Viewpoints on Managing DR: Addressing Moderate-to-Severe NPDR

Introduction

The rising prevalence of diabetes—and diabetic retinopathy alongside it—has become a serious public health issue. As part of the patient care team, ophthalmologists play an important role in actively screening, referring, and managing patients with diabetic eye disease. As clinical trial results continue to accumulate, best practices for managing diabetic retinopathy (DR) continue to be refined. This activity will examine the latest data surrounding the management of non-proliferative diabetic retinopathy (NPDR) and its implications on clinical practice.

Pathophysiology of DR

DR is an important indicator of the overall microvascular and macrovascular health in patients with diabetes. Patients with DR commonly have comorbid hypertension, dyslipidemia, and nephropathy, which are also contributors of disease progression.[1] Additionally, DR is an independent risk factor for cardiovascular disease and mortality.[2]

Physiologically, chronic hyperglycemia that characterizes diabetes causes oxidative stress and systemic inflammation that in turn leads to a cycle of blood vessel damage.[Kushara2018] This damage manifests as retinal angiogenesis and vascular leakage, which are mediated by vascular endothelial growth factors (VEGF).[3] Early on, changes to the retina are faint with the appearance of microaneurysms and dilated blood vessels.[4] As DR progresses, vascular abnormalities increase in number and become more visible. Eventually, vitreous/preretinal hemorrhage and/or neovascularization occur, which are the hallmarks of sight-threatening proliferative DR (PDR).[4]

Classification of DR

The Diabetic Retinopathy Severity Scale (DRSS) that classifies various stages of DR was originally developed by the Early Treatment for Diabetic Retinopathy Study (ETDRS) group and remains the gold standard for clinical trials.[5] However, the International Clinical Diabetic Retinopathy Severity Scale is more commonly used in daily practice (Table 1).[4] This scale defines nonproliferative diabetic retinopathy (NPDR) based on ophthalmoscopic criteria found in one or more quadrants of the retina, which is also known as the 4-2-1 rule.[4] An estimated 50% of patients with NPDR will progress to PDR and be at risk for vision loss within one year.[6] As such, appropriate diagnosis and management of these patients is critical to preventing vision loss.

Table 1. International Clinical Diabetic Retinopathy Severity Scale[4]

Disease Severity	Observable Findings on Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms, but less than severe NPDR
Severe NPDR	No signs of PDR with one or more of the following:

	• >20 intraretinal hemorrhages in all 4 quadrants • Venous beading in 2+ quadrants • Prominent intraretinal microvascular abnormalities (IRMA) in 1+ quadrant
PDR	Severe NPDR and one or more of the following: • Neovascularization • Vitreous/preretinal hemorrhage

Patient Case

A 54-year-old woman presents for a DR evaluation. She has a 11-year history of type 2 diabetes. Her blood pressure is 150/97mm Hg and laboratory results show an A1C of 10.1% with a slightly elevated BUN and creatinine with protein in the urine. Her past medical history is significant for coronary artery disease, hyperlipidemia, and hypertension. Today her visual acuity is 20/30 OD and 20/40 OS. Fundus imaging shows dot-blot hemorrhages in all four quadrants along with venous beading in the right eye (Figure 1). Intraretinal hemorrhages are observed in three quadrants of the left eye along with cotton wool spots. Fluorescein angiography demonstrates areas of capillary nonperfusion in both eyes (Figure 2). The right eye also shows the early signs of neovascularization of the optic nerve head. OCT imaging confirms normal macular thickness and foveal contour. The patient is diagnosed as having pre-proliferative retinopathy with non-high-risk characteristics in the right eye and moderate to severe NPDR in the left eye.

Figure 1. Fundus imaging showing intraretinal hemorrhages in all four quadrants of the right eye.

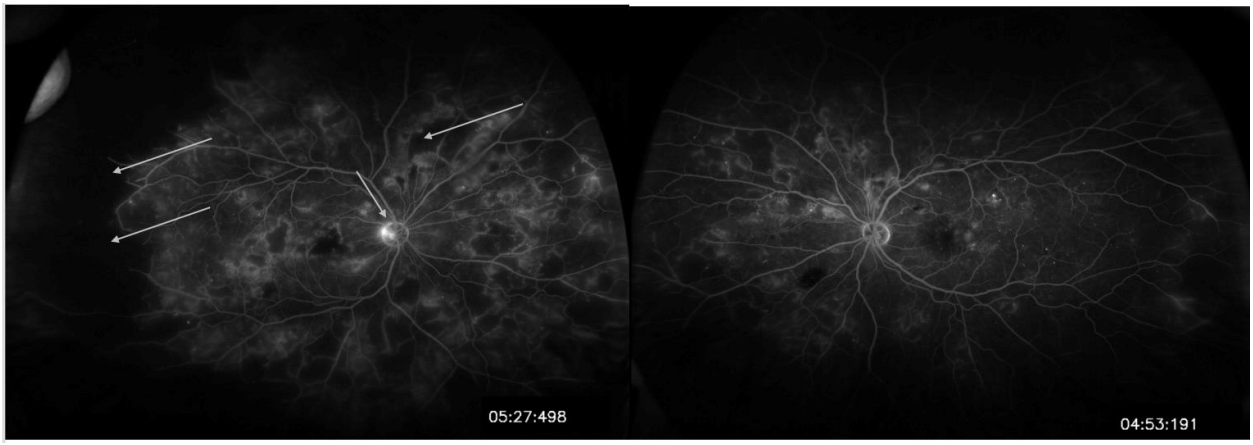


Figure 2. Fluorescein angiography demonstrating noncapillary perfusion and early neovascularization of the optic nerve head in the right eye.

Non-Pharmacologic Treatment of DR

In some patients with severe NPDR at high risk of progression, early use of panretinal laser photocoagulation (PRP) may be considered.[1] PRP functions by destroying ischemic areas of the peripheral retina.[7] This destruction results in an overall reduction in the production of vascular VEGF, which is a known driver of neovascularization. However, PRP causes permanent retinal damage that commonly leads to decreased peripheral, color, and night vision.[7]

Treatment of DR in the Presence of DME

Pharmacologic agents are available that can directly inhibit VEGF without further damaging the retinal tissue. This was first demonstrated in the landmark Diabetic Retinopathy Clinical Research (DRCR) Protocol I and Protocol S studies where intravitreal ranibizumab was superior to laser in treating patients with DME.[8,9] Ranibizumab is also associated with a lower risk of developing DME and less visual field loss in high-risk PDR than laser.[8,9] However, it was data from the RISE/RIDE studies, where patients with DME treated with ranibizumab exhibited a slower rate of progression to PDR, that indicated the potential efficacy of anti-VEGF in treating DR.[10] The cumulative probability of DR progression for eyes treated with 0.5mg of ranibizumab was 11.5%, versus 33.8% of the sham injected group.[11] Analysis of the effects of ranibizumab on DR severity in RISE/RIDE participants after 2 years found overall improvements from a baseline of moderately severe NPDR to mild NPDR compared to sham injected patients who remained classified as moderately severe NPDR. Eyes treated with ranibizumab were also significantly more likely to experience $\geq$2 and $\geq$3 step improvements on the ETDRS severity score compared with sham treatment (Figure 3).[11] Similar data were also found in the VIVID/VISTA trials, which evaluated the efficacy of the anti-VEGF agent aflibercept for the treatment of DME.[12] Both dosing schedules were associated with marked improvements of $\geq$2 steps on the DRSS after one year (Figure 4).[12] Together, the results from RISE/RIDE and VIVID/VISTA signify that anti-VEGF treatment is effective in reducing the severity of DR in individuals with DME.

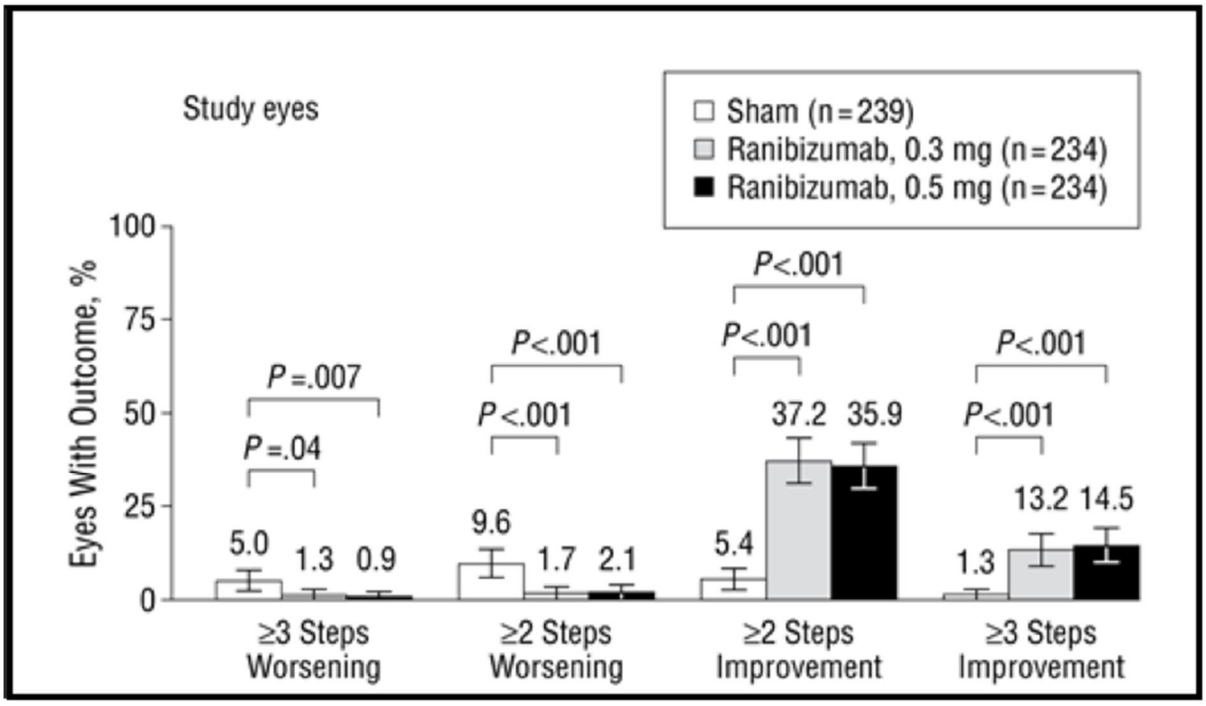


Figure 3. RISE/RISE study patients with a change from baseline in ETDRS DR severity level at 24 months.[11]

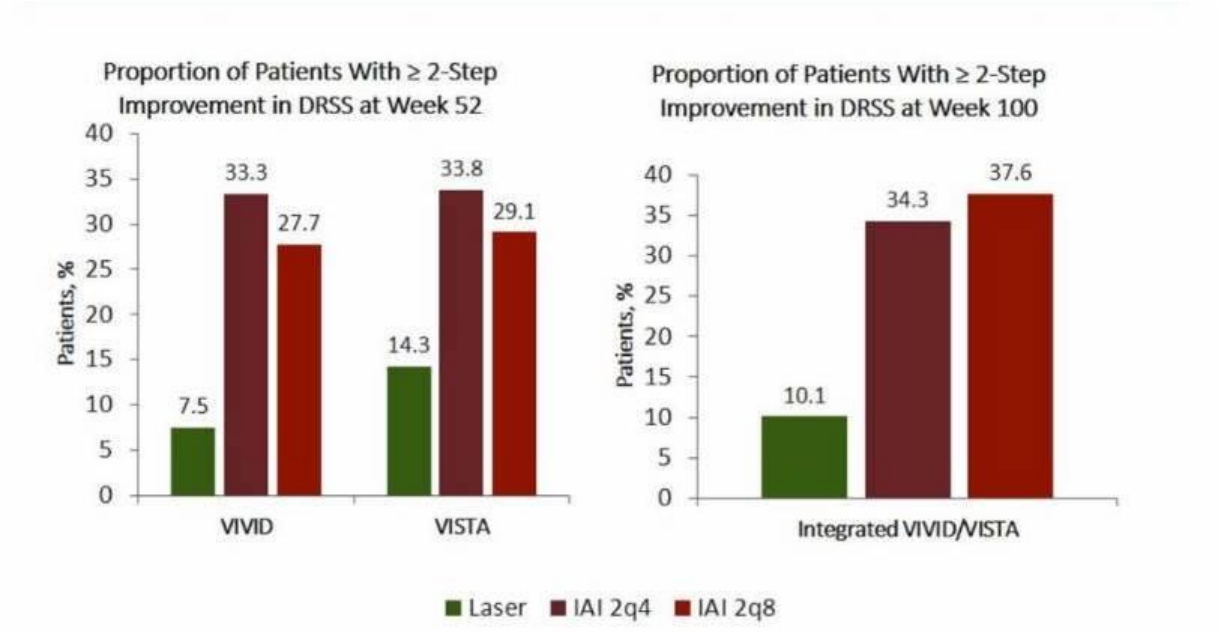


Figure 4. VIVID/VISTA study patients with a ≥2 step improvement in DRSS score from baseline to 52 weeks.[12]

Treatment of NPDR in the Absence of DME

The observation that treatment with anti-VEGF leads to the regression of DR in the presence of DME has led researchers to study whether the same effects occur in patients without DME. Currently, there are two ongoing prospective clinical trials designed to study this. PANORAMA and DRCR Protocol W are 2- and 4-year studies, respectively, that are evaluating the efficacy and safety of intravitreal aflibercept in eyes with moderately severe to severe NPDR (DRSS Level 47 or 53) without center-involved DME (CI-DME).[13,14] Protocol W includes patients with a best corrected visual acuity (BCVA) ETDRS letter score of ≥79 letters (Snellen equivalent of 20/25 or better).[13] Conversely, PANORAMA includes patients with a BCVA ETDRS letter score of ≥69 letters (Snellen equivalent of 20/40 or better).[15]

One-year data from the PANORAMA study are now available.[14] The 402 patients were equally randomized to either sham injection or one of two dosing schedules (Q8 weeks or Q16 weeks) with 2mg intravitreal aflibercept (Figure 5). After one year, the proportion of patients improving ≥2 steps on the DRSS was significantly greater for both treatment arms (Figure 6). Additionally, patients treated with aflibercept experienced significant reductions in the development of vision-threatening complications, defined as PDR, anterior segment neovascularization, or CI-DME (Figure 7). Importantly, no new evidence of treatment-related adverse effects was identified.[14]

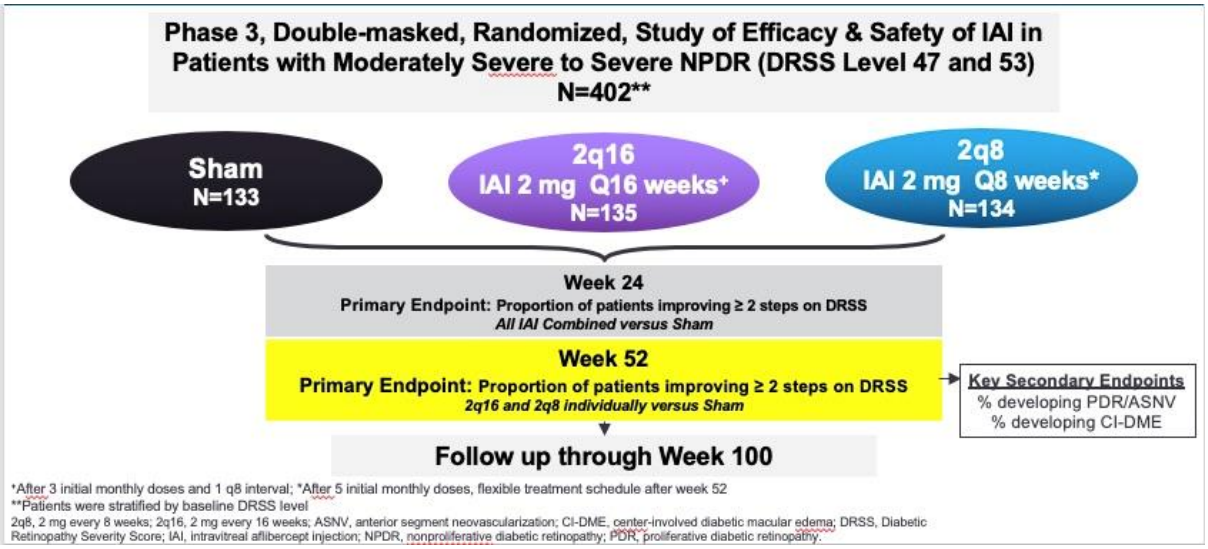


Figure 5. PANORAMA study design.[14]

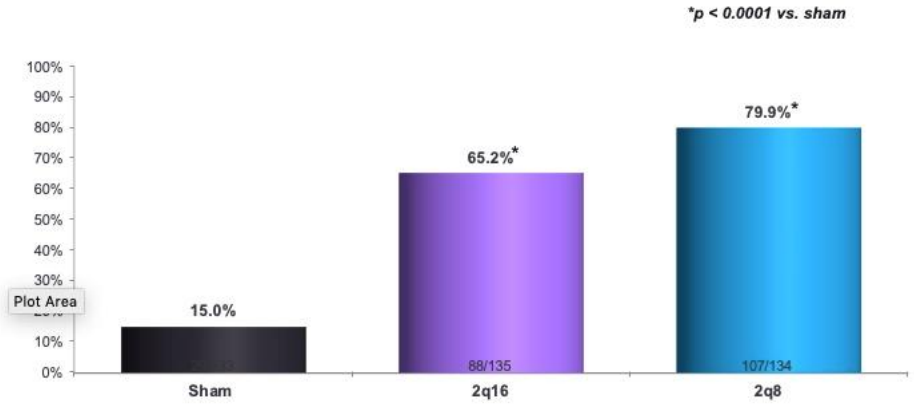
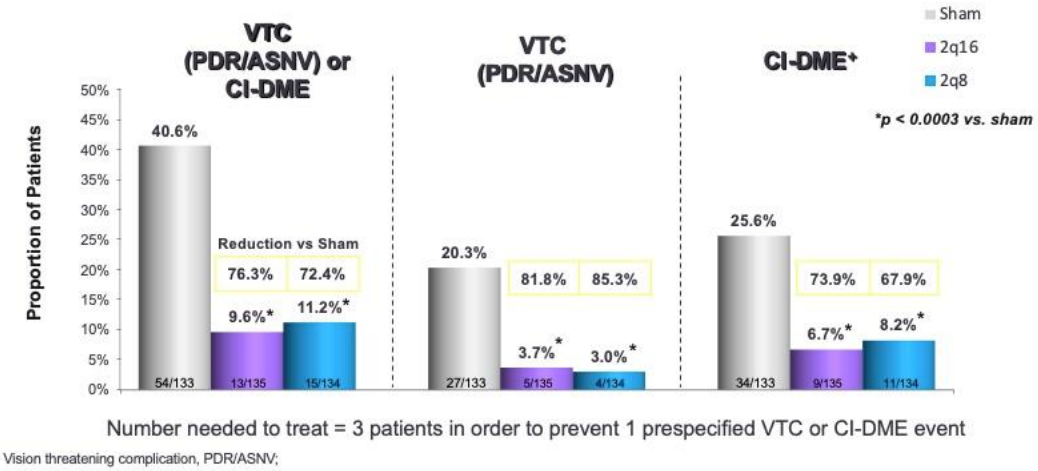


Figure 6. PANORAMA patients with ≥2-step improvement in DRSS at 52-weeks.[14]



VTC = Vision threatening complication, PDR/ASNV;

Figure 7. PANORAMA patients with vision-threatening complications or CI-DME at 52-weeks.[14]

Patient Case (continued)

Management options of observation or intravitreal anti-VEGF therapy with aflibercept were discussed with the patient along with the risks and benefits of each strategy. For anti-VEGF treatment, this included the risk of endophthalmitis and retinal detachment following intravitreal injection, elevations in intraocular pressure, and arterial thromboembolic events.[16] After consultation, the patient initiated a series of monthly, bilateral aflibercept injections that were then extended over a period of time. One year later, fundus imaging showed significant retinopathy regression with resolution of intraretinal hemorrhages in both eyes along with the cotton wool spots in the left eye (Figures 8 and 9).

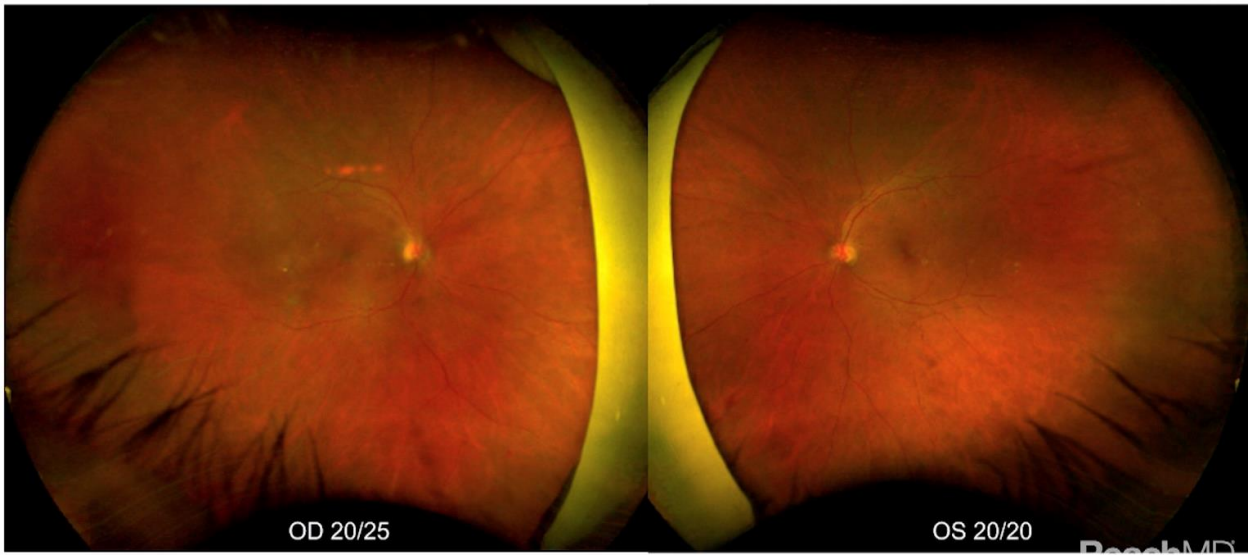


Figure 8. Fundus imaging 1 year after initiating anti-VEGF treatment.

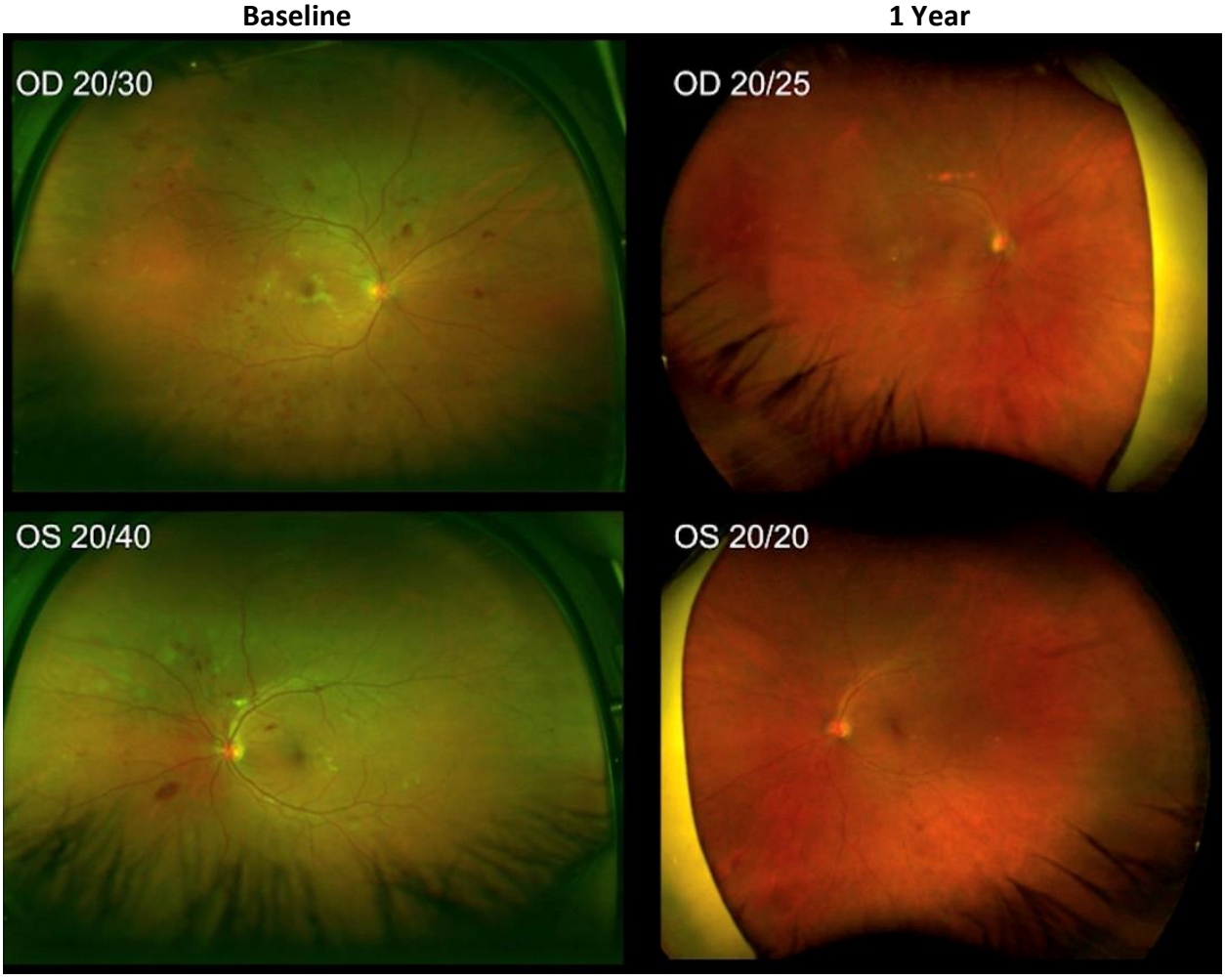


Figure 9. Comparison of fundus photographs from baseline and 1 year after initiating anti-VEGF treatment.

Clinical Practice Implications

Ophthalmologists should refer patients with moderate or even mild DR to a retinal specialist for evaluation with a fluorescein angiogram. This allows for individual assessment of risk for developing proliferative disease. Ultra-widefield imaging also fosters easier identification of neovascularization and capillary nonperfusion occurring in the peripheral retina, which may otherwise be missed when modalities with more limited fields are used. In turn, assessment of the peripheral retina can lead to earlier identification of patients with severe NPDR or PDR prior to the development of vitreous hemorrhage or tractional detachment.

Importantly, a comprehensive evaluation by a retina specialist can determine whether a patient has mild, moderate, or severe disease, which requires close monitoring for disease progression. Those with mild NPDR may continue to be followed for disease progression by an ophthalmologist. Conversely, patients diagnosed with moderately severe to severe NPDR may now consider the use of anti-VEGF therapy based on the collective data from the RISE/RIDE, VIVID/VISTA, and PANORAMA studies.

Call to Action

The key to good vision outcomes is be assertive with screening. Regular and timely dilated fundus exams, even in the absence of visual symptoms, allows for early disease identification before vision-threatening symptoms are present. Additionally, there is the opportunity to initiate anti-VEGF therapy earlier in the DR disease course, which promotes the chance for a longer period of good visual acuity. DR is also an important indicator of microvascular health in patients with diabetes. Its presence is highly correlated with neuropathy and nephropathy and is an independent risk factor for cardiovascular risk and mortality. Optimization of diet, exercise, and systemic medications helps prevent DR progression in addition to mitigating the systemic effects of diabetes. It is incumbent upon ophthalmologists to work together with endocrinology and primary care clinicians to educate patients and providers about the risk for retinopathy progression, its implications on overall health, and management options for preventing vision loss.

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