

Treatment of early diabetic retinopathy: a currently unmet need

Early identification and treatment are key priorities to reduce the morbidity of diabetic eye disease. Apart from its effects on vision, the presence of diabetic retinopathy (DR) also signifies a heightened risk of life-threatening systemic vascular complications.¹ At diagnosis of type 2 diabetes, around 20% of patients already have a significant degree of retinopathy.²

Treatment strategies in primary and secondary prevention

Retinopathy ranks among the commonest complications of diabetes, it should be borne in mind that retinopathy is not just damage to the retina, but also an indicator of damage to the whole microcirculatory system. Retinopathy is a risk factor for coronary heart disease and myocardial dysfunction. It is an indicator that renal damage and other complications might occur. There is also emerging evidence to suggest that DR may share common genetic linkages with systemic vascular complications.¹

Currently, guidelines recommend tight glycaemic and blood pressure (BP) control as the principal strategy to delay or prevent microvascular complication (HbA1c < 7% and blood pressure below 130/80 mmHg).^{3,4} There is evidence to support intensive control from major prospective studies such as the United Kingdom Prospective Diabetes Study (UKPDS) in both type 1 and type 2 diabetes. Nevertheless, large outcome trials (ADVANCE, VADT, ACCORD) have demonstrated that a substantial burden of microvascular disease remains even after intensive intervention against conventional microvascular risk factors.⁵

Lack of therapies targeting specific pathogenetic mechanisms remains a serious limitation to the prevention of diabetes-related blindness. It is therefore vital that other therapeutic targets be considered for potential benefit in the treatment and prevention of DR. Experimental evidences suggests involvement of the renin-angiotensin system (RAS) given that a physiologically active RAS is present in the eye, where angiotensin-2 appears to promote retinal expression of vascular endothelial growth factor (VEGF) through AT-1 receptors, and endothelial cell proliferation.⁶ On the other hand, it has been found that atherogenic dyslipidemia (low HDL-C, high triglycerides) could have a role in the pathogenesis of diabetic retinopathy.⁷ A body of evidence supports a role for lipid-modifying therapy in reducing diabetic retinopathy endpoints, particularly for macular oedema and exudation.⁸ Notably, this finding did not seem to be attributable to measurable changes in lipid profile, suggesting that other as yet unknown mechanisms could contribute to the protective effect of those agents.⁹

However, questions remain concerning the ideal glycemic and BP levels required to prevent DR development and progression in primary prevention, as well as the relative efficacy of various agents in regulating these levels. The role of lipid lowering agents in secondary prevention needs also to be discussed. These questions are addressed in more detail in the roundtable discussion.

Laser photocoagulation and anti-vascular endothelial growth factor (VEGF)

▶ Laser photocoagulation is currently the gold standard for the treatment of more advanced non-proliferative and proliferative diabetic retinopathy.¹⁰ It is indicated when new vessels in the retina or new vessels on the optic disc are at risk of bleeding.¹¹ Results from two landmark clinical trials in ophthalmology—the Diabetic Retinopathy Study (DRS)¹² and the Early Treatment Diabetic Retinopathy Study (ETDRS)—suggested that less severe stages of diabetic retinopathy might not benefit from laser treatment.¹⁰ In addition to not being appropriate in earlier DR, the destructive nature of laser photocoagulation is associated with significant side-effects.⁸ Furthermore, it is not completely effective, as reversal of visual loss is uncommon.¹³

▶ In advanced stages of DR, intravitreal anti-vascular endothelial growth factor (VEGF) agents have emerged as new treatments. In response to hypoxia, retinal endothelial cells express VEGF, stimulating neovascularisation and increasing capillary permeability.¹⁰ Thus the goal of anti-VEGF therapy is to reduce these phenomena that are the hallmarks of proliferative DR and DMO. Several anti-VEGF therapies that are delivered by injection directly into the vitreous of the eye (to avoid systemic side-effects) have been assessed in clinical trials.¹⁴ Most of these have shown some benefits for both DMO and proliferative DR. However, the long-term safety of anti-VEGF agents has not yet been established.^{15,16}

Conclusion

The retinal complications that arise from chronic hyperglycaemia have a significant impact on the lives of diabetic patients. Amelioration of these complications and their damaging effects will greatly benefit these patients and impact overall healthcare. While treatment strategies for proliferative DR and DMO exist, these have limitations and are not appropriate for less severe non-proliferative DR. This highlights the need for effective screening and the development of new treatment strategies as soon as retinopathy is first diagnosed.

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