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Recent Advancements in Diabetic Retinopathy Treatment from the Diabetic Retinopathy Clinical Research Network

Carl W. Baker, MD¹, Yi Jiang, MD², and Thomas Stone, MD²

Carl W. Baker: eyedude3@paducaheyeyes.com; Thomas Stone: Drstone@retinaky.com

¹Carl W. Baker, MD, Paducah Retinal Center, 4630 Village Square Dr., Suite 102, Paducah, KY 42001, 270-443-4393, 270-443-7779 (fax)

²Retina Associates of Kentucky, 6420 Dutchmans Parkway, Suite 70, Louisville, KY 40205, 800-627-2020, fax: (859) 263-3737

Structured Abstract

Purpose of Review—Diabetic retinopathy (DR) and diabetic macular edema (DME) are common eye diseases leading to vision loss. The Diabetic Retinopathy Clinical Research Network (DRCRnet), a collaboration of private and academic practices supported by the National Eye Institute and the National Institute of Diabetes, Digestive and Kidney Diseases have studied diabetic eye disease for 13 years. This review will discuss the network's findings over the last year, when some of their most important contributions were reported.

Recent Findings—The DRCRnet reported intravitreal bevacizumab, ranibizumab and aflibercept all improve visual acuity in DME. With baseline vision of 20/30 to 20/40, all agents had similar efficacy. With baseline vision of 20/50 or worse, aflibercept resulted in superior visual improvement. Protocol S, which compared panretinal photocoagulation to intravitreal injections of ranibizumab for proliferative diabetic retinopathy (PDR), found vision outcomes and surgery rates were not inferior in the injection group. Secondary outcomes indicate improved functional results with ranibizumab supporting injections as a possible alternative treatment for PDR.

Summary—The DRCRnet has helped clarify the role of various treatments for both DME and PDR, and will continue to evaluate treatments for these vision-threatening conditions.

Keywords

Diabetic Retinopathy; Diabetic Macular Edema; Intravitreal injection

Introduction

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a group of private practice and academic retina practices that have been studying multiple aspects of the

Correspondence to: Carl W. Baker, eyedude3@paducaheyeyes.com.

Conflicts of interest

Dr. Baker performs clinical research for Genentech, Regeneron, Alcon, Ophthotech, Iconic, Allergan, Thrombogenics, Acucela, Alimera, GlaxoSmithKline, National Institutes of Health. He has served on an advisory board for Roche.

Dr. Stone performs clinical research for Genentech, Regeneron and owns stock in Regeneron.

treatment of diabetic retinopathy (DR) for the past 13 years. The group was established as a collaborative effort between the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, and has had participation from over 200 sites. The network is a unique collaboration between physicians, private and academic centers, as well as industry. The strength of the DRCR.net lay in its multicenter nature and the ability to recruit large numbers of patients across the country with a rigor that is required in clinical trials. It has transformed the way we can perform clinical trials and has given the ophthalmology community great insight into the rapidly changing landscape of the treatment of diabetic eye disease.

This paper will evaluate some of the more recent findings of the DRCR.net and how they influence our care of the diabetic patient.

DRCR Network History-Targeting Vision Loss from Diabetic Retinopathy

The DRCR network established a protocol-labeling convention by naming their first study “Protocol A” with progression down the alphabet as each new study was added. A summary of past and ongoing DRCR network trials can be found in Table 1. The early trials within the DRCR network helped evaluate techniques of laser for the treatment of diabetic macular edema (DME)[1] and helped define the natural history of progression of DME as observed using the newly available tools of OCT.[16,17] Special interest in the utilization of triamcinolone for the treatment of DME was investigated with protocol B and the clinical efficacy of this steroid for DME was found to be inferior to macular laser.[2] The focus of the DRCR network was then turned to the use of anti-VEGF agents and the network’s first trial evaluating bevacizumab for DME was published in 2007. [3] Although the initial anti-VEGF study results did not identify a significant visual benefit of bevacizumab, data from that trial regarding dosing and duration of effect were very useful in designing subsequent trials evaluating anti-VEGF agents.

Protocol I

In 2010, the DRCR.net released the initial 1-year results of Protocol I, a prospective randomized trial looking at the role of anti-VEGF (ranibizumab) with either prompt or deferred laser as well as triamcinolone for patients with center involved diabetic macular edema.[4] Two and three year results of the same study were published in subsequent years bringing to the forefront the prominent role of anti-VEGF medications.[5,6] At the end of year three, a subset of patients in the two ranibizumab groups enrolled in a two-year extension and the results were published in 2015.[7]

Protocol I helped highlight the superior effect of ranibizumab (with or without deferred macular laser) on visual acuity and macular thickening when compared to laser alone when treatment was performed following the DRCR network protocol algorithm. The long-term data from Protocol I reveals important information regarding the number of ranibizumab injections required to provide adequate DME treatment. The subjects required a median of 8 to 9 injections for the 1st year, 3 to 4 in the second year, and 1 to 2 in the third year for the ranibizumab+prompt laser and ranibizumab+deferred laser groups, respectively. In year 4, the median number of injections was 0 for the prompt and 1 for the deferred group. In year

5, the median number of injections was 0 for both groups. While the visual improvements achieved at year 1 were retained through year 5, there was a slight increase in the number of injections required in the deferred laser group. More than half of the eyes in the deferred-laser group did not require macular laser treatment throughout the 5-year follow-up.

Focal/grid laser had been the definitive DME treatment since 1985[18]. The five-year follow-up of Protocol I confirms the superior visual acuity outcomes from anti-VEGF treatment and also presents encouraging information that the maintenance of improved vision requires few additional treatments 4–5 years after treatment is initiated. The DRCR network's anti-VEGF treatment algorithm from protocol I was used as a model for subsequent DRCR network trials.

Protocol T

In a landmark study released in March of 2015 in the New England Journal of Medicine, the DRCR.net demonstrated 1-year results of protocol T, a comparison of the three commonly used anti-VEGF medications for DME.[15] Prior to its publication, uncertainty persisted over the comparative efficacy of the different anti-VEGF medications on visual acuity and OCT changes. In this study, 660 patients at 89 sites were randomized to intravitreal treatment for center-involved DME with aflibercept, ranibizumab, or bevacizumab on a monthly basis. Treatment was continued unless there was no further improvement after two consecutive injections or there was treatment success defined as 20/20 VA or <250 μ m on central subfield thickness on OCT. If DME worsened after deferral of injections then injections were re-started following the initial guidelines for treatment. Patients were allowed to receive focal/grid laser after 24 weeks if there was still persistent diabetic edema.

Protocol T results at 1 year (Figure 1) demonstrate a significant improvement of aflibercept over the other two medications in letter score 13.3 vs. 9.7 ($p<0.0001$) vs. bevacizumab and 13.3 vs. 11.2 ($p=0.01$) vs. ranibizumab. A pre-planned subgroup analysis revealed that the difference in visual acuity improvement between the groups was driven by those eyes with worse baseline visual acuity. The differences between baseline and 1 year visual acuity in patients with baseline 20/32–20/40 vision were not statistically significant between any of the three groups. For patients with 20/50 or worse initial visual acuity, the mean letter improvement for aflibercept vs. bevacizumab was 18.9 ± 11.5 vs. 11.8 ± 12.0 ($p<0.001$). For aflibercept vs. ranibizumab, the difference was 18.9 ± 11.5 vs. 14.2 ± 10.6 ($p=0.003$).

Anatomic results from the Protocol T trial indicate bevacizumab treatment does not lead to as much resolution of macular thickening when compared to aflibercept and ranibizumab. The overall change in macular thickness was less with bevacizumab and a greater percentage of eyes had persisting macular thickening with bevacizumab compared to aflibercept and ranibizumab regardless of baseline visual acuity.

Encouragingly, Protocol T demonstrated all three anti-VEGF agents resulted in significant gains in vision with similarly low rates of systemic adverse events. When baseline visual acuity was 20/30–20/40, there were no differences in vision outcome at 1 year between the groups. However, in eyes with baseline acuity of 20/50 or worse, aflibercept resulted in superior visual outcomes.

Cost analysis of Protocol T

Associated with the release of protocol T results, the DRCR network has followed-up up the comparisons between ranibizumab, bevacizumab, and aflibercept with a cost effectiveness analysis.[19] The three drugs were compared regarding estimated medical cost and quality-adjusted life-year (QUALY) over the 1 year of the protocol T trial. Because of the high incremental costs of aflibercept and ranibizumab over bevacizumab, to become cost effective over 10 years, the cost of aflibercept would need to decrease approximately 69% and the cost of ranibizumab would need to decrease 80%. The results of this analysis expose the challenges of safety and efficacy vs. cost-effectiveness in an era when public health policy is increasingly influencing medical management.

Proliferative Diabetic Retinopathy

Medical treatment for proliferative diabetic retinopathy management has had minimal advancement over the past 40 years since panretinal photocoagulation was established as an effective treatment to reduce the incidence of severe vision loss.[20] However, several trials evaluating anti-VEGF treatment for DME both within the DRCR network[21] and outside the network reported reduction in DR severity with anti-VEGF treatment.[22,23]

Protocol S

The DRCR network developed Protocol S to compare intravitreal ranibizumab with panretinal photocoagulation for the treatment of proliferative diabetic retinopathy (PDR). The 2-year results of Protocol S were published in November, 2015.[14] The primary outcome of the study was a non-inferiority vision comparison between PRP and ranibizumab. Secondary endpoints of interest also included visual field changes, DME development, and safety issues including need for vitrectomy, injection-related complications and systemic adverse events.

In this randomized study, 394 eyes were assigned to receive ranibizumab or PRP for the treatment of PDR. The ranibizumab eyes were treated with monthly injections until the PDR stabilized or resolved then as needed to treat worsening or recurrences of retinal neovascularization. Eyes in both groups were treated with ranibizumab when DME was present. In eyes treated with ranibizumab, a median of 10 injections were administered in eyes without DME at baseline and 14 injections in eyes with DME at baseline over 2 years. In eyes randomized to PRP, supplemental PRP was required 45% of the time. Also, 53% of PRP-treated eyes received ranibizumab for DME. (35% had DME at baseline and another 18% developed DME during the 2 year follow-up).

At 2 years, the visual outcome of the ranibizumab-treated eyes was non-inferior to the PRP-treated eyes with a mean visual acuity difference of +2.2 letters (-0.5 to $+5.0$, $p < 0.001$ for non-inferiority) favoring the ranibizumab group (Figure 2). Visual acuity area under the curve analysis indicates a significant visual benefit in eyes treated with ranibizumab over the 2 year course of treatment. Importantly, eyes treated with ranibizumab had significantly less loss of sensitivity in the peripheral vision, fewer vitrectomies and a much lower incidence of DME. Systemic adverse event rates were similar between both groups.

The results of this trial suggest ranibizumab injections are a safe and effective alternative to PRP in the management of proliferative diabetic retinopathy. The DRCR network plans to continue to assess the outcome of this study for 5 years. With confirmation from long-term follow-up, this DRCR network study will likely impact the management of diabetic retinopathy more than any other advancement since the advent of panretinal photocoagulation.

Other recent contributions to diabetic retinopathy research

Protocol N: Anti-VEGF or Saline for vitreous hemorrhage from PDR

In 2013, the DRCR.net performed an exploratory study looking at the rates of vitrectomy and completion of PRP in patients with vitreous hemorrhage from PDR treated with a series of three intravitreal injections of either ranibizumab or saline.[9] At the primary outcome time frame of 16 weeks, there was a non-significant difference in the cumulative probability of vitrectomy. There was, however, was a significant difference in improvement in visual acuity and in the rate of completion of PRP suggesting some biologic activity from the ranibizumab. An update of 1 year results[10] published in July 2014 showed that there was still little change to the rate of vitrectomy and there was no difference in visual acuity improvement at 52 weeks. There is continued interest within the DRCR Network to evaluate vitrectomy as an intervention in the management of proliferative diabetic retinopathy and vitreous hemorrhage. Data from protocol N will be used to help design this trial.

Protocol R: Topical NSAIDs and DME

The DRCR performed a phase II, masked, RTC on patients with non-central diabetic macular edema with one arm receiving nepafenac vehicle and the other arm receiving the drug. While the treatment was well tolerated, the results published this year did not show any significant improvement in visual acuity scores, difference on OCT thickness, and progression to center involving DME.[13] At present, the DRCR Network is not planning further study of topical treatments for DME.

Protocol M: Diabetic Glycemic Control Through Educational Intervention

In an evaluation of individualized office based care and education on long-term diabetic glycemic control in patients with type 1 and type 2 diabetes, the DRCR.net looked at the impact of ophthalmic provider educational interventions on HbA1c, blood pressure, and BMI at 1 year follow-up.[8]

Disappointingly, the authors did not find a significant effect of intervention on glycemic control whether the subjects were being evaluated for diabetic retinopathy annually or more frequently. It was speculated in the article published this year that perhaps the standard of care already provided sufficient patient education whereby the interventions did not add additional value. Unfortunately, methods of educational intervention aimed at improvement of glycemic control remain a challenge.

Protocol O: OCT Reproducibility and Conversion Equivalence

The implementation of OCT technologies have revolutionized the clinical management many macular diseases. The use of OCT has been instrumental in the analysis, follow up, and treatment decisions of patients in DRCR.net studies. Time-domain OCTs (TD-OCT) were largely in use at DRCR studies until about 2011. Most clinical research is now performed using spectral domain OCT (SD-OCT) technology and the transition from time-domain to spectral domain has had uncertain effects on study design and interpretation. The DRCR Network has published 2 manuscripts in the last year that provide some metrics for the conversion of SD-OCT data from the Cirrus (Carl Zeiss Meditec), the Spectralis (Heidelberg Engineering), and the RTVue (Optovue) to TD-OCT (Carl Zeiss Stratus) standards.[11,12] The analysis provided by the network is useful in evaluating and comparing results across trials and developing machine-specific thresholds on SD-OCT for interventions in subsequent clinical trials.

Conclusion

The DRCR Network has provided major clinical research results in 2015 that will impact the management of diabetic macular edema and proliferative diabetic retinopathy. Important questions regarding diabetic retinopathy treatments and innovations are being answered within the Network that would otherwise not be answered by industry or other entities. The collaboration between academics and private practices has led to study results that apply well to current clinical practice. Furthermore, new DRCR network protocols and longer-term follow-up of the Protocol S and Protocol T studies will continue to guide clinical decision-making regarding diabetic retinopathy for many years to come.

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KEY POINTS

- DRCR Protocol T results published this year demonstrate significant visual gains are attained with intravitreal aflibercept, ranibizumab and bevacizumab and aflibercept is the more effective agent in eyes with 20/50 or worse vision.
- Recently published 2-year results from DRCR Protocol S propose ranibizumab is an effective alternative to panretinal photocoagulation for the treatment of proliferative diabetic retinopathy.
- The DRCR network is a productive collaborative network of clinical researchers that have recently made major contributions to the management of diabetic retinopathy.

A. Overall

B. Stratified by Baseline Visual Acuity (~Snellen Equivalent)

Figure 1.

Mean Change in Visual Acuity over Time, A) Overall, B) Stratified by baseline visual acuity (approximate Snellen equivalent): 20/50 or worse (solid lines) and 20/32–20/40 (dashed lines). Change in visual acuity was truncated to 3 standard deviations from the mean.

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Figure 2.
Visual Acuity Results from Protocol S. [14]

Table 1**Summary of DRCR Network Protocols**

A-Pilot Study of Laser Photocoagulation for DME [1] Modified ETDRS focal photocoagulation resulted in more reduction in retinal thickening than Modified Macular Grid (MMG) technique of macular laser. Also, in eyes with 20/40 vision or worse, modified ETDRS laser resulted in 59% of eyes improving 2 or more lines of vision.
B-Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for DME [2] Focal/grid laser is more effective and has fewer safety concerns than the preservative-free intravitreal triamcinolone over a 2-year study.
C- Temporal Variation in OCT measurements in DME OCT measurements have little meaningful variation between 8AM and 4PM. Center Subfield measurements that change 11% are likely to indicate a real change in retinal thickness.
D- Evaluation of Vitrectomy for DME Vitrectomy for DME and vitreomacular traction generally leads to reduction in macular thickening. Visual acuity improvement was more common than visual acuity loss and complication rates were low. No definitive guidance regarding indications for vitrectomy for DME can be inferred from the study results.
E-Pilot study of Peribulbar Triamcinolone Acetonide for DME. Peribulbar triamcinolone injections do not improve outcomes for eyes with DME and result in increased IOP, cataract rates and ptosis. Anterior peribulbar injections had the highest risk for IOP increases and cataract formation.
F-An Observational Study of the development of DME Following Scatter Photocoagulation Meaningful differences in retinal thickness and vision were not found between cohorts that were treated in 1 sitting vs. 4 sittings of pan-retinal photocoagulation.
G-Subclinical DME study A longitudinal assessment of eyes that had retinal thickening on OCT without thickening on clinical exam revealed a progression to clinically apparent DME occurred in 23–58% of eyes within 2 years.
H-A Phase 2 Evaluation of Anti-VEGF Therapy for DME: Bevacizumab (Avastin) [3] Bevacizumab can reduce DME in some eyes and 4 weeks is the likely interval for appropriate assessment of its use. Results from this protocol assisted in the design of Protocol I and Protocol T.
I-Intravitreal Ranibizumab or Triamcinolone in Combination with Laser Photocoagulation for DME [4,5,6,7] The use of Ranibizumab with deferred or prompt focal/grid laser for the treatment of DME was superior to focal/grid laser alone. Using the Protocol I treatment algorithm the median number of injections required to achieve and sustain the vision improvements was 8–9 in the first year of treatment but diminished to around 1 in the later years of treatment (4 and 5 years). The risk of worsening diabetic retinopathy was decreased with Ranibizumab and Triamcinolone treatment.
J-Intravitreal Ranibizumab or Triamcinolone Acetonide as Adjunctive Treatment to PRP for PDR Better visual acuity and less macular thickening was seen at 14 weeks after one intravitreal triamcinolone injection or two intravitreal ranibizumab injections in eyes undergoing PRP. Long-term benefits of this adjunctive therapy were not assessed.
K-The Course of Response to Focal Photocoagulation for DME DME in eyes treated with focal laser that improves but does not resolve completely by 16 weeks often continue to improve without additional improvement.
L- Evaluation of Visual Acuity Measurements in Eyes with DME Autorefractometry was not found to be an acceptable substitute for manual refraction in a multi-center clinical trial setting.
M- Effect of Diabetes Education During Retinal Ophthalmology Visits on Diabetes Control [8] A large multicenter assessment was performed to evaluate the effect of educational intervention at retinal evaluations for diabetic retinopathy on HbA1c levels. No changes in glycemic control were measured after the educational intervention.
N- An Evaluation of Intravitreal Ranibizumab for Vitreous Hemorrhage due to Proliferative Diabetic Retinopathy [9,10] Intravitreal injections of ranibizumab and saline were compared in eyes with PDR-related vitreous hemorrhage. At the 16-week outcome, vitrectomy rates were lower than expected in both groups with little evidence of a difference between groups. Some secondary outcomes suggest a positive biologic activity of ranibizumab in this clinical situation.
O- Comparison of Time Domain OCT and Spectral Domain OCT Retinal Thickness Measurement in DME [11,12] Macular thickness measurements in eyes with no or little diabetic retinopathy were compared between the Zeiss Stratus OCT and other SD OCT machines. Relationship equations between SD-OCT machines and the Stratus TD OCT can be determined for group comparisons but individual patient measurements cannot be reliably converted by the same equations. The 250 micron threshold for OCT thickening on Stratus OCT is comparable to gender specific thickness thresholds of 320 microns for men and 305 microns for women using the Heidelberg Spectralis OCT.
P- Pilot Study in Individuals with Center-Involved DME undergoing Cataract Surgery Heterogeneous perioperative treatment strategies and poor recruitment of this study limits the feasibility of an interventional trial on cataract surgery patients and DME.
Q- An Observational study in Individuals with Diabetic Retinopathy without Center-Involved DME Undergoing Cataract Surgery

<p>10–12% of eyes with diabetic retinopathy but without center involved DME progressed to center involved DME after cataract surgery. Eyes with non-central DME or a history of previous treatment for DME were more likely to have center-involved DME 16 weeks after cataract surgery.</p>
<p>R- A Phase II Evaluation of Topical NSAIDS in Eyes with Non-Central involved DME [13] No difference in progression to central involved DME was seen in eyes with or without the use of topical nepafenac.</p>
<p>S-Prompt PRP versus Intravitreal Ranibizumab with Deferred PRP for PDR (In Follow-up) [14] Intravitreal Ranibizumab was not inferior to PRP for PDR at 2 years. Ranibizumab provided better functional vision outcomes with less need for vitrectomy and less frequent DME than PRP.</p>
<p>T-Comparative Effectiveness Trial of Aflibercept, Bevacizumab, and Ranibizumab for DME treatment. (In Follow-up) [15] All three drugs provided substantial improvement in vision at 1 year using the DRCRnet treatment algorithm. Overall, Aflibercept provided more visual improvement than the other 2 drugs especially when baseline vision was 20/50 or worse. No substantial safety differences were seen in the three treatment groups although HTN-related MEDra reports were higher in the subjects treated with Ranibizumab.</p>
<p>U-Short-term Evaluation of Combination Corticosteroid+Anti-VEGF Treatment for Persistent Central-Involved DME following Anti-VEGF Therapy (Enrolling) Evaluation of Dexamethasone implant with anti-VEGF in eyes that have incomplete responses to anti-VEGF treatment alone.</p>
<p>V- Treatment for Central-Involved DME in eyes with Very Good Visual Acuity (Enrolling) Randomized trial comparing immediate anti-VEGF vs Observation vs focal laser as initial therapy in eyes with center-involved DME and 20/25 or better vision</p>
<p>AA- Peripheral DR Lesions on Ultrawide-field Fundus Images and Risk of Diabetic Retinopathy Worsening Over Time (Enrolling) A comparison of UWF imaging to standard 7-field imaging for assessing risk factors for DR progression.</p>
<p>GEN – Genes in Diabetic Retinopathy (Enrolling) Development of a genetic repository associated with known phenotypic information gathered from DRCRnet subjects to assess genetic risk factors for development and progression of diabetic retinopathy.</p>