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Contributions of the DRCR Network

Diabetic retinopathy (Figure 1) and diabetic macular edema (DME) are common eye diseases leading to vision loss. The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaboration of private and academic practices supported by the National Eye Institute and the National Institute of Diabetes, which has studied diabetic eye disease since 2004.

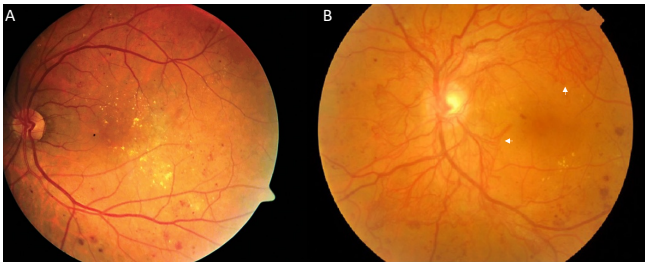

Figure 1: A) Non-proliferative diabetic retinopathy. B) Proliferative diabetic retinopathy. Arrows indicate neovascular vessels.

DRCR.net's early studies evaluated laser techniques for the treatment of DME[1] (Figure 2) and helped define its natural history with OCT.[2] Utilization of triamcinolone in DME was investigated with protocol B[3] after which the focus turned to anti-VEGF agents, and the network's first trial evaluating bevacizumab for DME was published in 2007.[4] The strength of the DRCR.net lies in its multicenter nature and the ability to amalgamate large data on diabetic eye disease. It has given the eyecare community great insight into the rapidly changing landscape of the treatment of these complex conditions. This review will summarize some of the network's most important contributions.

Protocol D: Vitrectomy for DME[5]

Vitrectomy for DME with vitreomacular traction led to reduction in macular thickening and visual acuity (VA) improvement was more common than VA loss. However, the study could not offer definitive guidance regarding specific indications for vitrectomy for DME. In modern clinical practice, vitrectomy is generally reserved for DME patients with poor response to maximum medial therapy.

Protocol I: Ranibizumab or Triamcinolone in Combination with Laser Photocoagulation for DME[7]

This was the first trial that showed effectiveness of anti-VEGF agents for DME. Ranibizumab with deferred or prompt focal/grid laser for DME was superior to focal/grid laser alone or to triamcinolone with laser. The median number of injections required to achieve and sustain the vision improvements was 8-9 in the first year of treatment but decreased to around 1-2 by year 3. The study also noted that about 40% of eyes did not achieve complete resolution of edema. This study guides the retina community as to the expected course for DME patients receiving anti-VEGF treatment - the majority can achieve a substantial reduction in injection frequency over time and many will continue to have some residual edema.

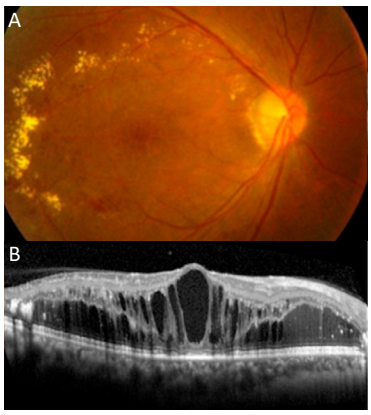

Figure 2: A) Clinically significant macular edema (CSME). B) Center involving diabetic macular edema (DME).

Protocol N: Ranibizumab for Vitreous Hemorrhage (VH) from Proliferative Diabetic Retinopathy (PDR)[8]

Intravitreal ranibizumab versus saline for diabetic VH (Figure 3) demonstrated faster clearing of VH and decreased recurrent VH at 16 weeks, but at 52 weeks there was no difference in rates of vitrectomy or in VA. The decision of whether to inject these patients is evaluated on a case-by-case basis and takes into consideration factors such as prior PRP (Figure 4) and presence of traction.

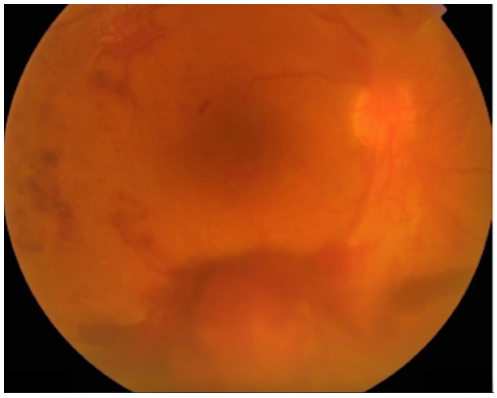

Figure 3: Diabetic vitreous hemorrhage

Protocol Q: Cataract Surgery without Center-Involved DME[9]

Eyes with non-central DME or a history of previous treatment for DME were more likely to have center involving DME 16 weeks after cataract surgery (10-12%). Cataract surgery can worsen DME, and it is generally recommended to have this condition controlled prior to undergoing cataract surgery.

Protocol R: Non-Central DME NSAIDs Study[10]

There was no difference in progression from non-center to center involved DME in eyes with or without topical nepafenac.

Protocol S: Prompt PRP versus Ranibizumab with Deferred PRP for PDR Study[11]

This study demonstrated that anti-VEGF is a safe and effective alternative to PRP. There were equal VA and rates of neovascularization and VH, and the anti-VEGF (ranibizumab) group developed less new DME and had less center-involving tractional retinal detachments (Figure 5). Ranibizumab was also shown to improve the severity of diabetic retinopathy, which has guided retina specialists to use anti-VEGF to treat not only PDR, but certain cases of non-proliferative diabetic retinopathy as well. Whereas PRP is a lasting treatment for PDR, anti-VEGF therapy requires ongoing administration - the ranibizumab group without DME required 7 injections in the first year and 3 in each subsequent year. Therefore, this approach is only appropriate for patients with reliable follow up. A concern with PRP is peripheral visual field loss, and this study showed a greater early reduction in peripheral visual field sensitivity in the PRP group, but after 2 years the gap in visual field sensitivity between groups narrowed each year and there was no subjective difference between groups. The decision of whether to treat PDR with PRP, anti-VEGF, or a combination of the two is made on a case-by-case basis.

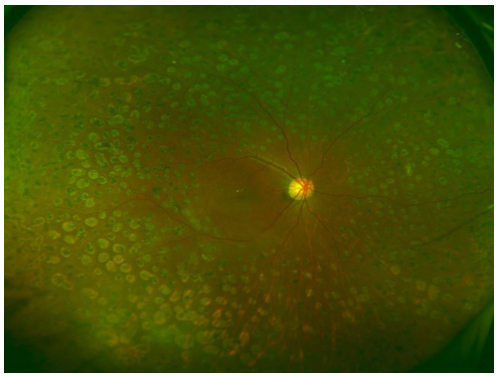

Figure 4: Panretinal photocoagulation (PRP)

Protocol T: Aflibercept, Bevacizumab, and Ranibizumab Comparison Study for DME.[12]

This study demonstrated that all three drugs provided substantial visual improvement and that there were no substantial safety differences between drugs. For VA ≥20/40, each drug demonstrated similar visual outcomes, whereas anatomic responses with ranibizumab and aflibercept were superior to bevacizumab and were equal to each other. However, for VA ≤20/50, aflibercept provided greater visual and anatomic improvement than the other two drugs. This data provides useful guidance, but real-world considerations also influence which drug a patient receives.

Protocol TX: Protocol T Extension[13]

This study followed protocol T patients from after the initial 2-year study up to year 5. They did not receive protocol defined treatment after the initial study. VA was better at year 5 than at baseline but declined from years 2 to 5 even though retinal thickness was stable during this period. This may have been due to change in care from protocol defined treatment or to development or cataract or ischemia.

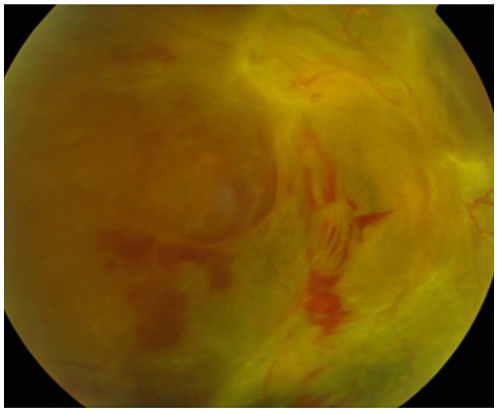

Figure 5: Center involving tractional retinal detachment

Protocol U: Phase II Combination Steroid and Anti-VEGF for Persistent DME[14]

Evaluated combined dexamethasone implant (Figure 6) and anti-VEGF therapy in eyes with incomplete response to anti-VEGF alone. The combined group showed a greater reduction in retinal thickness but there was no difference in VA improvement between groups. However, pseudophakic subgroup analysis (i.e. excluding for steroid-induced cataract development) noted better VA outcome with combination treatment but the effect was small and the study size was likely insufficient to achieve significance. In clinical practice, many retina specialists will use intravitreal steroids, usually either Triesence (triamcinolone suspension) or Ozurdex (dexamethasone implant), for DME incompletely responsive to anti-VEGF treatment alone.

Protocol V: Treatment for Central-Involved DME in Eyes with Very Good Visual Acuity[15]

Compared immediate anti-VEGF (aflibercept) vs observation vs focal laser as initial therapy in eyes with center involving DME and ≥20/25 vision. A 5-letter or more decrease in VA at 2 years was not significantly different between groups. This study guides the retina community that these patients can be safely observed. Most patients in this study were well-controlled diabetics with moderate or milder diabetic retinopathy and <300nm thickness, so protocol V may not be applicable to patients not meeting these criteria.

Protocol AB: Vitreous Hemorrhage from PDR[16]

Compared anti-VEGF (aflibercept) vs vitrectomy with endolaser for diabetic VH. VA at 6 months and 2 years were equivalent between groups. As expected, more dense hemorrhages took longer to clear. Thus, diabetic VH can be treated medically with a good final outcome. Retina specialists generally give these patients at least 1 to 2 months to clear before considering vitrectomy, but patient specific factors and patient preferences factor into the decision of whether and when to proceed with vitrectomy.

In summary, The DRCR network has made important contributions to our understanding of the management of diabetic eye disease. We have had an ever-increasing number of treatment options for this complex disease and are fortunate to have the scientific insight of the DRCR network's research in guiding our treatment decisions. Although we have seen a shift in management from focal and PRP lasers towards intravitreal therapy with anti-VEGF agents and steroids, all of these treatments continue to have a role in the management of diabetic eye disease on a case-by-case basis. Additionally, real world factors including diabetic control and compliance with follow up also influence treatment decisions.

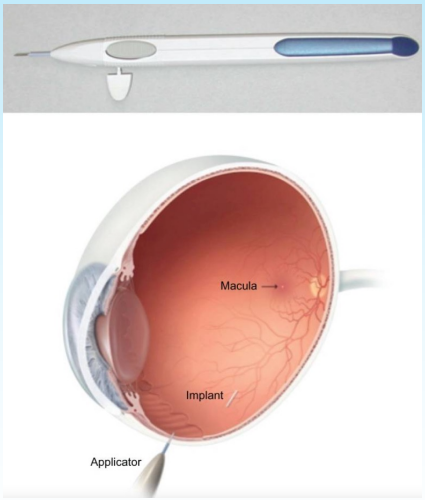

Figure 6: Dexamethasone implant

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Figure References

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Diabetic Macular Edema (DME)
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Gleam: A Prospective, Randomized, Double-masked, Active Comparator-Controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Secondary to Treatment-naive Diabetic Macular Edema.

Diabetic Retinopathy
Teaneck
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Edison
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Toms River
Opthea Shore: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

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