Diabetic retinal disease: an update on the use of anti-VEGF agents

Nigel Davies, Kevin Shotliff

In May 2011 we wrote a leader about the use of anti-VEGF agents in diabetic retinal disease. Here we provide an update on the change in practice that these agents have brought to the management of sight-threatening disease. The UK National Screening Programme offers every person with diabetes annual screening to detect potential sight-threatening retinopathy. Patients with proliferative retinopathy and with diabetic maculopathy are referred to the hospital eye service for further assessment.

Control of risk factors for progression is vital. The DCCT1 and UKPDSS have clearly shown that tight control of blood glucose and blood pressure is beneficial in the long term. The use of lipid-lowering agents, particularly the statin group is highly recommended and the FIELD study showed reduction in the need for laser therapy in the group of patients treated with fenofibrate.4 The instigation of tighter control, however, can lead to a transient worsening of retinopathy for a year or thereabouts but in the longer term reduces the risk of progression.5

While the initial treatment for proliferative retinopathy is urgent pan-retinal photocoagulation (PRP) with laser, diabetic maculopathy is the most frequent cause of central visual loss with sight-threatening maculopathy characterised by oedema within 500 microns of the fovea, with or without exudate or a larger area of oedema and exudate greater in extent than one disc diameter and any part of which encroaches within 1000 microns of the fovea. Patients with these findings should have an optical coherence tomography (OCT) scan to document oedema and fluorescein angiography to identify areas of leakage and areas of ischaemia. Areas of leakage are treated with focal or grid pattern laser burns. The laser energy is reduced in comparison with that used in PRP, to reduce the chance of damage to retinal pigment epithelium (RPE) cells and photoreceptors in the macula area. This form of laser treatment has been shown to reduce the rate of vision loss.6 The use of laser is limited, however, when oedema begins to collect at the fovea which itself cannot be treated. The fovea provides essentially all of our fine detailed vision and is only 0.5mm in diameter. A 6/60 letter has a retinal extent of around 0.3mm and a 6/6 letter 0.03mm. The fovea is the only part of the retina with the neuroanatomy to resolve at a level of 6/12 or better. Consequently, saving this tiny area of tissue is paramount for each individual.

Vascular endothelial growth factors

Hypoxia can be caused by diabetes and in this situation one of the responses of the retina is to upregulate release of VEGF. The major isoforms of VEGF-A expressed in the eye are the 121 and 165 isoforms.

Ranibizumab is an affinity-matured Fab fragment that binds non-selectively to all VEGF-A isoforms. Ranibizumab was originally licensed for use in wet age-related macular degeneration (AMD), and subsequently has been licensed for use in diabetic macula oedema and in retinal vein occlusion.

New data

There are now some interesting new data of up to three years of follow up in cohorts of patients treated with ranibizumab with or without retinal laser.

The DRCR.net study, comparing intravitreal ranibizumab with prompt or deferred laser and intravitreal triamcinolone, recently published three-year results for the ranibizumab groups.7 This study showed a clinically small (3 letters) but statistically significant benefit in terms of visual acuity for the use of ranibizumab with laser applied after 24 weeks if oedema persisted in comparison with ranibizumab and prompt laser. The one-year data from the same patients were also analysed to try to identify baseline factors associated with changes in visual acuity and central retinal subfield thickness.8 Young age, less severe diabetic retinopathy overall, less surface wrinkling retinopathy and reduction in central subfield thickness were all independently associated with an improved visual acuity outcome. Interestingly, after correcting for baseline retinal thickness, eyes with exudates were more likely to have a reduction in thickness in comparison with eyes without exudate. The presence of exudate is relatively easy to detect on colour fundus photography and therefore a very valuable feature in diabetic retinal screening.

The data collected from patients participating in the RISE and RIDE studies of ranibizumab in diabetic macula oedema have been examined in terms of progression of diabetic retinopathy overall.9 Ranibizumab-treated eyes had significantly less progression (defined as ≥2 and also ≥3 steps on the ETDRS [Early Treatment Diabetic Retinopathy Study] severity scale) and regression (≤2 and ≤3 steps) was also significantly more likely.

The READ-2 study for months 24–36 involved monthly visits and patients received ranibizumab if the central retinal thickness was 250 microns or greater.10 At 36 months, there was a gain in visual acuity (10.3 letters at 36 months vs 7.2 letters at 24 months), and thickness was reduced (mean 282 microns vs 352 microns). The number of patients in each group at three years was rather small (<30 patients).

Bevacizumab has been used off-label to treat patients with diabetes. In the absence of a comparative trial, an indirect analysis of the effects of ranibizumab in comparison with bevacizumab has been published recently.11 From this analysis it was not possible to conclude a better or worse outcome for either drug.

Clinical practice in the UK

There is little doubt that the anti-VEGF agents are successful in preventing central vision loss and to some extent restoring vision in patients with sight-threatening retinopathy. Their use is set to become a new gold
standard of care, and there are other agents soon to be licensed which will add to the armamentarium available in the next few years. The drugs are expensive and need to be administered into the eye directly and fairly frequently. For the patient, however, this is a wonderful hope in an otherwise darkening view of the world.

NICE guidance published in 2011 did not support the use of ranibizumab as their assessment and calculations showed that, although effective, it was too costly to warrant NHS funding.

Novartis has now removed the ranibizumab reimbursement scheme and it has been replaced by a patient access scheme for all licensed indications of ranibizumab. This allows the NHS to purchase ranibizumab at a reduced price. NICE has reconsidered the use in diabetic macula oedema and new guidance is expected imminently. This guidance is very likely to support the use of ranibizumab in patients with central retinal thickness >400 microns, with the proviso of supply at a reduced price from the manufacturer. The mean central thickness of the patients enrolled in the DRCR.net study was 406 microns, which may be why the 400 micron threshold value was chosen.

This is very exciting news for patients who have fovea-involving disease, but regrettably the threshold value of 400 microns will limit the number of patients whose treatment will be funded by the NHS without bureaucratic difficulty. Funding can still be applied for in patients who do not meet these criteria, via the lengthy and time-consuming process of individual funding request. Ophthalmic department profit from other work (e.g. cataract surgery and AMD treatment) could also be used to fund treatment.

**Measurement of retinal thickness**

There are many OCT machines available and each manufacturer will use different line segmentation software to delineate the retinal layers. A very good study was published a few years ago, comparing the result of six different OCT machines in measurement of central retinal thickness. This study clearly shows that the different devices measure different central retinal thickness in the same people and that this difference can be up to 50 microns.

The overall measurement of central retinal thickness therefore depends not only on the disease, but also on the machine used to measure it. A difference of 50 microns is significant. As most ophthalmic units have machines from only one manufacturer, the possibility arises that patients attending one department may systematically be denied treatment with ranibizumab, whereas if measured on another device (in another department) they may qualify for treatment. Secondly, understanding how the retinal thickness measurement is made, this value will change if the inner limiting membrane (ILM) layer changes position and it will also change if the reference plane moves as well. If the reference plane moves anteriorly (which can happen if the disease worsens) this may lead to an apparent reduction in central retinal thickness.

It would seem important then for the NICE guidance to specify the retinal layers across which the measurement should be taken, to standardise the measurement across the country.

We propose that this measurement be taken from the ILM to the RPE layer (it is unusual for the RPE to move in diabetes). This definition would allow ophthalmologists to make uniform decisions despite differences in how the data are acquired.

**Classification**

There have been several classification schemes of diabetic maculopathy in the past, and it now seems sensible to propose an OCT-based classification that also integrates with the National Screening Programme classification. OCT will undoubtedly become the anatomical assessment tool of choice (if not already), with the type of pathology leading to the oedema being characterised by angiography (angiogenic, ischaemic or mixed). Below we propose such a classification, essentially a quantified modification of the Diabetic Maculopathy Disease Severity scale:

- **M0** – no oedema.
- **M1** – diabetic retinal screening referral for oedema (i.e. a colour photograph based correlate of maculopathy).
- **M2** – oedema not involving central subfield.
- **M3** – oedema involving central subfield but mean central subfield thickness < T microns (ILM-RPE).
- **M4** – oedema involving central subfield but mean central subfield thickness > T microns (ILM-RPE).

We have left the retinal thickness value for staging between M3 and M4 as ‘T’ for two reasons. Firstly, to allow for the differences in this measurement that might arise from the use of different machines; and, secondly, we do not want to suggest that the 400 micron threshold for treatment set by NICE is by any means definitive or fixed.

Using this system, patients in screening programmes with M1 grading from the colour photograph would be referred to the hospital eye service and further classification made based on the OCT. Patients with M4 grade with T set at 400 microns from ILM to RPE would be the first wave being able to have ranibizumab funded by the NHS.

**Conclusion**

The introduction of the anti-VEGF agents is a huge move forward in the management of diabetic retinal disease. It should always be remembered, however, that once a patient reaches the stage of needing laser and/or anti-VEGF treatment, their eye disease is advanced and the treatments are essentially attempts at salvage in a difficult situation. The greatest benefit is likely to be achieved by early detection of diabetes itself, the education of the patient of the needs of tight control of risk factors and the long-term compliance with diet, exercise and medication for glycaemic control, hypertension and dyslipidaemia.

**Nigel Davies,** Consultant Ophthalmologist  
**Kevin Shotliff,** Consultant Physician; President of British Association of Retinal Screening (BARS)  
**Beta Cell Diabetes Centre, Chelsea and Westminster Hospital, London, UK**

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available in *Practical Diabetes* online at www.practicaldiabetes.com.
References