCT, OCT angiography (OCTA), and widefield fundus imaging may enhance the clinician's ability to identify and characterize signs of disease, even in eyes with compromised media. Imaging may be employed in cases where more information about the optic nerve, vitreoretinal interface, sensory retina, RPE, Bruch's membrane, and the choroid is desired.

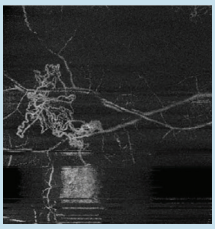
CASE REPORT

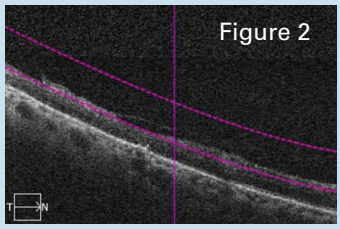
A 67-year-old black male with a history of hypertension and Type 2 diabetes with proliferative diabetic retinopathy (PDR) presented after panretinal photocoagulation (PRP) of both eyes. He reported gradual central blurring in the right eye. His entering visual acuity of 20/60 did not improve with pinhole. His recent HbA1c level was 6.9%, and in-office blood pressure measured 122/81 mmHg.



In addition to bilateral PRP laser, dilated fundus examination showed hard exudates, microaneurysms, and retinal thickening involving the foveal center, all in the right eye. The center-involved macular edema was confirmed on an OCT Macular Cube scan (Figure 1). A suspicious area of vascularization was noted in the retinal periphery of the right eye. Cirrus 5000 OCT with Angioplex (Zeiss) confirmed the presence of neovascularization elsewhere (NVE) (Figure 2). The patient was referred to his retina specialist for treatment of the macular edema and additional laser for the NVE.







TREATMENT AND FOLLOW-UP

The patient's right eye was treated with a series of intravitreal injections of ranibizumab (Lucentis, Genentech), as well as additional laser therapy for the NVE. We continued to monitor the patient post treatment. He practiced good adherence to his scheduled visits and maintained effective glycemic and blood pressure control.

Although the patient has since moved to another state, HIPAA-compliant communications with his current retina clinic revealed that the treatments achieved a stable visual acuity of 20/30 OD for the past year with no further areas of neovascularization.

KEY CLINICAL TAKEAWAYS

- OCT is a noninvasive means to confirm a suspicion of macular edema, as well as to characterize and quantify that edema.
- Imaging of normal and abnormal retinal vasculature with OCTA is helpful not only for establishing a diagnosis, but also for providing a better understanding of the pathophysiology of retinal vascular disease.
- Along with explaining the results of the dilated retinal examination, reviewing with the patient the results of fundus imaging and OCT/OCTA provides valuable education and motivation for continued adherence to care.

Kirsti Ramirez, OD, and Carolyn Majcher, OD, contributed to this case.

"National health survey data indicate that only about half of patients with diabetes undergo an annual dilated retinal exam.[1]"

keep their appointments. Missed medical appointments disrupt the continuity of care, thereby interfering with regular preventive screening and timely intervention.

Patients who frequently cancel appointments may do so because of lack of transportation, inadequate insurance, occupational obligations, family responsibilities, or limited English language skills.

Many factors predispose patients to avoiding medical appointments, such as young age, limited education, and low income, so we need to be mindful and take extra care to educate patients in these groups. In addition, patients may be skeptical about the effectiveness of their care or the efficacy of medications, or they may be concerned about the complexity of therapy, out-of-pocket costs, polypharmacy, or hypoglycemia.

National health survey data indicate that only about half of patients with diabetes undergo an annual dilated retinal exam.[1] The statistics for patients with diabetic eye disease keeping appointments with their retina specialists are also troubling. A recent study found that patients with diabetic macular edema were about three times more likely to miss appointments than patients with wet AMD.[2]

Making Appointments a Priority

We explain to patients that we want to see them at least once per year — and we pre-schedule their next visits — because diabetes can affect virtually every ocular tissue. If we wait until they have new symptoms before we see

CONTINUOUS GLUCOSE MONITORING AND DIABETIC RETINOPATHY

Glycemic control is vital to diabetes management. Among the methods used to monitor blood glucose are in-office glycosylated hemoglobin (HbA1c) measurement, self-monitoring of blood glucose, and continuous glucose monitoring (CGM).

While HbA1c is the gold standard in diabetes management, it has limitations.[1] For example, HbA1c is significantly influenced by systemic conditions that affect red blood cell life span, and it has been shown to vary by race and ethnicity.[1-3] Further, because HbA1c is a mean measurement, it cannot accurately predict or reflect acute glycemic changes, which is of great importance in diabetes management.[1,3]

Recognizing these limitations, researchers and clinicians have become interested in combining measurement methods or utilizing alternative blood glucose monitoring methods such as CGM.

CGM provides real-time or intermittently viewed measurements of blood glucose levels.[3] This method of monitoring is gaining ground in blood glucose management because of increased understanding of the importance of tight glycemic control in both preventing and managing complications. Landmark clinical studies have shown the benefit of increased glycemic control (apart from early transient reversible initial worsening) with respect to diabetic retinopathy (DR), and additional follow-up studies have highlighted the ability to maintain this reduced risk.[4]

CGM employs small sensors that are placed on the body to painlessly collect information about blood glucose levels. These levels are then transmitted to a monitor that displays them, typically at 1-, 5-, 10-, or 15-minute intervals.

While CGM is used mostly by patients with type 1 diabetes, there is interest in using it for type 2 diabetes as well, because of its ability to track maintenance and to generate information on quality of therapy.[5] Even with these benefits, however, concerns regarding CGM remain, including cost, standardization, necessity, and implementation.

Among the measurements that CGM provides is time in range (TIR), the amount of time a patient spends within his or her target glucose range.[2,3,5] TIR provides a better understanding of glycemic control as it gives greater information about daily acute fluctuations, which can then be used to improve control over time.[5]

A recently published study evaluated the relationship between TIR and diabetic retinopathy in 3,262 subjects with type 2 diabetes. The investiga-

them again, significant damage may already have occurred. We emphasize that most early ocular complications associated with diabetes are treatable and not immediately sight-threatening. Asking patients to briefly summarize our discussion ensures that they understand and appreciate its importance.

Long-term, sustained reductions in poor attendance rates remain difficult to achieve. Common tactics include reminders and educational videos, as well as print and online material from the American Diabetes Association (diabetes.org), the American Optometric Association (aoa.org), and other sources. (See "Educational Assets for Patients With Diabetes," page 10).

We show patients images of their affected retina alongside an image of a retina without retinopathy for comparison. Reviewing with them the results of their structural OCT and OCT angiograms also serves to educate and empower patients to take control of their care and keep appointments.

Coordinated Care

As primary eye care physicians, we must coordinate care with the other key players on a patient's diabetes care team, which may include a retina specialist, an endocrinologist, a nephrologist, and a primary care provider. Of course, we must always remember that the central member of that team is the patient!

"One of the most challenging aspects of caring for patients with diabetes is that many of them have a tendency to not keep their appointments. Missed medical appointments disrupt the continuity of care, thereby interfering with regular preventive screening and timely intervention."

Individual providers on the diabetes care team should remember that we are not alone. Referring patients for sessions with a certified diabetes educator (CDE) has been shown to improve adherence and is usually covered by insurance.[3] A CDE is the ideal professional to counsel

tors found that diabetic retinopathy and its severity are inversely related to TIR, as subjects with more severe cases of retinopathy spent less time in range and, thus, had higher variation in glycemic control.[2,5] Although some limitations were noted within the study, TIR shows potential as a measurement of glycemic control that can provide new, important information independent of HbA1c metrics.

The same study also considered the concept of glycemic variability, which is categorized as the fluctuations in blood glucose during a 24-hour period, and the differences in blood glucose fluctuations during the same time periods on different days.[2,4,5] Research on the role of glycemic variability in improving glycemic control is ongoing, with studies also evaluating its potential association with micro- and macrovascular complications.[6]

One major issue in the use of glycemic variability is standardized measurements, as currently there are several ways to evaluate glycemic variability.[6] Further research and standardization are needed for more practical use of this metric. However, the combination of glycemic variability, TIR, and HbA1c would provide a more complete picture of glycemic control apart from HbA1c alone. By assessing time in target glucose range using a continuous glucose monitor, providers may now have a measurable risk for development and severity of DR.

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"We can positively influence patients' perceptions of their disease by effectively communicating information about self-care, medications and therapies, and long-term prognosis ... we must strive to be our patients' most enthusiastic cheerleaders and advocates."

patients in detail about *how* to implement specific lifestyle changes to improve their HbA1c and other measures of glycemic status and overall health. (For more information, see "Continuous Glucose Monitoring and Diabetic Retinopathy," page 12.)

Good self-care and regular follow-up with an interprofessional team of providers are fundamental to optimal diabetes management.

Education Empowers Patients

We can positively influence patients' perceptions of their disease by effectively communicating information about self-care, medications and therapies, and long-term prognosis. We believe it's important to share details in small amounts at a time, particularly immediately following a diabetes or diabetic retinopathy diagnosis, and at an appropriate level that is culturally and linguistically relevant to that individual. In the end, we must strive to be our patients' most enthusiastic cheerleaders and advocates. ■

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OPTIMIZING COMMUNICATION AMONG PROVIDERS

Keeping primary care providers up to date about the status of their patients' diabetic eye disease helps those physicians determine the severity of their patients' diabetes from a systemic standpoint. For that reason, we always ask patients for contact information for their primary care physician and any specialists they're seeing regularly, such as endocrinologists or nephrologists.

I don't personally phone the patient's team of doctors unless I've been requested to do so, but I believe sending them written updates every 3 to 6 months is important. My letters are generated through my EMR system, and they are specific to each patient. I try to limit each letter to 1 page, and I focus on the impression and plan. I also send letters to referring ophthalmologists or optometrists periodically.

Engaging Staff in Diabetic Eye Care

Tips for promoting practice-wide support for patients

BY MICHAEL A. SINGER, MD, ROXANNE GOMEZ, COA, AND MELISSA PERKINS

Helping patients who have diabetic eye disease maintain their best vision for a lifetime is a team effort, involving not only the expertise of physicians, but also the support of every staff member who interacts with patients.

We teach patients about potential vision-threatening complications, explain how they can minimize their risks, and describe what we can accomplish with today's therapies. While we strive to be supportive and encouraging, we also emphasize the importance of adhering to scheduled follow-up visits and treatments and, of course, maintaining control of their diabetes.

We start preparing our staff for these important interactions as soon as they join the practice.

Consistent, Well-informed Messaging

Typically, new employees view a series of training videos — BSM (bsmconnection.com) has some good options — that explain the basic science of ophthalmology. Specific to diabetes, we make sure everyone has at least a rudimentary understanding of the findings from the Early Treatment Diabetic Retinopathy Study, particularly the emphasis on controlling blood glucose levels.

Having everyone on the same page from the beginning ensures that patients hear the same information from any member of our staff, because as we know, consistent messaging, whether delivered verbally, in print, or online, avoids confusion and is easier for patients to retain.

Continuing education is an important aspect of our staff education, particularly in the field of diabetic eye disease, as we have seen rapid advancements in both treatment and imaging technologies. We offer a number of educational opportunities for our staff; some we require, and some are optional. For instance, we schedule monthly conferences that may include training sessions or lectures by invited speakers — clinical experts or representatives from pharmaceutical or device companies — who present information on the latest developments in the field.

Our involvement in research also offers our staff some unique educational opportunities, as we provide monthly updates on our current clinical trials. This gives the team a preview of what's in development, and it also highlights how every member of the practice is contributing to the future of eye care. The knowledge and enthusiasm of our staff instill confidence and optimism in patients undergoing treatment.

"The value of imaging in a retina practice cannot be overstated. Not only do accurate, timely scans and photographs drive every treatment decision, but our staff's proficiency with this technology ensures smooth patient flow, improving efficiency, and the patient's experience."

Efficient, Accurate Imaging

The value of imaging in a retina practice cannot be overstated. Not only do accurate, timely scans and photographs drive every treatment decision, but our staff's proficiency with this technology ensures smooth patient flow, improving efficiency, and the patient's experience.

OCT is the workhorse imaging technology in most practices. We use it for almost every patient at almost every visit, which is why everyone in our clinical practice is trained to use our Cirrus OCT (Zeiss).

Fluorescein angiography is also essential in a retina practice. Two or three people in our main clinic and one

person in our satellite clinic are specifically trained in-house by our head photographer to perform fluorescein angiography with our Optos widefield technology.

Staff members who perform diagnostic testing are also qualified to scribe and perform patient workups, which adds to our efficiency. As you might expect, cross training is important in our practice. A dedicated member of our staff is responsible for ensuring that all staff members are trained on all of our systems and equipment, including EMR, inventory, patient tracking, and diagnostic equipment. They are required to maintain their COA certifications and to stay current with software updates.

Financial Assistance Expertise

For the most part, patients being treated for complications of diabetes are working-age adults, who must navigate the sometimes confusing, often overwhelming world of private healthcare insurance. Our staff is trained to help.

Given the high cost of the medications we use to treat diabetic retinopathy and DME, we strongly encourage all patients, regardless of their perception of their financial need, to apply for assistance from the various pharmaceutical companies. Our surgical coordinators guide them through the process.

"Having staff members who understand all aspects of the diabetes journey reassures patients that they are receiving the best care possible."

Genentech has several options to help patients pay for ranibizumab (Lucentis) through its Lucentis Access Solutions program. Eligible patients may be referred to the Lucentis Co-pay Program or independent co-pay assistance foundations for help with out-of-pocket expenses. The Genentech Patient Foundation provides free Genentech medications to people without insurance coverage or who have financial concerns and who meet income criteria.

Regeneron helps eligible patients receive aflibercept (Eylea) through its EYLEA4U program. Patients must demonstrate financial need, and they must re-enroll annually for this program. Both Alimera Sciences, maker of a fluocinolone acetonide intravitreal implant (Iluvien), and Allergan, maker of a dexamethasone intravitreal implant (Ozurdex) offer similar assistance programs.

While each company's level of assistance and criteria for eligibility may differ, we believe it is worthwhile for all patients to apply. One study found that patients with DME incurred $20,000 to almost $30,000 in annual inpatient, outpatient, and pharmaceutical expenses.[1] Annual costs for patients with DME and vision impairment were even higher, ranging from $27,000 to $42,000.[1]

Inventory Management

The branded drugs we use to treat diabetic eye disease cost anywhere from $2,000 to $8,500 per dose. An automated inventory management system along with due diligence by staff helps us avoid costly errors that can impact a patient's out-of-pocket costs or the practice's bottom line.

We use PODIS (besse.com), a system that automatically orders medications and uses barcode technology to track each dose from delivery to receipt of payment. It labels drugs that are patient-specific, integrates with our EMR system, and verifies that patients are being treated at appropriate intervals.

While this system streamlines inventory management, saves time, and helps us maintain tight control, we still rely on staff to ensure accuracy. Each scribe is responsible for managing the drug inventory for that day. They match each patient with the prescribed drug through the PODIS system and at the end of the day, our front desk supervisor and our technical supervisor review the day's activities as a final check.

Value of the Care Team

Our team approach to caring for patients with diabetic eye disease starts even before a patient arrives at the office, with scheduling and insurance verification, and continues through until checkout. To be successful, it takes a team in which every member adds value to the patient's experience.

Having staff members who understand all aspects of the diabetes journey reassures patients that they are receiving the best care possible. This helps patients feel that their experience is worth their time and helps to ensure that they will return for their next visit. ■

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Best Practices for Referrals in Diabetes

The complexities of the disease require focused, comprehensive evaluations and timely, relevant referrals

BY SHERROL A. REYNOLDS, OD, DIANA L. SHECHTMAN, OD, AND RASHID TAHER, MD

The statistics are undeniable — diabetes is a major public health problem. Nearly half of all Americans are affected. More than 30 million U.S. adults have the disease (7 million of them are unaware they have it) and 84 million have prediabetes.[1] If current trends continue, the prevalence of diabetes will have increased by 54% to more than 54.9 million Americans between 2015 and 2030.[2]

Diabetic retinopathy and its associated pathology, including diabetic macular edema (DME), is the leading cause of vision impairment and blindness in Americans of working age (20 to 74 years).[3] Given the predicted increase in diabetes, it is expected that diabetic retinopathy will also be on the rise. In fact, the National Eye Institute projects diabetic retinopathy to climb to 11 million by 2030.[3]

Reducing vision-threatening diabetes complications requires efforts on many fronts, so much so that the American Diabetes Association (ADA) recently published a new position statement on diabetic retinopathy, the first such update since 2002.[4]

This article addresses some best practices for referral of patients with diabetes, including patient education, early diagnosis, diagnostic technologies, treatment, telemedicine screening, and collaborative care among members of the healthcare team to produce the best outcomes.

Promote Health Literacy

A major hurdle in diabetes care is poor health literacy, which is prevalent among individuals with diabetes and has been associated with increased diabetes-related complications. Eyecare professionals tend to see diabetes patients more often than their primary care providers do, therefore, we play an important role in counseling patients on modifiable risk factors, the ABCs of diabetes — (A) glycosylated hemoglobin (HbA1c), (B) blood pressure, (C) cholesterol, and (S) smoking cessation — to reduce the risk or slow the progression of diabetic retinopathy. The patient described in case 1 — a 52-year-old black female with an HbA1c of 11 and proliferative diabetic retinopathy (PDR) in both eyes — is an example of someone who would benefit from such counseling.

Good glycemic control (HbA1c ≤7), as observed in major diabetes studies, is key to reducing or preventing progression of diabetic retinopathy.[5-7] Yet, a study evaluating perceptions of diabetes control found that a high proportion of patients believe they have "good" or "excellent" control of their diabetes, despite an average

REMOTE RETINAL SCREENING

Multiple studies have argued both in support of and against the idea that telemedicine is an improvement over eye care provider-based screening.[1,2] The recently published ADA position statement discussed retinal telemedicine screening for diabetic retinopathy. Although there is no consensus, this may be an effective means of identifying diabetic retinopathy in people living in underserved areas, perhaps where the providers-to-patients ratio is low or where the distance to reach a provider is prohibitive, particularly when the alternative is no screening.

Retinal photographs are not a substitute for comprehensive dilated eye examinations, but they may alert providers to the presence of disease and open a dialogue with patients about the need for prompt treatment and regular follow-up.

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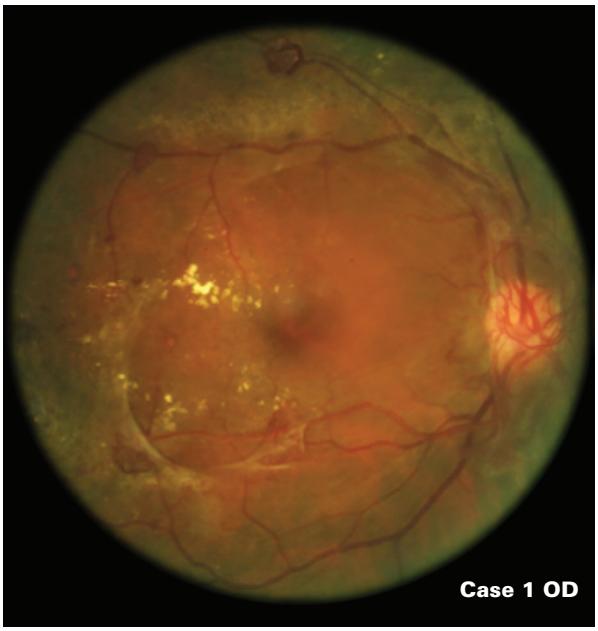
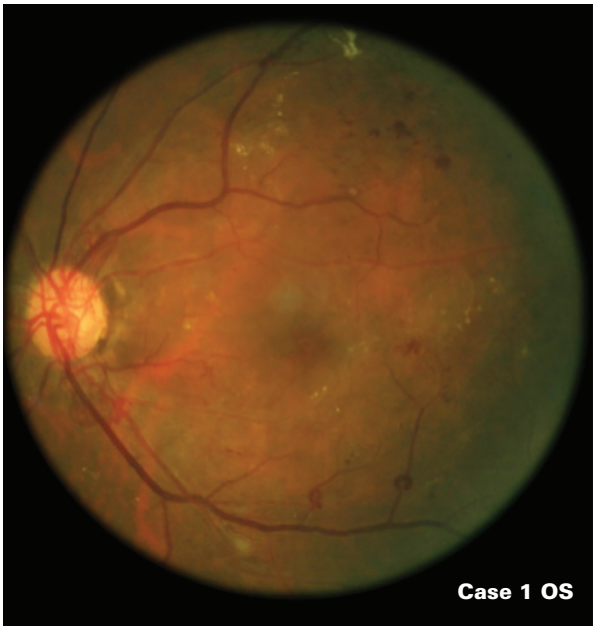




HbA1c of 9.5.[8] We recommend asking patients about their HbA1c in simple terms that they understand, such as "your 3-month blood sugar" results, and emphasizing the direct link between these readings and disease progression.

According to recently published hypertension guidelines, patients with diabetes should make sure their blood pressure is 130/80 mm Hg.[9] As observed in the Fenofibrate Intervention and Event (FIELD) study, cholesterol-lowering medications are beneficial in slowing the progression of diabetic retinopathy.[10] Advise patients to stop smoking, as it can exacerbate vascular disease, and emphasize proper nutrition and weight loss for those with diabetic retinopathy.

◀ Case 1: 54-year-old black female with HbA1c of 11 and proliferative diabetic retinopathy in both eyes

We also encourage patients to record their ABCs along with their current medications in a journal that they bring to every appointment. Not only does this useful tool encourage patients to feel ownership over their disease, it also facilitates communication with their healthcare professionals.

Other measures include providing educational information and brochures to patients in their preferred language and in large print. Trained staff members also can assist in diabetes education.

Stress the Need for Regular Dilated Examinations

To detect signs of sight-threatening retinopathy, all patients with diabetes should have dilated retinal exams early and regularly to identify problems and ensure that treatment begins promptly. Yet, too many patients do not show up for regular examinations and evaluations. According to a recent study, about 60% of Americans with diabetes do not adhere to recommendations for annual eye examinations.[11] Therefore, all members of the diabetes health care team must consistently reinforce the importance of regular dilated retinal examinations. (See "Remote Retinal Screening," page 17.)

All patients with type 2 diabetes should receive annual dilated retinal examinations beginning at diagnosis. Patients with type 1 diabetes should receive a dilated retinal examination within 5 years of disease onset, and annually thereafter. All women with diabetes who become pregnant should have a dilated retinal examination during each trimester of pregnancy.

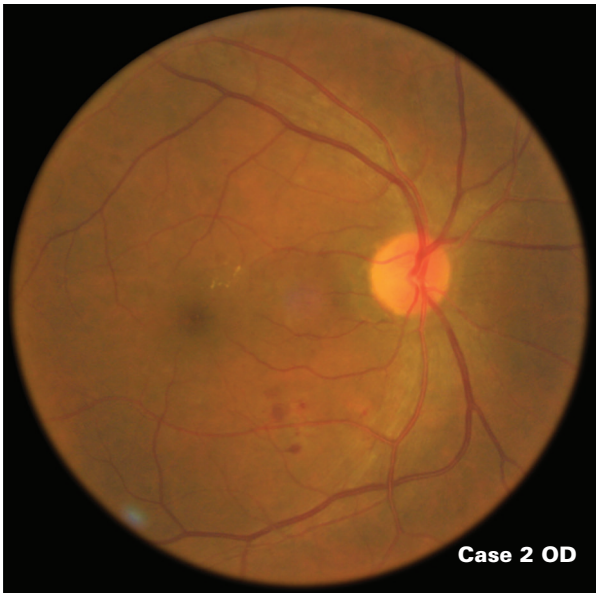
Although longer disease duration is an important predictor of diabetic retinopathy, about 30% of patients with type 2 diabetes have diabetic retinopathy at the time of diabetes diagnosis.[12] Most of these patients likely had diabetes for several years before they were diagnosed. Case 2 is an example: a 48-year-old Hispanic male without a history of diabetes who has diabetic retinopathy.

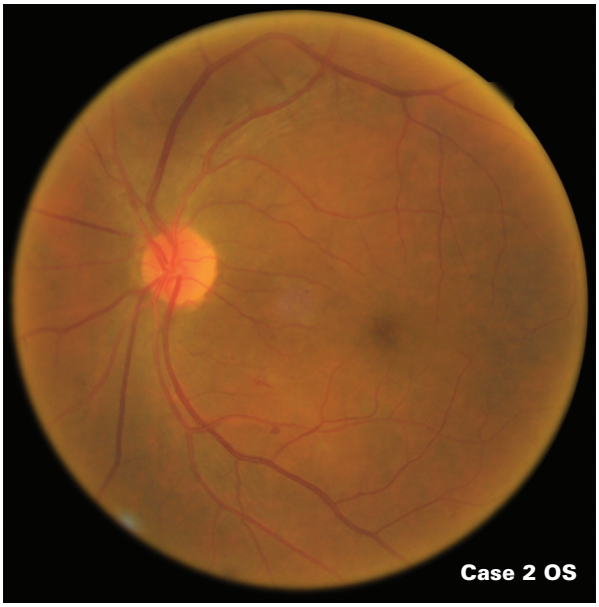
With these realities in mind, we must ensure patients schedule follow-up appointments before they leave our offices, and we must have a reliable reminder system, which may include text messages and phone calls, to prompt patients to attend their appointments.

▼ Case 2: 48-year-old Hispanic male with moderate diabetic retinopathy at the time of diabetes diagnosis

Stay Current With Imaging Technology

Recent advances in imaging technologies have significantly improved our ability to detect diabetic retinopathy and maculopathy. Although baseline retinal photography is still considered the gold standard for diabetic retinopathy imaging, it has some drawbacks that limit its use in clinical work. For instance, standard retinal photographs limit the view to about 30 degrees of the posterior pole and can sometimes miss early signs of diabetic retinopathy. The introduction of ultra-widefield (UWF) imaging has changed the landscape.

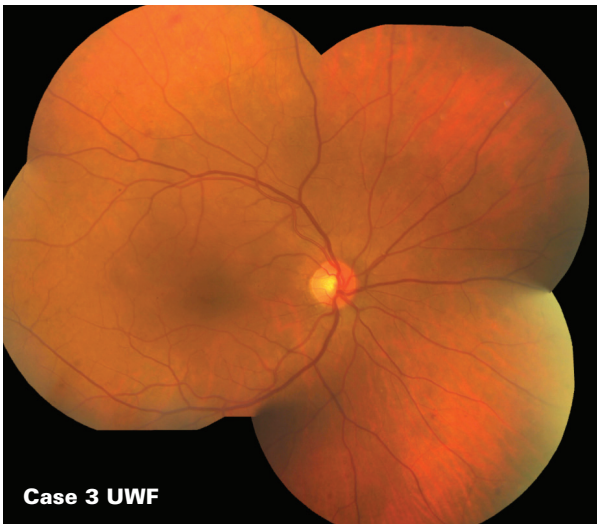

Case 2 OD


Case 2 OS

UWF imaging allows for a larger field of view, so we can see more of the retina and detect peripheral changes. This is illustrated by case 3, a patient who had diabetic retinopathy lesions in the periphery. Not only does this technology facilitate early detection, but it also gives us a platform for educating patients on the importance of follow-up care.

▼ Case 3: Ultra-widefield imaging detected peripheral diabetic retinopathy lesions in a 60-year-old white male with proliferative diabetic retinopathy

In fact, UWF imaging is becoming the new standard for detecting diabetic retinopathy. Various studies have found that peripheral lesions suggest more severe disease in about 10% of eyes.[13] (See "Diabetic Retinopathy Severity Scale, page 22.) The study also evaluated the effect of these peripheral lesions on retinopathy progression and found that eyes with peripheral lesions had a 2.2-fold increased risk of progressing from mild to possibly moderate disease. For some patients, the study found a 3.2-fold increase in risk of progressing from mild to severe disease.[13]

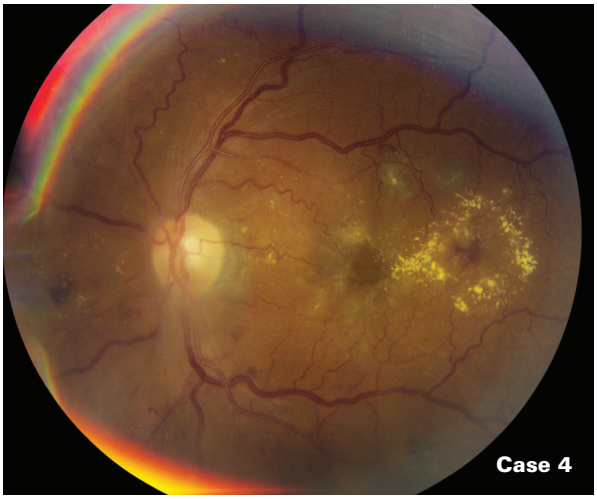

Case 3 UWF

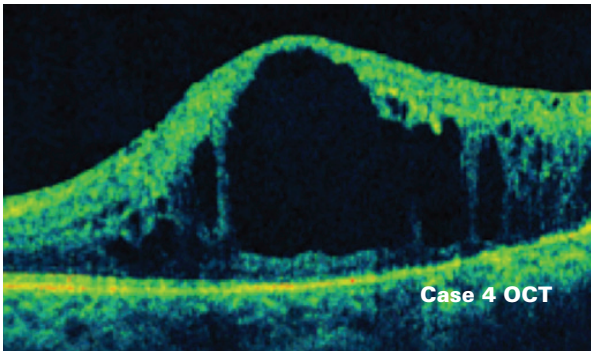
OCT and OCT angiography (OCTA) have dramatically improved early detection and care of diabetic retinopathy and maculopathy. OCT allows for the early identification and management of DME, rather than the presence of clinically significant macular edema, a diagnosis made by macula slit lamp examination. Currently, DME is categorized as center-involved versus non-center-involved based on spectral domain OCT. Center-

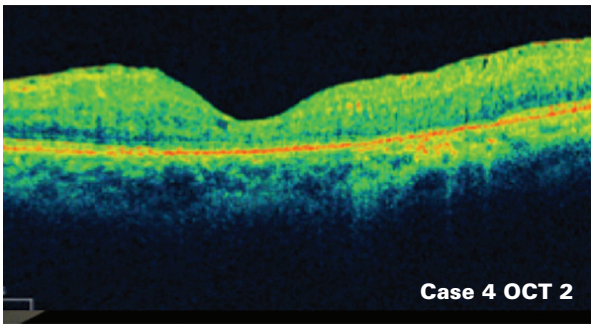
involved DME is characterized by loss of foveal contour, cystoid macula edema (CME) involving the center of the fovea, neurosensory detachment involving the center of the fovea and increased central subfield thickness as shown in case 4. Non-center-involved DME is characterized by retinal thickening and/or cystic spaces not directly involving the center of the macula.

▼ Case 4: 57-year-old male with center-involved DME of the left eye; note improvement status post anti-VEGF therapy

OCTA detects blood flow without the use of intravenous dye, therefore eliminating the risk for complications, such as anaphylaxis. It is an excellent tool to detect subclinical microaneurysms, the earliest sign associated with diabetic retinopathy, that are often not perceived through a dilated retinal examination as depicted in case 5.

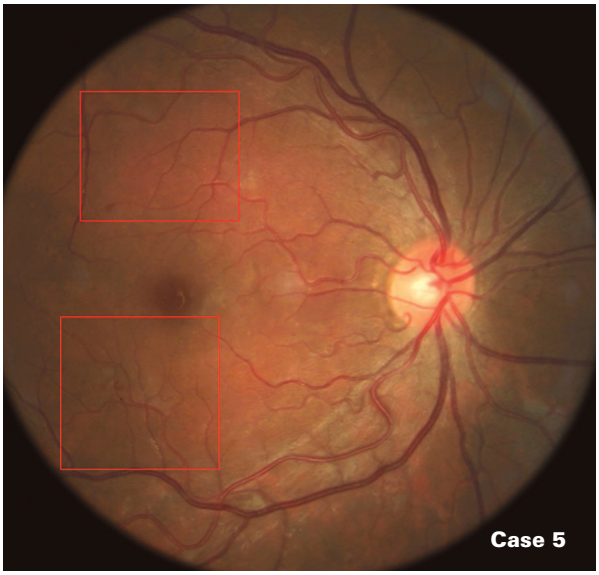

Case 4

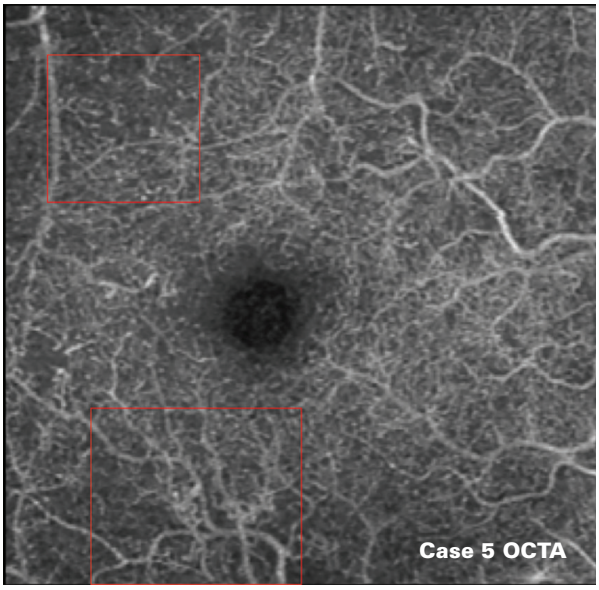

Case 4 OCT


Case 4 OCT 2

▼ Case 5: OCTA imaging detected multiple hyper-reflective microaneurysms and neovascular changes of PDR

OCTA can detect other vascular anomalies, such as vascular loops, tortuosity, and dilation of the vessels, as well as intraretinal microvascular abnormalities and superficial neovascularization. It also detects diabetic macular ischemia (DMI) with clinical signs of paramacular areas of capillary nonperfusion, impairment of the choriocapillaris


Case 5

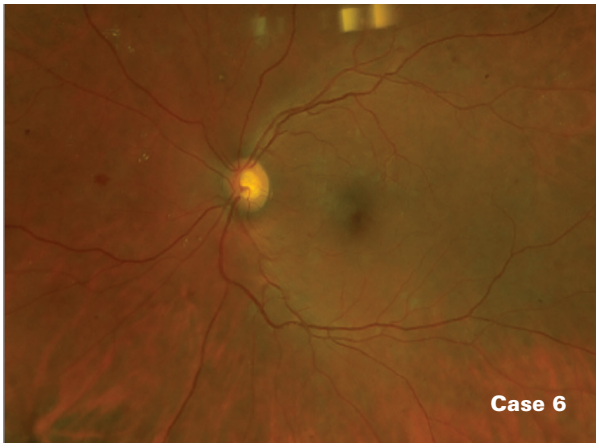

Case 5 OCTA

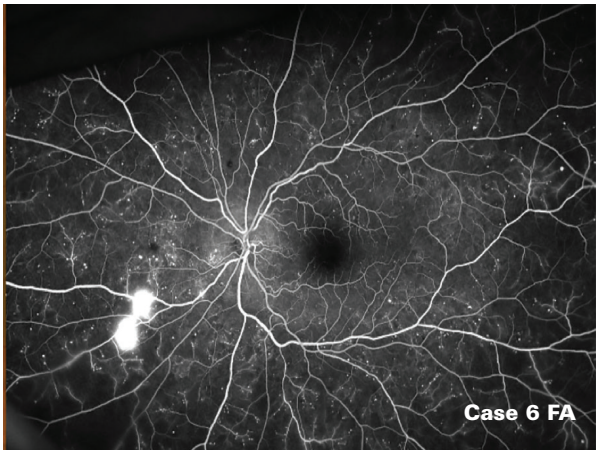
flow, and enlargement of the foveal avascular zone (FAZ). Abnormalities in the structure or perfusion of the FAZ not only results in vision impairment but a poor prognosis, because the condition cannot be treated. DMI should be ruled out in patients with poor vision at presentation or despite attempted treatment for DME.

All patients with diabetic retinopathy should be monitored closely with follow-up examinations every 3 months. However, patients with severe nonproliferative diabetic retinopathy (NPDR), PDR, and DME should be referred to a retina specialist, even patients with 20/20 vision and no visual complaint as seen in case 6.

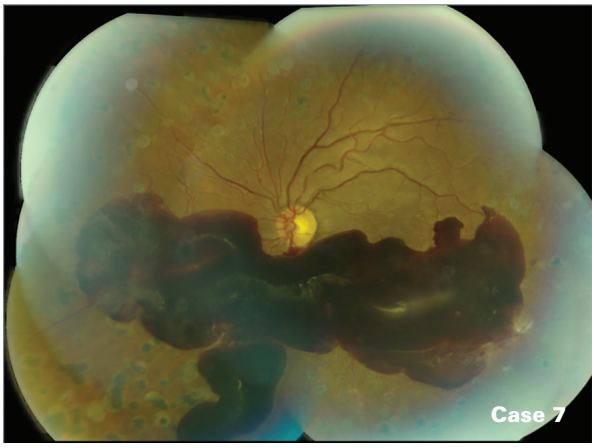
▼ Case 6: Asymptomatic PDR patient with an area of neovascularization observed on UWF angiography

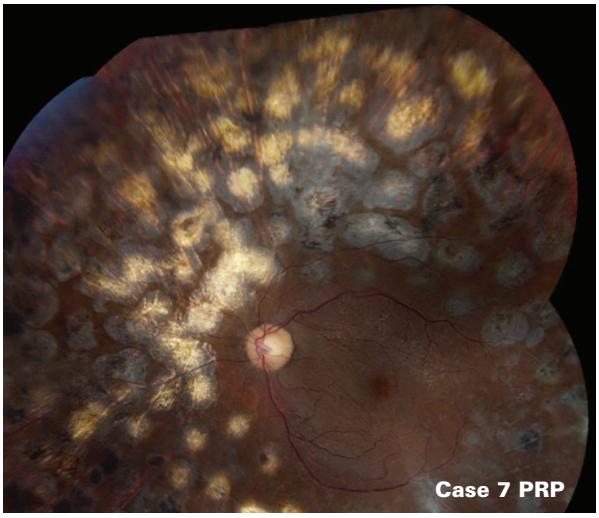
Anti-VEGF is the first-line treatment for any patient with center-involved DME and PDR.[14,15] In some cases of persistent edema after three to six injections, the retina specialist may elect to switch to a different anti-VEGF agent, add laser, or use a steroid. For patients with non-center-involved DME, treatment may be focal laser, anti-VEGF, or observation if vision is not compromised. However, some cases, such as case 7 benefit from PRP.


Case 6


Case 6 FA

▼ Case 7: Non-clearing vitreous hemorrhage treated with PRP


Case 7


Case 7 PRP

Collaborative Care

It is important to establish partnerships with other health care providers and provide consistent communication with all providers who participate in the care of patients with diabetes. A progress report should be sent in a timely manner to the patient's primary care physician or health care team, even when no diabetic retinopathy is detected. This is an important component of HEDIS (the Healthcare Effectiveness Data and Information Set), as primary care physicians are required to obtain documentation that annual eye examinations were performed on their patients with diabetes.

When coordinating care with a retina specialist, it may not be ideal to rely on the patient to schedule appointments, but rather the referring doctor should

make an appointment for the patient. Primary care providers should also be informed if additional care is warranted, such as referrals to a retina specialist. An exam summary report should be given to the patient and faxed to the retina specialist.

To ensure that patients adhere to the recommended care, a follow-up appointment should be made to the primary eye care physician's office. This ensures continuity of care and allows patients to discuss any concerns they may have about treatment.

Rein in Diabetes

Battling the emerging epidemic of diabetic retinopathy requires collaboration by all members of the diabetes health care team to ensure better outcomes for these patients. The new ADA position statement not only provides valuable clinical practice updates and recommendations regarding diabetic retinopathy, it also may serve as a guide to improve interaction among the patient's entire health care team to prevent the onset and progression of diabetes-related vision loss. ■

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DIABETIC RETINOPATHY SEVERITY SCALE

In an effort to improve communication between eye care providers and primary care physicians caring for patients with diabetes, the latest diabetic retinopathy scale is provided here.[1]

- **Diabetic retinopathy absent:** no abnormalities
- **Mild nonproliferative diabetic retinopathy (NPDR):** microaneurysms only
- **Moderate NPDR:**
  - –More than just microaneurysms but less than severe NPDR
  - –Intraretinal microaneurysms and dot and blot hemorrhages of greater severity, in 1 to 3 quadrants
  - –Cotton wool spots, exudates, venous caliber changes, including venous beading, and intraretinal microvascular abnormalities are present but mild[1]
- **Severe NPDR:**
  - –Any of the Early Treatment Diabetic Retinopathy Study (ETDRS) 4-2-1 criteria
  - –The ETDRS "4-2-1 rule" indicates the presence of severe intraretinal hemorrhages (>20) and microaneurysms in each of 4 quadrants, venous beading in ≥2 quadrants, or intraretinal microvascular abnormality in ≥1 quadrants
  - –No signs of proliferative diabetic retinopathy
- **PDR:** ≥1 of the following:
  - –Neovascularization
  - –Vitreous/preretinal hemorrhage

Reference

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LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

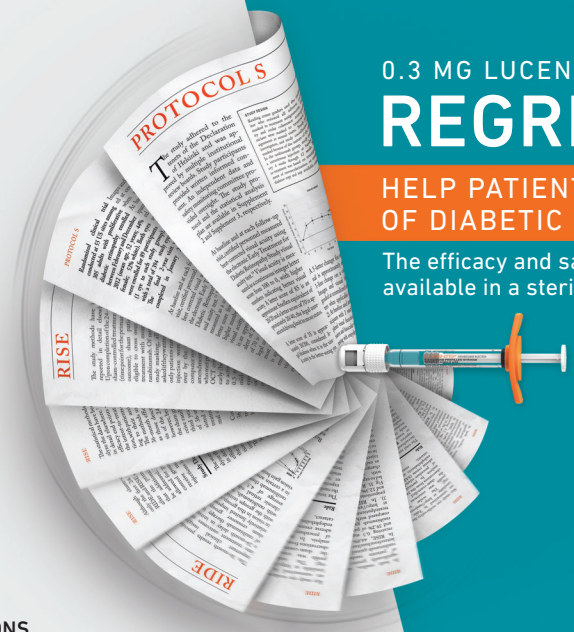
8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017



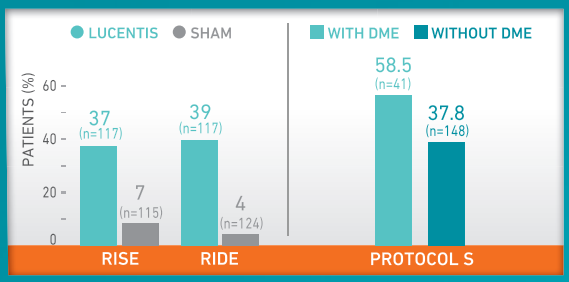
0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a sterile glass prefilled syringe.[1]

≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE
- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S
- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

Please see Brief Summary of LUCENTIS full Prescribing Information on following page.

*The following clinical trials were conducted for the **DR & DME** indications: ***RISE & RIDE***—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2-3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

DME, diabetic macular edema.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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RANIBIZUMAB INJECTION