

## Sight-threatening diabetic eye disease:

an update and review of the literature

Diabetic eye disease is the third most important cause of visual loss in England and Wales, after age-related macular degeneration and glaucoma.<sup>1</sup> In contrast to the first two, the evidence shows that effective treatment for diabetic eye disease begins not in the eye clinic, but in the GP practice. Vision-threatening consequences of diabetes include proliferative retinopathy and maculopathy. Proliferative retinopathy may cause vitreous haemorrhage and retinal detachment with catastrophic loss of vision. Maculopathy refers to oedema at the macula, secondary to retinal capillary leakage, with consequent loss of central visual acuity.

### SCREENING PATIENTS WITH DIABETES

In the UK, all patients with diabetes who are not already under the care of the eye clinic should be enrolled in a retinopathy-screening programme.<sup>2</sup> Patients are referred to an ophthalmologist if there is evidence of proliferative or pre-proliferative retinopathy or maculopathy. Letters about the patient will refer to the retinopathy grade, which is potentially bewildering, but can be readily decoded (Table 1). In the English system, the retinopathy grades R1, R2, and R3 are equivalent to 'background', 'pre-proliferative', and 'proliferative'. The Scottish system is different and incorporates three grades of non-proliferative retinopathy.<sup>2</sup> Therefore, (in the English system; Table 1) a patient graded 'R2 M1 P0' will have pre-proliferative retinopathy, evidence of maculopathy, and no visible photocoagulation scars.

### TREATMENT FOR ESTABLISHED SIGHT-THREATENING DISEASE

Laser photocoagulation remains the mainstay of treatment for proliferative retinopathy and has also traditionally been the treatment for clinically significant maculopathy. More recently, ranibizumab (Lucentis®, Novartis), a synthetic antibody that binds to vascular endothelial growth factor (VEGF), has

been approved by the National Institute for Health and Care excellence (NICE) to treat maculopathy. This drug, which needs to be injected into the vitreous cavity, was originally developed to treat patients with 'wet' age-related macular degeneration, but its efficacy in treating diabetic maculopathy is now well established.<sup>3</sup> A major drawback of ranibizumab is the requirement for repeated injections, initially at monthly intervals. Another treatment for diabetic maculopathy, Iluvien® (Alimera, fluocinolone acetonide), has recently been licensed in the UK.<sup>4</sup> This is an implant which, when injected into the vitreous cavity, releases the steroid fluocinolone acetonide over a 3-year period. Although this significantly reduces the burden of treatment, the risk of side-effects, including cataract progression and glaucoma with Iluvien is high, and, so many ophthalmologists have reservations about this drug. The costs associated with these new treatments are not inconsiderable: the current *British National Formulary*-listed price for a Lucentis dose is £742.17 and £5500 for an Iluvien implant.

In the context of these new developments, it is easy to overlook the very significant benefits that can be achieved in the primary care setting before the patient has even set foot in the eye clinic.

### GLYCAEMIC CONTROL

The importance of good glycaemic control in reducing the risk of diabetic retinopathy progression has been demonstrated in two landmark trials. The UK Prospective Diabetes Study (UKPDS) (type 2 diabetes) and the Diabetes Control and Complications Trial (DCCT) (type 1) showed that lowering glycosylated haemoglobin (HbA1c) to 7% significantly reduced the development and progression of diabetic retinopathy.<sup>5</sup> Essentially, every per cent reduction in HbA1c translates to a reduction in retinopathy risk of 30–40%, and this effect appears to last for a period of time even if diabetic control is subsequently lost.<sup>6</sup> The

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**Table 1. Making sense of the diabetic patient's screening letter**

Retinopathy	English screening system	Scottish screening system	Outcome
No retinopathy	R0	R0	Rescreen at 12 months
Background retinopathy	R1	R1, R2 depending on severity of background changes	R1; rescreen at 12 months. R2 (Scotland only); rescreen at 6 months <i>or</i> refer to eye clinic if this is not feasible
Pre-proliferative retinopathy	R2	R3 (termed 'severe background')	Refer to eye clinic
Proliferative retinopathy	R3 (subdivided into R3a: active and R3s: inactive)	R4 (if active)	Refer urgently to eye clinic
No maculopathy	M0	M0	Rescreen 12 months
Maculopathy present	M1	M1 or M2 depending on severity	M1; refer to eye clinic (English system). Rescreen at 6 months <i>or</i> refer to eye clinic if this is not feasible (Scottish system). M2; (Scotland only) refer to eye clinic
Photocoagulation (laser) scars	P0 (absent) P1 (present)	A comment may be added regarding absence of photocoagulation scars	

evidence for reducing the HbA1c below 7% is less clear cut. The large Action in Diabetes and Vascular Disease (ADVANCE) trial and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial studies gave conflicting results for aggressive glycaemic control (HbA1c<6.5%) and in the ACCORD study, for an unknown reason, there was an increased overall mortality associated with this aggressive approach.<sup>6</sup>

#### BLOOD PRESSURE CONTROL

Hypertension is associated with a higher incidence and increased progression of diabetic retinopathy. It has been suggested that mechanical stretching of retinal blood vessels contributes to endothelial cell damage and the release of VEGF. In general terms, every 10 mmHg increase in blood pressure is associated with a 10% risk of progression to early retinopathy and 15% risk of progression to proliferative retinopathy.<sup>6</sup> The UKPDS demonstrated that tight blood pressure control (average 144/82 mmHg) reduced the need for laser treatment by one-third in individuals with type 2 diabetes.<sup>6,7</sup> Intensive blood pressure control (systolic <120 mmHg) did not show any additional benefit beyond this in ACCORD.<sup>7</sup>

#### ACE INHIBITORS/ANGIOTENSIN II RECEPTOR INHIBITORS

These drugs may have significant beneficial

effects on retinopathy over-and-above their effect on blood pressure control for both type 1 and 2 diabetics. This has been supported by three studies: EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus (EUCLID), Diabetic RETinopathy Candesartan Trials (DIRECT), and Renin Angiotensin System Study (RASS), and, although these findings were not reproduced in ADVANCE, the evidence suggests that drugs targeting the renin-angiotensin system should be an early choice for blood pressure control in diabetics.<sup>6</sup> The important question as to whether these drugs would be beneficial even in normotensive subjects with diabetic retinopathy remains unresolved.

#### FENOFIBRATE

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and ACCORD-Eye studies have both demonstrated a significant beneficial effect of fenofibrate on the rate of retinopathy and maculopathy progression. In FIELD, there was a 31% reduction in laser treatments for both proliferative diabetic retinopathy and vision-threatening maculopathy over 5 years.<sup>5</sup> The number needed to treat (NNT) to prevent retinopathy progression was 9 in FIELD and 14 in ACCORD-Eye.<sup>8</sup> The mechanism of action in this context is not fully understood, but appears to be independent of the lipid lowering effect; that is, that the drug is effective even in subjects with a good lipid profile. This raises the question as to whether all patients with diabetic retinopathy should receive fenofibrate. As yet, consensus of opinion among ophthalmologists is lacking.

#### THIOZOLIDINEDIONES (GLITAZONES)

Pioglitazone is the sole drug from this class still available in the UK. The thiozolidinediones have been associated with the development of diabetic maculopathy in a small number of case reports and were modestly associated with the development of diabetic maculopathy in one observational study.<sup>9</sup> Although this association was not reproduced in an ACCORD substudy,<sup>10</sup> it is possible that GPs may be asked by ophthalmologists to consider alternatives in cases of treatment-refractory sight-threatening macular oedema.

The evidence shows that the management of the diabetic patient in the primary care setting can delay, reduce, and regress the development of vision-threatening diabetic retinopathy and maculopathy. In the future, there is likely to be an increased collaboration between ophthalmologists and GPs in the management of this important disease.

#### Provenance

Freely submitted; externally peer reviewed.

#### Competing interests

The authors have declared no competing interests.

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