Recognizing Eye Complications in Diabetes: Diabetic Retinopathy and Diabetic Macular Edema

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Prevention of Diabetic Retinopathy

Visual loss from diabetes remains a major cause of blindness in the world. Untreated, diabetes affects not only the lens (cataracts), but more importantly, the retina. Fortunately, there are treatments available to mitigate, and sometimes reverse, visual loss from diabetic retinopathy (DR). Diabetes is a growing health problem in the United States; its prevalence is expected to rise to 21% of adults in 2050 from the estimated 11.3% of the US population in 2010. In the United States, it is the seventh leading cause of death.

In the prevention and treatment of DR, systemic factors are very important. Numerous epidemiologic studies and trials have documented the importance of glycemic and blood pressure control in patients with diabetes. The Diabetes Control and Complications Trial (DCCT, 1982-1993) compared intensive with conventional control for onset and progression of DR in type 1 diabetics. The Epidemiology of Diabetes Interventions and Complications study (1994-present) followed the DCCT cohort. At baseline in the DCCT, 726 of the 1,441 participants had no DR (primary prevention cohort) while 715 had mild DR (secondary intervention cohort). Participants were followed for a mean of 6.5 years. The median HbA1c was 7% for the intensive control group compared with 9% for the conventional control group. The intensive control showed a 76% reduction in the adjusted mean risk for the development of DR compared with the conventional control group. In addition, intensive control slowed progression of DR by 54% compared with conventional control. Although subsequent HbA1c levels in the original intensive and conventional groups converged to approximately 8% for both groups by year 8, initial assignment to intensive therapy continued to significantly lower the incidence of further DR progression (hazard reduction 53%-56%). Thus, earlier optimization of glycemic levels continues to have effects many years later on the progression of DR.

Other studies, such as the United Kingdom Prospective Diabetes Study, which studied type 2 diabetics, the Wisconsin Epidemiology Study of Diabetic Retinopathy, and the Early Treatment of Diabetic Retinopathy Study (ETDRS), also support the importance of glucose control in reducing the incidence and progression of DR. In addition, these studies also showed the importance of control of blood pressure, lipids, renal function, and body weight on the incidence and progression of DR. Thus, systemic diabetes control significantly impacts patients’ eyes. Approximately one third of patients with diabetes has DR.

The American Academy of Ophthalmology and the American Diabetes Association recommend that a dilated eye exam be performed within 3 to 5 years for type 1 diabetics and at the time of diagnosis for type 2 diabetics. Yearly dilated eye exams are recommended thereafter for both types. Unfortunately, studies have shown that patients do not get regular eye exams and they are unaware of the existence of sight-threat-
Diabetes retinopathy can be classified by the level of DR and also by the presence or absence of diabetic macular edema (DME), swelling in the area within the vascular arcades, temporal edge of the optic nerve head, and the equivalent area temporal to the foveal center. Diabetic retinopathy is generally divided into non-proliferative (NPDR) and proliferative (PDR) DR. NPDR has three stages: mild, moderate, and severe. These levels, defined by ETDRS, refer to the severity of the disease and have associated prognostic implications for acceleration of disease. A patient with mild NPDR may be seen yearly, whereas a patient with severe NPDR may need to be seen as often as every 3 months. In NPDR, microaneurysms are present. Depending upon the severity of the disease, retinal hemorrhages, cotton wool spots, venous beading, and intraretinal microvascular anomalies may be seen. There is typically none to minimal visual loss. However, if there is concomitant DME, there may be significant visual acuity loss.

In eyes with PDR, neovascular vessels sprout from the retinal venous circulation. These vessels are immature and prone to bleeding, which can result not only in preretinal hemorrhages but also vitreous hemorrhages with significant loss of vision. Depending on the location of the neovascularization and presence/type of hemorrhage, the PDR may be graded as high risk for visual acuity loss. PDR on the nerve head or within 1 disc diameter of the nerve head is termed neovascularization of the disc (NVD); neovascularization elsewhere is termed NVE. NVD and NVE will continue to progress over time. Fibrosis and scarring can occur, and these can result in retinal detachment. Fortunately, panretinal laser photocoagulation (PRP) is highly effective in curbing the growth of these blood vessels and can help prevent visual loss. In fact, in the Diabetic Retinopathy Study, panretinal laser photocoagulation resulted in a 50% reduction of severe visual loss.

In the ETDRS, prompt laser was again associated with reduction in progression and visual loss even in less severe levels of retinopathy.

In some eyes with significant ischemia, neovascular vessels may develop on the iris (rubeosis). These fragile vessels can result in a hyphema (anterior chamber bleed) as well as glaucoma (neovascular or rubeotic glaucoma). Unmitigated growth will cause the anterior chamber angle to scar. These patients will present with painful eyes and elevated eye pressure. Glaucoma eyedrops and treatment to cause regression of the neovascularization is urgently needed. Depending upon the view to the retina, PRP may be performed. An anti-vascular endothelial growth factor (VEGF) drug is also frequently injected into the eye to help cause regression of the neovascular vessels. In cases in which no view of the retina is possible, vitrectomy surgery with PRP is urgently needed to prevent blindness.

Diabetic Macular Edema

DME occurs in 13% of DR eyes. The presence of DME has been found to be associated with higher risks of myocardial infarction (2.5X) and stroke/cerebral vascular accident (2X) than in patients without DME. If the central foveal area is involved, visual acuity loss may be severe. The term clinically significant macular edema (CSDME) is used specifically to refer to the subtype of DME with high risk for severe, and perhaps permanent, visual acuity loss, if not treated. There are three types of CSDME as defined in the ETDRS: 1. Edema involving the foveal center or within 500 microns of the fovea; 2. Edema...
within 1 disc diameter of the fovea and at least 1 disc diameter in size; and 3. Edema associated with any exudate that is within 500 microns of the foveal center.11

CSDME is typically detected through the use of clinical examination with either a contact lens on the patient’s eye or through a non-contact lens. Ancillary tests are helpful to document the presence and extent of DR or CSDME. Objective measurements of the degree of thickening are made with the use of optical coherence tomography (OCT), a quick, noninvasive, in-office procedure. Using OCT, the amount of thickening in various regions of the macula is measured (microns) (see Figure). These measurements are very helpful in following a patient’s response to therapy. OCT is frequently repeated during treatment of CSDME.

At the time of CSDME diagnosis, a fluorescein angiogram (FA), in which a vegetable-based dye is injected through a peripheral vein and special filters are used that allow the retinal vasculature to be imaged, is helpful to determine the presence and extent of ischemia. Sometimes, edema may result from ischemia in the absence of active vascular leakage and this affects the treatment plan. A FA is also helpful to detect areas of retinal neovascularization (leaks profusely). However, a good clinical exam alone is often all that is needed to make a diagnosis of CSDME or PDR.

Treatment options for CSDME include laser, intravitreal steroid, and intravitreal injection of anti-VEGF drugs. The ETDRS showed that focal or grid laser of CSDME reduced the risk of moderate visual loss (3 lines) by approximately 50%.12 Focal laser treatment may need to be repeated at 4-month intervals until a response or complete treatment is achieved.

**Recent Clinical Trial Results: Advancements in Therapy for DME**

Most recently, treatments other than laser or in combination with laser have been shown to be efficacious for treatment of DME-associated edema. These include corticosteroids and anti-VEGF therapies. Corticosteroids stabilize the blood-retinal barrier. The use of VEGF as a target was predicated by findings that increased levels of VEGF have been well documented in eyes with DME or DR.13,14 In general, the more severe the DME and the higher the level of DR, the higher the VEGF level.15 The efficacy of intravitreal injections of anti-VEGF has been well documented in numerous clinical trials. Most noteworthy are the DRCR Protocol I results16 and the RIDE/RISE17 and VISTA/VIVID18 studies. These phase 3 clinical trials led to the approval of the anti-VEGF drugs ranibizumab and aflibercept. The DRCR presented an alternative dosing regimen to the monthly injections used in RIDE and RIDE for ranibizumab. The VISTA and VIVID studies showed that aflibercept was superior to laser treatment but was not compared directly to ranibizumab.18 The use of bevacizumab is off-label for DME, but is often used due to its lower cost and evidence of efficacy.19 At present, a large, randomized DRCR study is comparing the effects of ranibizumab, aflibercept, and bevacizumab in the treatment of CSDME eyes.

Adverse events associated with anti-VEGF therapies include local adverse events and potential systemic risks in patients with diabetes, such as the ocular potential for infection or damage to ocular structures during the intravitreal injection itself. The risk of damage to ocular structures is extremely low in trained hands, and the risk of endophthalmitis is about 1 in 1000. Potential systemic adverse events include Antiplatelet Trials’ Collaboration (APTC)-defined arterial thromboembolic events. There was a trend for the higher dose of ranibizumab (0.5 mg) to be associated with more APTC events than the lower dose of ranibizumab (0.3 mg).17 Because of this potential, the lower (0.3 mg) dose was approved for use in diabetes instead of the 0.5 mg dose. However, one should remember that these studies were not powered to detect a difference in systemic risks between anti-VEGF-treated eyes and control (laser-treated) eyes.

The dosing regimen used in RIDE and RISE was monthly intravitreal injections of either 0.3 mg or 0.5 mg ranibizumab versus a sham injection.17 Patients were followed monthly, and OCT was performed at each visit. Laser photocoagulation was allowed beginning at month 3, and could be given every 3 months. Using this regimen, the visual acuity improved 11 to 12 letters (RIDE) and 12 to 13 letters (RISE) versus 2.3 letters (RISE control) and 2.9 letters (RISE control) at 24 months. After 24 months, the sham group was allowed to receive ranibizumab 0.5 mg monthly. At the end of 3 years, the visual acuity improved 10.5 to 11.4 letters (RISE) and 11 to 14.2 letters (RISE) versus 4.7 (RISE/sham/ranibizumab) and 4.3 (RISE sham/ranibizumab).17

In the eyes that received 0.3 mg ranibizumab monthly, 39% to 36% received rescue laser by 24 months in the RIDE/RISE studies. In contrast, 70% (RISE) or 74% (RISE) of the sham group received laser treatment. Furthermore, it was rare (1.6% RIDE and 0% RISE) for ranibizumab 0.3 mg treated eyes to require PRP as compared with the sham-treated eyes (12.3% RIDE and 11% RISE). In fact, the overall retinopathy severity of the an-ti-VEGFtreated eyes improved in over one third of the ranibizumab-treated eyes versus only 4% (RIDE) to 7% (RISE) of sham-treated eyes.17 It is unclear at this time whether the effects will persist or wane over time after frequent therapy is decreased or stopped.

In the DRCR study, anti-VEGF was given at baseline and monthly for a total of 3 injections. If the visual acuity was not 20/20, or if the OCT still showed edema, 2 more injections spaced monthly were given.16 A computerized algorithm was used to determine the need for further treatments. Using this method, a total of approximately 9 to 10 injections were given in the first year, 3 to 4 in the second year, and 1 to 2 in the third year of the study. Thus, it appears that continuous therapy is not required to achieve sustained visual acuity improvement. The timing of laser therapy immediately with the first anti-VEGF treatment was compared to deferred laser therapy (6 months) in the DRCR study. The results were similar. In fact, it was found that 70% of the deferred eyes never required laser. Many questions about the timing of laser therapy remain to be answered: whether to add, when to add, and what long-term benefit occurs with combined anti-VEGF and laser in the treatment of DME.

Most recently, the VISTA and VIVID results have been reported. In these multicenter, randomized studies, eyes with CSD-ME were randomized to laser therapy (as needed every 12 weeks) versus aflibercept...
2 mg monthly versus aflibercept 2 mg monthly for 3 doses and then every 8 weeks.18

In VIVID, aflibercept eyes improved 10.5 letters (2 mg monthly) and 10.7 letters (2 mg q 8) versus laser eyes, which improved 1.2 letters. In VISTA, aflibercept eyes improved 12.5 letters (2 mg monthly) and 10.7 letters (2 mg q 8) versus laser eyes, which improved 0.2 letters. More aflibercept-treated eyes improved 2 steps in the severity of DR than sham-treated eyes (33% to 27% vs 7.5% [VIVID; 33.8%–29% vs 14.3% [VISTA]). Results were maintained at 100 weeks.

The use of corticosteroids is usually restricted to pseudophakic or phakic eyes, due to risk of cataract formation. In fact, in the DRCR studies, corticosteroids given every 4 months decreased macular edema, but visual acuity decreased later due to cataract formation.16 When a subgroup of pseudophakic eyes was studied, no subsequent secondary drop in visual acuity occurred. In fact, the visual acuity improvement in these eyes receiving laser with corticosteroid injected intravitreally was similar to that seen in eyes given anti-VEGF intravitreally with or without prompt laser.

Sustained release implants have been studied in the treatment of DME. In the dexamethasone implant study, eyes with DME of at least 90 days duration were randomized to either 350 µg or 700 µg dexamethasone implant.20 The primary endpoint, a 10 or more letter increase at day 90, was seen in 33.5% of the 700 µg and 21.1% of the 350 µg group versus 12.3% in the observation group (P = 0.007 for 700 µg). At day 180, a 10 or more letter increase was seen in 30% of the 700 µg and 19% of the 350 µg group, and 23% in the observation group (P > 0.4 for treated vs observed eyes). Greater improvements in central retinal thickness and fluorescein leakage were found in treated eyes than observed eyes (P = 0.03; day 90). The dexamethasone implant was well tolerated.

Another steroid, fluorocinolone, has also been studied in eyes with DME. In the FAME study, more eyes gained visual acuity in either the 0.2 µg/day (28.7%) or the 0.5 µg/day (27.8%) fluorocinolone implant groups compared with control (18.9%) (P = 0.018).21 In a preplanned subgroup analysis, there was a doubling of benefit compared with sham injections in patients who reported a duration of DME for ≥3 years at baseline; ≥15 gain at month 36 was 34.0% (low dose; P = 0.001) or 28.8% (high dose; P = 0.002) compared with 13.4% (sham). In addition, an improvement ≥2 steps in the ETDRS retinopathy scale occurred in 13.7% (low dose) and 10.1% (high dose) compared with 8.9% in the sham group. Complications included cataract in almost all phakic patients, but their visual benefit after cataract surgery was similar to that in pseudophakic patients.22

One must remember that intravitreal infection is a real risk with all intravitreal treatments. Therefore, if the edema does not involve the center and the visual acuity is better than 20/40, one should consider focal laser treatment. The timing of focal laser with anti-VEGF therapies and the treatment of chronic DME is not yet established. For eyes with chronic edema, intraocular steroids may be more beneficial than anti-VEGF drugs.

Summary
Novel treatments in development include drugs that inhibit pericytes and those that affect non-VEGF pathways. At present, we are fortunate that there are several drugs that can reduce the edema and cause regression of DR. For eyes in which DME does not involve the center of the fovea, laser remains an important treatment. Laser is also the main treatment for eyes with PDR. Studies are ongoing to determine the benefit of anti-VEGF and laser combination therapy in eyes with CSDME as well as eyes with PDR. However, with all of these treatments, one needs to remember that earlier stages of disease are more readily treated and have better potential outcome. Prompt diagnosis and treatment of retinopathy combined with concomitant systemic glycemic, blood pressure, lipid, and weight control will result in lower rates of morbidity from DR.

References