Lessons Learned From Recent Clinical Trials on DR

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A total of 347 million people worldwide have been diagnosed with diabetes mellitus (DM) [World Health Organization. *Diabetes Fact Sheet*. 2013]. In his introduction to this symposium on current diagnosis and treatment of diabetic retinopathy (DR), Lawrence J. Singerman, MD, Case Western Reserve University, Cleveland, Ohio, USA, pointed out that almost 8 million people had DR in 2010; that number is projected to rise to about 11 million in 2030 and to 14 million in 2050 [National Eye Institute. *Projections for Diabetic Retinopathy (2010-2030-2050)*. 2010].

Several classification systems for DR have been developed. Two of the simpler ones are based on dilated ophthalmoscopy observations. A system developed by the Early Treatment Diabetic Retinopathy Study Research Group categorized DR as mild, moderate, or severe nonproliferative DR or mild, moderate, or severe proliferative DR (PDR). Another system classified DR as mild, moderate, or severe nonproliferative DR or PDR [Wilkinson CP et al. *Ophthalmology*. 2003].

According to Dr Singerman, a new classification system based on new diagnostic techniques and treatments is needed. He suggested that a new classification might include findings from wide-field photography and angiography, ocular coherence tomography (OCT), autofluorescence photography, OCT angiography, and other multimodal imaging techniques.

RANIBIZUMAB PLUS PROMPT VS DEFERRED LASER FOR DIABETIC MACULAR EDEMA

The 2-year results of the Diabetic Retinopathy Clinical Research Network Protocol I randomized trial [DRCR Protocol I; Elman MJ et al. *Ophthalmology*. 2011] demonstrated that treatment with the intravitreal anti–vascular endothelial growth factor (anti-VEGF) agent ranibizumab, with prompt or deferred laser, was more effective than laser alone. However, the 3-year comparison of ranibizumab groups concluded that prompt laser was no better and possibly worse than deferred laser [Elman MJ et al. *Ophthalmology*. 2012]. The 5-year analysis, presented by John A. Wells III, MD, Palmetto Retina Center, West Columbia, South Carolina, USA, compared the longer-term course of the ranibizumab groups.

Eyes assigned to prompt vs deferred laser needed fewer ranibizumab injections over 5 years (Table 1).

The median number of laser treatments before the 5-year visit was 3 in the prompt laser group vs 0 in the deferred laser group. Prior to the 5-year visit, 0 eyes assigned to prompt laser vs 56% assigned to deferred laser had not received laser treatments.

The estimated mean change in retinal thickening (OCT central subfield [CSF]) at 5 years was –170 with prompt laser vs –162 with deferred laser (estimated difference, –8; 95% CI, –30 to 14; $P = .48$). Endophthalmitis developed in 1 of 187 eyes (1%; 0.04% per injection) assigned to prompt laser and in 2 of 188 eyes (1%; 0.06% per injection) assigned to deferred laser.

More than half the patients assigned to deferred laser had not received laser therapy through 5 years. Eyes assigned to prompt laser needed fewer injections over 5 years. Few eyes in either group had substantial visual acuity (VA) loss, but about one-third were still thickened.

CHRONIC PERSISTENT CENTRAL-INVOLVED DIABETIC MACULAR EDEMA

Data from the DRCR Protocol I trial showed that 41% of eyes had persistent or recurrent edema (CSF ≥ 250 µm) 2 years after treatment initiation [Elman MJ et al. *Ophthalmology*. 2011]. Susan B. Bressler, MD, Johns Hopkins University, Baltimore, Maryland, USA, presented an analysis of OCT and VA changes through 3 years among eyes with chronic persistent central-involved diabetic macular edema (CI-DME) 24 weeks after initiating intravitreal ranibizumab (n = 117 [38%]; median, CSF = 309 µm). Included patients received ≥ 4 intravitreal ranibizumab injections before the 24-week visit.

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Table 1. Injections Through 5 Years: Ranibizumab + Prompt/Deferred Laser

	Prompt (n = 124)	Deferred (n = 111)
Median injections, no.		
Year 1	8	9
Year 2	2	3
Year 3	1	2
Year 4	0	1
Year 5	0	0
Before 5-year visit	13	17
Eyes receiving ≥1 injection, %		
In year 4	46	55
In year 5	38	48

Table 2. Anti-VEGF Therapy for DR and Risk of Progression or Need for PRP

Study	Results
Intravitreal bevacizumab for PDR [Avery RL et al. *Ophthalmology.* 2006]	Rapid regression of retinal and iris neovascularization secondary to PDR with 1 bevacizumab injection
DRCR Protocol I [Elman MJ et al. *Ophthalmology.* 2010]	VH or PRP more likely with sham + prompt laser (8%) vs ranibizumab + prompt laser (3%; $P = .002$) or triamcinolone + prompt laser (3%; $P = .02$) during 1-y follow-up
RISE/RIDE [Ip MS et al. *Arch Ophthalmol.* 2012]	Patients treated with ranibizumab vs sham had a 3-fold lower risk of DR progression, need for PRP, VH, or slit lamp grade 0 at baseline to > 0; cases identified by ophthalmoscopy, iris neovascularization, or retinal neovascularization over 3 y ($P < .001$ for all)
DRCR Protocol J [DRCR.net 2011]	Traction or rhegmatogenous retinal detachment after intravitreal saline (8%) vs intravitreal ranibizumab (8%); ranibizumab was safe in most eyes with PDR, without traction threatening the macula

DR, diabetic retinopathy; DRCR, Diabetic Retinopathy Clinical Research; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor; VH, vitreal hemorrhage.

Approximately 40% of eyes had chronic persistent CI-DME through 3 years with continued ranibizumab treatment and laser. The cumulative probability of chronic persistent CI-DME decreased over time (85%, 58%, and 42% by years 1, 2, and 3, respectively).

Eyes without chronic persistent CI-DME had better VA outcomes, and substantial loss of VA (≥ 2 lines) was uncommon through 3 years, even for eyes with chronic persistent CI-DME. Among eyes with chronic persistent CI-DME, 45% had VA improvement ≥ 10 letters, and 13% had VA worsening ≥ 10 letters at 3 years.

Dr Bressler concluded that chronic persistent CI-DME may not be as common or as ominous for vision outcomes as previously thought. Caution should be exercised when considering specific approaches for future management of chronic persistent DME.

Table 3. Preferred Practice Patterns for DR

	Highlighted Findings and Recommendations
1	The prevalence of DM is increasing; as such, the prevalence of DR is expected to increase dramatically.
2a	Patients with type 1 DM should have annual screenings for DR beginning 5 y after disease onset.
2b	Patients with type 2 DM should have a prompt exam for DR at the time of diagnosis and at least annual exams thereafter.
3	Currently, only about 60% of people with diabetes have yearly screenings for DR.
4a	Maintaining near normal glucose and blood pressure levels lowers the risk of retinopathy development and progression.
4b	Patients should be informed of the importance of maintaining good HbA_{1c}, lipid, and blood pressure levels.
5	Patients with diabetes may use aspirin without adverse effects on the risk of retinopathy.
6a	Women who develop gestational diabetes do not need an eye exam during pregnancy.
6b	Pregnant patients with DM should be examined early in the pregnancy.
7	Referral to an ophthalmologist is required when NPDR, PDR, or macular edema is present.
8a	Ophthalmologists should communicate their findings to the primary care physician.
8b	Ophthalmologists should emphasize the need to optimize metabolic control.
9	Intravitreal injections of anti-VEGF agents are effective for the treatment of center-involving DME. This is a major change from the 2011 Preferred Practice Patterns, which recommended laser photocoagulation for the treatment of DR.
10	Laser photocoagulation remains the preferred treatment for noncenter-involving DME.
	Other Recommendations per Indication
PRP	Some severe NPDR Some non-high-risk PDR High-risk PDR
Vitrectomy	Severe vitreous or preretinal hemorrhage Traction macular detachment Combined traction-rhegmatogenous retinal detachment Vitreal hemorrhage precluding PRP

DM, diabetes mellitus; DME, diabetic macular edema; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

American Academy of Ophthalmology. *Diabetic Retinopathy PPP–2014*. 2014.

CURRENT APPROACHES TO MANAGING DR

Jennifer K. Sun, MD, Harvard Medical School, Boston, Massachusetts, USA, discussed current treatment strategies for PDR. Panretinal photocoagulation (PRP) laser is a highly effective treatment for PDR, but it causes serious complications, including destruction of the retina, peripheral and night vision loss, changes in color perception, and burns to the fovea, lens, iris, and cornea.

Dr Sun reviewed studies of the effectiveness of anti-VEGF treatment for DR and the risk of progression or need for PRP (Table 2). Protocol S [NCT01489189] is another study currently underway to assess outcomes of prompt PRP vs intravitreal ranibizumab with deferred PRP for PDR.

New imaging techniques offer improved assessment of DR and response to treatment. Peripheral findings

Table 4. Clinical Studies in DR

Study	Results
DRCR Protocol M [NCT01323348]	Discussion with patients about importance of metabolic control plus in-office HbA_{1c} for glycemic control: no demonstration of benefit.
RESTORE [Mitchell P et al. *Ophthalmology.* 2011]	Ranibizumab alone and combined with laser superior to laser monotherapy for improving mean average change in BCVA letter score from baseline to months 1 through 12 (+6.1 and +5.9 vs +0.8; both $P < .0001$). Mean central retinal thickness significantly reduced from baseline with ranibizumab (–118.7 μm) and ranibizumab + laser (–128.3 μm) vs laser (–61.3 μm; both $P < .001$).
RISE/RIDE [Nguyen QD et al. *Ophthalmology.* 2012]	Mean change from baseline in BCVA letter score at 2 y for sham vs ranibizumab (0.3 mg) vs ranibizumab (0.5 mg): RISE, 2.6 vs 12.5 vs 11.9; RIDE, 2.3 vs 10.9 vs 12.0.
BOLT [Rajendram R et al. *Arch Ophthalmol.* 2012]	Gain in letters with bevacizumab vs laser at 2 y: median gain, 9.0 vs 2.5; mean gain, 8.6 vs –0.5; 10-letter gain, 49% vs 7%; 15-letter gain, 32% vs 4%.
Meta-analysis of anti-VEGF in DME [Regnier S et al. *PloS One*. 2014]	Ranibizumab and aflibercept were both statistically superior to laser for the treatment of DME.
DRCR Protocol T [NCT01627249]	Aflibercept demonstrated greater improvement in BCVA at 52 wk vs both bevacizumab and ranibizumab.
DRCR Protocol N [DRCRN. *JAMA Ophthalmol.* 2013]	Intravitreal ranibizumab vs saline for vitreous hemorrhage: 16-wk vitrectomy rate, 12% vs 17%; little likelihood of a clinically important difference.

BCVA, best corrected visual acuity; DME, diabetic macular edema; DR, diabetic retinopathy; DRCR, Diabetic Retinopathy Clinical Research; VEGF, vascular endothelial growth factor.

on ultrawide-field fundus photography and angiography allow visualization of the peripheral retina, which may lead to increased DR severity in about 10% of eyes and imply an increased risk of worsening. An upcoming study, Protocol AA [DRCR.net. 2014], will evaluate assessment of DR using ultrawide-field fundus images.

IMPACT OF RECENT CLINICAL TRIALS ON PREFERRED PRACTICE PATTERNS

Paul Sternberg Jr, MD, Vanderbilt Eye Institute, Nashville, Tennessee, USA, discussed the potential impacts of recent clinical trials on the 2014 American Academy of Ophthalmology's Preferred Practice Patterns [PPP; American Academy of Ophthalmology. *Diabetic Retinopathy PPP–2014*. 2014]. According to Dr Sternberg, the recently revised guidelines should be up-to-date, but they may not reflect some recent advances. The highlighted findings and recommendations of the PPP are summarized in Table 3.

The results of recent clinical studies that may affect the 2014 PPP are summarized in Table 4.

The importance of annual screening for DR will increase as the prevalence of DM rises. Dr Sternberg concluded that communication with the primary care physician and emphasis of metabolic control to patients are critical for the management of DR.

MEDICAL TEAM COMMUNICATION CRITICAL FOR OPTIMAL DIABETES EYE CARE

Lloyd Paul Aiello, MD, PhD, Harvard Medical School, Boston, Massachusetts, USA, discussed the importance of coordinating new retinal treatments with primary care providers for patients with DM. Patients with DM should be assessed for the presence, localization, and extent of retinal lesions and retinal thickening and for the risk of progression. The appropriate therapy should be initiated and follow-up maintained.

Glycemic control is critical for the prevention and control of DR. In a 1993 study, patients with controlled blood glucose were found to have 27% less retinopathy development, 78% less retinopathy progression, 47% less severe retinopathy, 23% less macular edema, and 56% less need for photocoagulation. In the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications cohort follow-up, insulin-dependent patients

with DM receiving intensive therapy (median HbA_{1c}, 7.3%) vs conventional therapy (median HbA_{1c}, 9.1%) had a 62% reduced risk of retinopathy over 7 years [DCCT/EDIC Research Group. *JAMA*. 2002].

Elevated lipid levels are associated with increased hard exudate and DME development. Other systemic conditions that affect development and progression of retinopathy include blood pressure, pregnancy, renal disease, anemia, and eating and psychological disorders.

Dr Aiello noted that severe DR can exist despite excellent vision. The risk of retinopathy being present when not observed by examination of a non–eye care provider through undilated pupils is approximately 50%. Furthermore, patients with DR are often unaware of their eye disease, a major factor in nonadherence to eye care guidelines and poor vision outcomes [Huang OS et al. *Ann Acad Med Singapore*. 2009; Schoenfeld ER et al. *Ophthalmology*. 2001].

A study currently under review by the Joslin Diabetes Center at Harvard Medical School evaluated 2853 patients with DM by telemedicine retinal imaging and asked questions to evaluate their awareness of retinopathy. Ninety-three percent with mild DR and 63% with vision-threatening DR were unaware of their eye disease.

Patient-reported timeliness of follow-up results showed that among all patients, follow-up was not timely in 49% with no DR, 49% with mild DR, and 83% with vision threatening DR. Among those with scheduled visits, follow-up was not timely in 6% with no DR, 5% with mild DR, and 71% with vision-threatening DR.

Dr Aiello concluded that for state-of-the-art DM eye care, full medical team communication is critical and must include the following: identification of individuals with DM, lifelong evaluation and education, optimized systemic factors, identification of complications, timely and appropriate intervention, and evaluation of novel treatment approaches.