Proliferative diabetic retinopathy: laser or eye injection?

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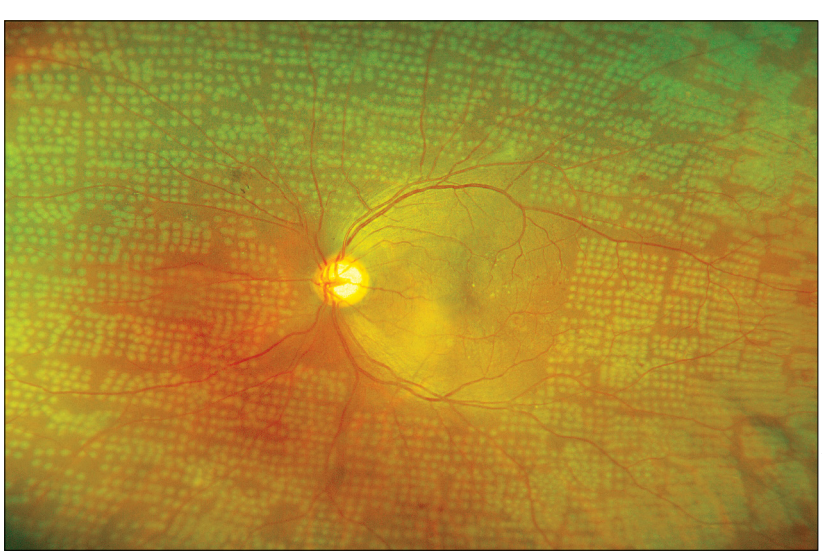
Diabetic retinopathy is a major microvascular complication of diabetes, and a leading cause of vision loss in middle-aged, working adults, in both developed and developing countries.[1,2] This condition progresses from mild to severe stages, and approximately 7% of people with diabetes will have proliferative diabetic retinopathy, the most advanced, sight-threatening level of the disease.[3]

Proliferative diabetic retinopathy occurs when there is sufficient retinal ischaemia that triggers the formation of fragile new blood vessels (neovascularisation), which then leak blood into the retina and vitreous, starting a process of fibrosis, and subsequently resulting in tractional retinal detachment. Without treatment, the risk of severe vision loss is 26% over 2 years.[4,5] Fortunately, for the past three decades, there has been a highly effective and cost-effective treatment: panretinal laser photocoagulation (PRP) is a laser technique that structurally destroys large areas of retinal ischaemia and non-perfusion, reducing the oxygen demand in the remaining retina, thus preventing new vessel formation and proliferation. PRP for proliferative diabetic retinopathy was first shown in the landmark Diabetic Retinopathy Study[6] to reduce severe vision loss by 50% or more. However, PRP has substantial side-effects, including reduced visual field and colour vision, and exacerbation of diabetic macular oedema. Furthermore, 15% of eyes with proliferative diabetic retinopathy continue to lose vision (≥10 ETDRS letters worsening) despite PRP.[7]

The fact that eyes with proliferative diabetic retinopathy have higher levels of vascular endothelial growth factor (VEGF) suggests that inhibition of VEGF might be a possible treatment for proliferative diabetic retinopathy.[8] This treatment was initially described in a case series,[9] and then assessed in a large clinical trial[7] from the US Diabetic Retinopathy Clinical Research Network (DRCR), which showed that intravitreous injection of the anti-VEGF agent ranibizumab (Novartis; Basel, Switzerland) was similar to PRP for high-risk proliferative diabetic retinopathy, with equivalent visual outcomes at 1 year. Ranibizumab resulted in less peripheral visual field loss, lower rates of vitrectomy surgery, and diabetic macular oedema. Furthermore, in a subgroup of eyes with both proliferative diabetic retinopathy and diabetic macular oedema at baseline, ranibizumab was possibly superior to PRP for visual acuity gain (8·0 *vs* 3·6 letters, p=0·08).[7] Despite these benefits, the clinical management of proliferative diabetic retinopathy has largely remained unchanged, mainly because such an intensive treatment regimen (monthly visits and a mean of seven injections in year 1 alone of the DRCR trial) was thought to be too substantial on clinic resources and health-care systems to believe anti-VEGF therapy would be more cost-effective than PRP.

Against this background, the CLARITY study[10] in *The Lancet* provides new and provocative data. CLARITY, a multicentre, randomised trial in the UK compared another anti-VEGF agent aflibercept (Bayer Pharma AG; Berlin, Germany) with PRP in eyes of patients with proliferative diabetic retinopathy and with no diabetic macular oedema. After 12 months, aflibercept showed superior visual outcome over PRP (mean best corrected visual acuity difference 3·9 letters [95% CI 2·3–5·6], p<0·0001). Importantly, only a mean of 4·4 (SD 1·7) aflibercept injections were needed, of which three were loading doses based on protocol, indicating possibly one to two injections were needed for the subsequent 9 months after initial treatment. The results of CLARITY also showed that anti-VEGF therapy resulted in numerically lower proportions of patients with diabetic macular oedema, a lower incidence of new or increasing vitreous haemorrhage,



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and less effect on peripheral visual fields than did PRP therapy.

Why would CLARITY show superior visual acuity outcomes with anti-VEGF therapy over PRP with fewer injections compared with DRCR? First, this result might reflect differences between the two anti-VEGF agents assessed, aflibercept in CLARITY and ranibizumab in DRCR. Theoretically, aflibercept has a higher binding affinity to VEGF-A, VEGF-B, and placental growth factor, and might last longer in the vitreous than ranibizumab.[11] Alternatively, differences might simply reflect variation in study design and patient characteristics. CLARITY included patients with a mixture of high-risk or low-risk proliferative diabetic retinopathy, who did not have diabetic macular oedema, and approximately 50% were previously treated with PRP. By contrast, in DRCR all patients were previously untreated and had high-risk proliferative diabetic retinopathy and about one in five patients also had diabetic macular oedema. Thus, inclusion of patients with less severe proliferative diabetic retinopathy in CLARITY might have led to greater visual gain and fewer injections. Regardless, interpretation of direct head-to-head comparison between the two studies should be done cautiously.

Where then does this situation leave patients with diabetes and ophthalmologists? Clearly, a larger clinical trial with longer-term visual outcome, safety, and cost-effectiveness should be done to provide more evidence to inform clinical practice. Trial patients are inherently different from patients in real-world settings. Many patients with proliferative diabetic retinopathy are active, working adults, whereas others have multiple comorbidities (eg, nephropathy and cardiovascular disease) that need specialised care and treatment.[2] These factors might limit enthusiasm for the intensive anti-VEGF treatment regimen offered. Loss to follow-up from a quick improvement in vision after a few injections (but where the disease remains active), or for treatment fatigue over time will be challenging issues to tackle. Clinics offering anti-VEGF therapy as the standard of care for proliferative diabetic retinopathy would require a robust system to monitor, track, and enhance compliance in patients with proliferative diabetic retinopathy. Experience in the real-world setting with anti-VEGF therapy for neovascular age-related macular degeneration showing a reduction in the numbers of injections and a decline in vision over time is a sober reminder that anti-VEGF therapy is not a quick-fix panacea.[12] For the millions of patients with proliferative diabetic retinopathy globally, the introduction of anti-VEGF therapy as the standard of care is promising, but more research is clearly needed to carefully assess the long-term visual, anatomical, safety, and cost-effectiveness outcomes.

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TYW is on advisory boards for Abbott, Allergan, Bayer, Novartis, Roche, and Pfizer and has received honoraria for travel, service on advisory boards, and research support from these companies, outside the area discussed in this Comment. TYW has provided expert testimony to Novartis for clinical use of ranibizumab for the treatment of age-related macular degeneration. DSWT declares no competing interests.

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