Rethinking Management Strategies for Proliferative Diabetic Retinopathy

by Peter H. Tang, MD, PhD, and Diana V. Do, MD

Diabetic retinopathy (DR) is the leading cause of vision impairment worldwide. It accounts for 2.6% of all blinding cases globally, and the prevalence within the United States is expected to rise to 16 million people aged 40 years or older by 2050. The most common culprit for vision loss in DR is diabetic macular edema (DME); however, complications from proliferative DR (PDR) such as vitreous hemorrhage (VH), tractional retinal detachment, and neovascular glaucoma can be significant. During the past decade, research into the pathophysiology of DR has revealed vascular endothelial growth factor (VEGF) to play a key role. Pharma-therapies to reduce ocular VEGF such as bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY) have revolutionized our treatment for DME and replaced laser photocoagulation, previously the mainstay of therapy. As more patients with DME undergo anti-VEGF therapy, there has been recent evidence to show a crossover benefit for PDR, as well. Can anti-VEGF therapy marginalize laser in treating PDR as greatly as it did for DME? Not surprisingly, the answer is complicated, and numerous factors including patient disposition and cost must be taken into account.

LASER PHOTOCOAGULATION

For more than four decades, panretinal photocoagulation (PRP) has been the de facto treatment for PDR. Seminal clinical trials such as the Diabetic Retinopathy Study showed that PRP could reduce the rates of severe vision loss in PDR by more than 50% during a 2-year period. The mechanism by which PRP works is not well understood; however, it is believed that destruction of areas of hypoxic retina reduces overall oxygen demand.
and decreases the amount of VEGF that is produced to promote neovascularization. Studies have shown that intravitreal VEGF levels are reduced after PRP, thus lending support to this theory. Numerous advantages exist for using PRP to treat PDR. There is a long record of its efficacy to promote long-term regression of PDR. A complete treatment can be delivered in one to three sessions, greatly alleviating the clinical burden to the patient as well as to the retina specialist.

The disadvantages of PRP can be significant, and careful consideration must be taken when recommending this treatment for PDR patients. Extensive PRP can lead to peripheral visual field constriction along with nystagmus, reduced retinal sensitivity, and rarely, uveitis. Media opacities such as cataract, corneal edema, and VH, as well as pain to the patient from the laser itself can prevent adequate treatment. Innovations have been made to address some of these shortcomings with the development of the pattern scan laser (PASCAL; Topcon Medical Laser Systems, Santa Clara, CA). It has been shown to achieve comparable results with conventional PRP in treating DR and provides the advantage of a quicker procedure by delivering a simultaneous grid of short-duration laser pulses.

**ANTI-VEGF THERAPY**

The superiority of anti-VEGF therapies to laser for treating DME has been extensively validated and was the primary focus of numerous clinical trials. Interestingly, an unexpected benefit observed was improvement in the severity of DR. The 2-year outcomes of the RISE/RIDE trials showed a lower probability of DR progression in ranibizumab-treated patients compared to the sham-control group. In the VISTA/VIVID trials, a greater number of patients treated with aflibercept demonstrated DR resolution compared to those receiving laser. Patients treated with ranibizumab and aflibercept showed greater DR resolution compared to bevacizumab after 1 year of follow-up in the Diabetic Retinopathy Clinical Research network (DRCR.net) Protocol T study. Although these differences were not maintained after 2 years of follow-up, a higher number of intravitreal injections was associated with greater improvement.

With these encouraging observations, two randomized clinical trials were developed to directly compare anti-VEGF therapy with PRP for the management of PDR. The DRCR.net Protocol S was a 2-year study of patients with treatment-naive, high-risk PDR randomized to receive scheduled intravitreal injections.
of ranibizumab or PRP. This study did not exclude patients with concurrent DME. At 2 years of follow-up, patients treated with ranibizumab demonstrated non-inferior outcomes compared to those treated with PRP with regard to visual acuity. Furthermore, ranibizumab-treated patients showed less DME, loss of peripheral field, and need for surgical intervention compared to eyes randomized to PRP. In this study, it is important to note that approximately half of the patients randomized to PRP subsequently received ranibizumab because those eyes developed DME. This study is currently collecting efficacy and safety data for 5 years of follow-up, which will conclude in 2018.

Recent results from the CLARITY study have also shown that anti-VEGF therapy with aflibercept is promising as a treatment option for PDR. This study was a randomized, controlled trial comparing intravitreal aflibercept with PRP for the management of high- and low-risk PDR. Importantly, patients with DME were excluded to avoid confounding results. At 1-year follow-up, patients treated with aflibercept demonstrated more improvement of PDR severity compared to those treated with PRP.

Although anti-VEGF therapy offers numerous advantages over PRP, there are some limitations. Intravitreal injections are associated with a very low risk of endophthalmitis, retinal tear, or cataract development. The success of anti-VEGF therapy necessitates frequent follow-up (eg, every 4 weeks to 8 weeks), which can pose a significant challenge to those with a history of poor compliance or with limited access to medical care. In addition, the cost burden of anti-VEGF therapy can be significant when compared to PRP. When analyzing the cost utility during a 2-year time frame based on the Protocol S study parameters, PRP was found to be 85% lower than ranibizumab therapy in the facility setting and 90% lower in the non-facility setting. When extrapolated to lifetime treatment, the median cost of PRP was approximately 12% that of ranibizumab therapy. A recent secondary analysis of patients from the Protocol S study concluded that, when compared to the cost of PRP, ranibizumab therapy was cost-effective for patients presenting with PDR and visually significant DME, but not for those with PDR without visually significant DME. It is important to note that both studies did not include cost analysis for bevacizumab.

CONCLUSION

The treatment paradigm for PDR is certainly evolving, with years of observation from previous trials of intravitreal anti-VEGF agents being corroborated by the Protocol S and CLARITY studies. Thus far, it appears that intravitreal anti-VEGF therapy is a highly effective alternative strategy for a subset of PDR patients who can reliably return for evaluation and intravitreal anti-VEGF injections. Until the safety and efficacy data from the Protocol S 5-year follow-up and beyond are analyzed and released, it is difficult to recommend anti-VEGF therapy as the long-term management standard for all PDR patients. Although the cost burden analyses conducted thus far favor PRP over ranibizumab therapy, repeat analysis with bevacizumab may alter these conclusions significantly as this medication is significantly less costly and generally just as effective.

With all of the new clinical trial data and analysis, how should we modify our clinical practice? Ultimately, treatment strategies must be adjusted to match the unique aspects of each individual patient. Those with a history of poor compliance or with significant barriers to follow-up may not be good candidates for intravitreal anti-VEGF therapy as the sole treatment for PDR. Many retina specialists will likely combine intravitreal VEGF blockade with PRP laser in the management of active PDR. In many patients with progressive DR, PRP will remain an important tool in the arsenal of a practical retina specialist.

REFERENCES


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