Anti-VEGF Pharmacotherapy as an Alternative to Panretinal Laser Photocoagulation for Proliferative Diabetic Retinopathy

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From 1976 to 1981, the results of the Diabetic Retinopathy Study identified that panretinal laser photocoagulation (PRP) for high-risk proliferative diabetic retinopathy (PDR) reduced the rate of severe visual acuity loss by more than 50% compared with the natural history of the disease.1,2 The Diabetic Retinopathy Study identified 4 key risk features of PDR (retinal neovascularization [NV]; NV within 1 disc diameter of the optic disc [NVD]; severe NV [NVD >1/4 to ½ disc diameters or NV elsewhere >½ disc diameter]; and preretinal or vitreous hemorrhage) and indicated that the presence of 3 or more risk factors constituted high-risk characteristics for developing severe vision loss.3 The results of the Diabetic Retinopathy Study have served as the basis for the accepted standard of care in the management of PDR for decades.

In this issue of JAMA, the investigators from the Diabetic Retinopathy Clinical Research Network (DRCR.net) present the results of a clinical trial comparing PRP and intravitreal ranibizumab among patients with PDR.4 This noninferiority study included 305 adults with PDR, including 89 participants who had both eyes enrolled, for a total of 394 study eyes. Patients in the ranibizumab group (n = 191 eyes) received intravitreal ranibizumab (0.5 mg) (and PRP if treatment failed) and received ranibizumab as needed for diabetic macular edema, whereas patients in the PRP group (n = 203 eyes) received PRP and ranibizumab as needed for diabetic macular edema. At 2 years, the mean improvement in visual acuity letter score was 2.8 in the ranibizumab group vs 0.2 in the PRP group (difference, 2.2; 95% CI, −0.5 to 5.0), meeting the prespecified 5-letter criterion for noninferiority.

The authors conclude that “among eyes with PDR, treatment with ranibizumab resulted in visual acuity that was noninferior to (not worse than) PRP at 2 years. Although longer-term follow-up is needed, ranibizumab may be a reasonable treatment alternative at least through 2 years for patients with PDR.”

This study represents a fundamental alternative therapeutic option that is now available to clinicians for the management of PDR. Some important clinical decisions need to be considered in the management of patients with high-risk PDR (ie, presence of PDR that the ophthalmologist intends to manage with patients with PRP alone and when PRP can be deferred for at least 4 weeks).

First and most important, the findings were based on a rigorous study design and result in an expanded treatment option for practicing ophthalmologists. By combining the known standards of care with the new alternative strategies, clinicians now have evidence for an effective pharmacotherapeutic option in the short-term management of patients with high-risk PDR. The noninferiority design supports the use of an intravitreal anti–vascular endothelial growth factor (VEGF) agent such as ranibizumab as an alternative to immediate PRP for initial management of patients with high-risk PDR.

Practicing ophthalmologists who care for patients with high-risk PDR should be aware of these important issues. In the context of a well-conducted randomized clinical trial, consistent and reliable follow-up of study participants usually occurs. However, the reality is that the practice and care of patients with diabetic eye disease in the community is not always ideal. Regular follow-up is a critical element in the management of patients treated with intravitreal anti-VEGF therapy. In the community, poor follow-up could prove disastrous for visual outcomes among patients who are nonadherent to recommended follow-up assessments and monitoring. For instance, if patients who are less adherent to recommended follow-up receive 1, 2, or 3 intravitreal anti-VEGF injections for high-risk PDR notice an improvement in visual acuity but fail to follow up for continued care, they may develop recurrent high-risk retinopathy and potentially incur vision loss. On the other hand, high-risk patients with PDR who have completed PRP and fail to return for care would likely have a better chance of sustaining an effective, long-term treatment and thus may reduce the long-term risk of severe vision loss. Clinicians with decades of experience observing and managing the long-term complications of PDR understand that most patients with adequate PRP have stable retinopathy for many years.5,6

The visual acuity data presented in the study by the DRCR.net investigators indicated that ranibizumab resulted in noninferior outcomes compared with PRP treatment at 2 years. Although the secondary visual acuity outcome based on the area under the curve favored the anti-VEGF therapy group, the long-term implications remain uncertain and the results are likely more due to anti-VEGF effects on diabetic macular edema. Approximately half of the eyes in the PRP group were eligible for anti-VEGF therapy for diabetic macular edema. The authors correctly acknowledge that “the protocol essentially tested ranibizumab for PDR vs PRP plus ranibizumab when needed for diabetic macular edema treatment.”

The authors reported a higher rate of vitrectomy in the PRP group (15%) vs the anti-VEGF group (4%). An earlier study
that compared the role of intravitreal ranibizumab to saline in the management of vitreous hemorrhage due to PDR demonstrated little difference in the rate of vitrectomy at 16 weeks. There is an important consideration for surgeons who manage more advanced PDR that requires vitrectomy—specifically, that PRP prior to vitrectomy adds meaningful stability to the peripheral retina during microdissection techniques and represents an important intraoperative advantage over eyes that have not had prior PRP. Although the study by the DRCR.net investigators was not designed to assess this benefit of PRP, experienced vitreoretinal surgeons may argue that a slightly higher rate of vitrectomy may be preferred to operating on eyes that have not had prior PRP.

Several other important and unanswered questions arise as a result of this study. What is the long-term role of the anti-VEGF alternative treatment for high-risk PDR? What happens to the PDR beyond 2 years? Does the PDR involute and eliminate the need for continued injections or PRP? Will high-risk features gradually recur once the anti-VEGF injections stop? If so, in what percentage of patients will high-risk features recur? Will the anti-VEGF treatment alternative lead to a lifetime of frequent visits and intravitreal injections? How often should stable patients be followed up in the absence of PRP? In younger patients with diabetes and PDR, should earlier PRP be selected to avoid the rare yet known potential complication of endophthalmitis that may result during a lifetime of anti-VEGF injections? Laser treatments are highly cost-effective in the management of PDR. How will the use of anti-VEGF injections affect the cost of care to society, especially given the high and increasing prevalence of diabetes in the United States? Looking beyond the United States to the global diabetes epidemic, current data suggest that an estimated 17 million individuals worldwide have PDR. Are multiple anti-VEGF injections warranted or even possible in regions where health care resources and qualified practitioners are more limited?

Ranibizumab has been demonstrated to be a highly effective anti-VEGF agent in the management of diabetic macular edema and was selected in this study to represent targeted therapy with specific inhibition of the VEGF protein. However, other studies have demonstrated that alternative anti-VEGF agents have a similar effectiveness on ocular angiogenesis, although these outcomes were observed in different disease states and with varying pharmacokinetics. Could the data from the study by the DRCR.net investigators be extrapolated to the off-label use of other anti-VEGF agents? How will payers respond? When will a sustained delivery anti-VEGF option become available and at what cost?

In summary, this important study by the DRCR.net investigators represents a major step forward for patients with PDR by providing the ophthalmologists who manage their retinal disease with new options. The short-term role (2 years) for using anti-VEGF agents seems to represent a viable alternative therapy for adherent patients with high-risk PDR. Nevertheless, PRP represents the standard of care for PDR and may represent the best long-term treatment option for high-risk PDR. It is certainly not time to abandon PRP in favor of exclusively treating patients with PDR using only intravitreal anti-VEGF injections. Clinical judgment and timing of initiation of either therapy are viable options, and the findings reported by the DRCR.net researchers provide clinicians with evidence to support the alternative option of anti-VEGF pharmacotherapy for high-risk PDR. Further advances in pharmacologic management and sustained delivery systems will help expand this alternative therapy for PDR.

**ARTICLE INFORMATION**

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