Update on the Diabetic Retinopathy Clinical Research Network

Recent data and status of some ongoing DRCR.net protocols.

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This information was provided by Drs. Solomon and Bressler as individuals, not on behalf of the DRCR.net.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network funded by the National Institutes of Health to facilitate multicenter clinical research on diabetic retinopathy, diabetic macular edema (DME), and related conditions, primarily through the design and execution of clinical trials. Established in 2002 with funds currently awarded through 2013 from the National Eye Institute (NEI) and also from funding by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the DRCR.net has promoted the collaboration of community- and academic-based practices with industry to pursue multicenter research initiatives that otherwise might not be undertaken. The Network currently consists of approximately 200 clinical sites throughout the United States, Europe, and Asia, with nearly 700 participating physicians. More than 3,500 patients have enrolled in at least one of the more than 15 DRCR.net clinical trials. Following is a review of some of the Network clinical trials that have had an impact on the current management of diabetic retinopathy and DME, as well as an update on what is on the horizon for the DRCR.net.

SOME RECENTLY COMPLETED TRIALS

A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide to Focal/Grid Photocoagulation for Diabetic Macular Edema.[1,2] Many of the current treatment paradigms for the management of DME have been derived from the Early Treatment Diabetic Retinopathy Study (ETDRS), a randomized, prospective clinical trial that demonstrated that eyes with macular edema treated with focal/grid laser were less likely to have moderate vision loss, at least a doubling of the visual angle (for example, from 20/20 to 20/40 or worse, or from 20/50 to 20/100 or worse) compared with untreated eyes in the control group.[3] Despite the universal application of ETDRS criteria in the management of DME, a 2002 American Society of Retina Specialists Preferences and Trends Survey revealed that 52% of retina specialists had used intravitreal triamcinolone acetonide (IVTA) in the management of diabetic macular edema, based on case reports of short-term improvement in visual acuity and

decreased retinal thickness on optical coherence tomography (OCT) and without long-term data on safety or efficacy.

The DRCR.net performed a prospective, multicenter, randomized clinical trial to compare the efficacy and safety of preservative-free IVTA, 1 mg or 4 mg, with focal/grid laser in the management of center-involved DME with at least some visual acuity loss. Eligible eyes had visual acuity (Snellen equivalent) of 20/40 to 20/320 with an OCT central subfield thickness (CSF) of greater than or equal to 250 µm and were randomized 1:1:1 to focal/grid laser, 1 mg IVTA, or 4 mg IVTA, with retreatment performed as often as every 4 months for persistent or new edema. Between July 2004 and May 2006, 840 eyes with DME, a mean visual acuity of 20/63, and a mean CSF of 424 µm at baseline were enrolled.

Observed differences in treatment effect among the three groups varied over the course of the clinical trial. At 4 months, mean visual acuity was better in the 4 mg IVTA group than in the 1 mg IVTA or laser groups. By 1 year, there was no observable difference in visual acuity among the treatment groups. Beginning with the 16-month visit and extending through the primary outcome visit at 2 years and the 3-year follow-up visit, the laser group appeared to be superior to either of the IVTA groups. The data did not support the hypothesis that IVTA was superior to focal/grid laser for DME. The effect of treatment on retinal thickening paralleled the visual acuity results. A greater reduction in CSF was observed at the 4-month visit for the 4 mg IVTA group compared with either the 1 mg IVTA or laser groups. By the 16-month visit, and extending through the primary outcome visit at 2 years and the 3-year follow-up visit, the laser group appeared superior to either of the IVTA groups in achieving reduction in central retinal thickening.

With respect to adverse events, more eyes in the 4 mg IVTA group than in either the 1 mg IVTA or laser groups experienced elevations in intraocular pressure from baseline that required either medical or surgical intervention. Similarly, more eyes in the 4 mg IVTA group underwent cataract surgery during the 3 years of follow-up than in the 1 mg IVTA or laser groups.

Although the ETDRS demonstrated that focal/grid photocoagulation reduced the frequency of vision loss in eyes with DME compared with no treatment, the results of this current trial re-established the importance of focal/grid photocoagulation as applied in the 21st century in the management of diabetic macular edema across a range of visual acuities when visual acuity loss already had occurred and across a wide range of CSF thicknesses on OCT. Although IVTA likely improves visual acuity compared with no treatment at all, this clinical trial could not demonstrate that IVTA was superior to focal/grid laser with respect to visual acuity or reduction in retinal thickness.

Most of the improvement in mean visual acuity in the two ranibizumab groups tended to occur by the 8 week study visit.

IVR or IVTA in Combination with Laser Photocoagulation for DME.[4] The observation that 4 mg IVTA had a greater positive treatment effect on visual acuity and retinal thickening at 4 months while laser photocoagulation had a sustained, long-term treatment benefit out to 3 years, but with half of eyes still with retinal thickening, prompted the DRCR.net to evaluate intravitreal ranibizumab (IVR) or IVTA in combination with laser photocoagulation for DME. In this prospective, multicenter clinical trial, eligible eyes (visual acuity Snellen equivalent of 20/32 to 20/320 and CSF greater than or equal to 250 µm) were randomized to sham injection plus prompt laser (3 to 10 days after injection), 0.5 mg ranibizumab plus prompt laser, 0.5 mg ranibizumab plus deferred laser (greater than or equal to 24 weeks after injection), or 4 mg triamcinolone plus prompt laser. Follow-up visits occurred every 4 weeks for the first year and then every 4 to 16 weeks thereafter, depending on the disease course and treatment administered. Between March 2007 and December 2008, 854 study eyes with median visual acuity Snellen equivalent of 20/50 and mean CSF of 405 µm at baseline were enrolled and randomized. Primary outcome measures were best corrected visual acuity and safety at 1 year.

For the 1-year primary outcome, the mean change in the visual acuity letter score from baseline was significantly greater in the IVR plus prompt laser group and in the IVR plus deferred laser group than in either the triamcinolone plus prompt laser or sham plus prompt laser groups. A greater proportion of eyes in the two IVR groups had at least two- or at least three-line improvement in visual acuity and were less likely to have at least two- or three-line decrease in visual acuity compared with either the triamcinolone plus prompt laser or sham plus prompt laser groups. Most of the improvement in mean visual acuity in the two ranibizumab groups tended to occur by the 8 week study visit, with continued improvement through the

1-year primary outcome visit and evidence of superiority for these eyes followed through at least 2 years for the data analyzed for the primary outcome manuscript. The effect of treatment on retinal thickening at the 1-year primary outcome visit for the IVR groups and the sham plus prompt laser group paralleled the overall visual acuity results and favored the two IVR groups. For the triamcinolone plus prompt laser group, the reduction in central subfield thickening appeared to be similar to that achieved in the ranibizumab groups but did not parallel the visual acuity outcome.

There was no evidence in this study to suggest that the administration of ranibizumab was associated with an increased risk of systemic adverse events, including stroke or cardiac events. Of the 3,973 ranibizumab injections administered through the first year of this trial, there were three cases of injection-related endophthalmitis.

The results from this DRCR.net protocol demonstrate that IVR with either prompt or deferred laser is superior to either ETDRS laser alone or a combination of triamcinolone plus prompt laser in reducing visual acuity loss and achieving maximal visual acuity through at least 1 year and should be considered as a treatment for some patients with DME.

ON THE HORIZON FOR THE DRCR.NET

Several clinical trials currently under way for the DRCR.net have the potential to significantly affect the current management of diabetic retinopathy and DME.

Randomized Trial Evaluating Short-Term Effects of IVR or IVTA on Macular Edema Following Panretinal Photocoagulation. The objective of this trial is to evaluate the effect of IVR or IVTA on exacerbation of macular edema in eyes requiring panretinal photocoagulation (PRP) and receiving focal/grid laser for DME. Enrollment has been completed, and 1-year outcome data should be available over the next year.

A Pilot Study in Individuals with Center-Involved DME Undergoing Cataract Surgery. The objective of this trial is to evaluate exacerbation of DME and visual acuity changes that may occur 16 weeks following cataract surgery while determining the feasibility of a randomized trial in eyes with center-involved DME prior to cataract surgery. Enrollment is currently under way.

An Observational Study in Individuals with Diabetic Retinopathy without Center-Involved DME Undergoing Cataract Surgery. The objective of this trial is to determine the incidence of progression to center-involved DME 16 weeks after cataract surgery in eyes with diabetic retinopathy and without definite center-involved DME. Enrollment is currently under way. ■

Supported in part by the James P. Gills Professorship (Dr. Bressler) and Katharine M. Graham Professorship (Dr. Solomon) and the Wilmer Retina Research Fund.

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Grants to investigators at The Johns Hopkins University are negotiated and administered by the institution (such as the School of Medicine) that receives the grants, typically through the Office of Research Administration. Individual investigators who participate in sponsored project(s) are not directly compensated by the sponsor, but may receive salary or other support from the institution to support their effort on the project(s).

1. Diabetic Retinopathy Clinical Research Network. Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema. *Ophthalmology*. 2008:115(9):1447-1459.
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4. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010. In press.

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