Introduction

Diabetic retinopathy (DR) is a chronic progressive and potentially sight-threatening disease of the retinal microcirculation associated with prolonged hyperglycaemia resulting from diabetes mellitus, which may be aggravated by other associated conditions such as hypertension and hyperlipidaemia.

This retinal microvascular damage manifests in two non-exclusive ways: breakdown of the blood-retina barrier resulting in retinal oedema, and capillary occlusion which leads to retinal ischaemia, hypoxia, and subsequent neovascularisation. The concept of a growth factor released by hypoxic retina was first postulated by Michaelson in 1948 and eventually characterised as a family of vascular endothelial growth factors (VEGF) in the 1990s. VEGF plays a crucial role in DR by stimulating the growth of new blood vessels but also increases vascular permeability, resulting in retinal oedema which is highly detrimental to visual function when the macula and fovea are affected.

The recognition of the importance of VEGF in both proliferative retinopathy and macular oedema has led to treatment with intravitreal injection of agents which block the effects of VEGF. Anti-VEGF therapy was first applied in the eye for the treatment of neovascular (or ‘wet’) age-related macular degeneration (AMD) where the clinical impact has been almost miraculous, and current options include ranibizumab, bevacizumab and, more recently, aflibercept. The experience with anti-VEGF therapy for AMD has confirmed the safety and effectiveness of repeated intravitreal injections, with low rates of endophthalmitis (less than 1:1000 injections), with no significant risk of inducing cataract or increasing intraocular pressure, but the need for regular and continuing treatment has created enormous logistical problems in treatment delivery.

Diabetic retinopathy is classified according to its clinical features as either proliferative (PDR) or...
New technologies and drugs in the management of diabetic retinopathy

Review

Ocular coherence tomography

Although all the UK screening systems specify the use of non-mydriatic digital cameras, pupil dilation practice varies between regions. Pupil dilation is, however, mandatory for the assessment and treatment of DR in eye clinics.

Ocular coherence tomography (OCT) utilises non-invasive laser interferometry to provide high resolution cross-sectional or topographic images of the retina in microscopic detail. This allows serial, quantitative analysis of retinal structural changes and has transformed the understanding and management of macular diseases in general and the vitreoretinal interface. The third generation of OCT scanners and software provide faster image acquisition, wider field of view, better imaging of the choroid, and visualisation of the retinal capillaries without the need for intravenous dye injection. Fundus fluorescein angiography (FFA) remains a very valuable investigational tool for retinal vascular disease as it can reveal neovascularisation and retinal capillary occlusion as well as leakage, but it does not provide the same exquisite structural detail and quantitative analysis as OCT. FFA is more labour intensive and requires an intravenous injection of fluorescein, the administration of which carries some associated morbidity.

Foveal thickness can now be measured with such unparalleled precision that it is likely that OCT will be utilised in screening for diabetic macular oedema (DMO) as an adjunct to digital retinal photography. Central foveal thickness (FTH) as measured by OCT is now routinely used to determine when to undertake further treatment.

Wide field retinal imaging

Advances in digital retinal imaging using wide field scanning laser ophthalmoscopes provides a much more extensive view of the retina with sensitivity and specificity similar to standard screening employing central one or two field protocols, but with a higher technical failure rate of around 11% compared with around 6% for standard imaging. This is too high for routine community screening but the ability to undertake wide field fluorescein angiography may be helpful in predicting and managing retinal ischaemia and neovascularisation. Wide field imaging can be undertaken through a normal undilated pupil.

Prevention of diabetic retinopathy

DR develops approximately 5–10 years after the onset of diabetes and potentially can be prevented or retarded in type 1 diabetes by ensuring tight diabetes control. The insidious development of type 2 diabetes often results in DR being detectable at diagnosis, and in this group good blood pressure control appears to be more effective than tightening diabetes control in retarding progression of DR. Good early glycaemic control also appears to have long-term legacy benefits even where subsequent control is less stringent.

Improving diabetes control, blood pressure, and hyperlipidaemia may result in the regression or amelioration of DR without the need for specific ophthalmic treatment (Figure 1). Rapid tightening of diabetes control may paradoxically result in an initial worsening of retinopathy features, thus necessitating close ophthalmic surveillance, although ultimately the long-term visual prognosis is improved in these patients.

Pioglitazone has been associated with an increased risk of DMO and this should be avoided or used with caution in patients with more severe background changes, who should have OCT undertaken to identify early macular thickening and oedema which may not be clinically evident.

Laser developments

Panretinal laser photocoagulation (PRP) remains the standard first-line treatment for PDR. Gas lasers (argon green and krypton red/yellow) have largely been superseded by solid state diode lasers including 810nm infrared, 577nm yellow, and 647nm red lasers.
Intravitreal drug delivery
Drug delivery into the eye by direct intravitreal drug injection was for many years considered an act of desperation. This dramatically changed during the HIV/AIDS era when the treatment of cytomegalovirus retinitis (CMVR) with intravitreal ganciclovir showed the route to be remarkably effective, safe, and repeatable.

The need for regular injections to maintain control of CMVR led to the development of a sustained-release intravitreal device (Vitrascert®) which delivered adequate therapeutic drug levels for about 30 weeks, and which could then be replaced if necessary. The need for continuous intravitreal therapy for CMVR has since diminished with improvements in systemic HIV treatment and restoration of immune competence, but the safety and effectiveness of sustained release intravitreal drug delivery had been established.

Intravitreal steroids for diabetic macular oedema
The safety of intravitreal injection of the crystalline long-acting steroid triamcinolone acetonide was recognised in the early 1980s, but it was nearly 15 years before clinical studies of its use for macular disease were reported. Intravitreal triamcinolone acetonide (IVTA) use was first investigated in neovascular age-related macular degeneration where it showed modest benefits before being eclipsed by anti-VEGF therapy.

IVTA was then shown to be very effective in the treatment of cystoid macular oedema due to intraocular inflammation (uveitis), and application of IVTA to diabetic macular oedema quickly followed. Anecdotal case reports, uncontrolled retrospective studies and the DRCR.net have subsequently shown modest benefits but also confirmed the significant complications of raised intraocular pressure and cataract.

A sustained release fluocinolone device (Retisert®) which delivers clinically effective drug levels for approximately three years has been successfully used in uveitis, but like the Vitrascert requires surgical placement thereby engendering higher risks of vitreous haemorrhage and retinal detachment than a single pass injection through the pars plana.

Ozurdex® is a polylactic-co-glycolic acid biodegradable polymer injected through a 22G applicator needle which releases dexamethasone for about four to six months. It has been shown to be effective in treating macular oedema secondary to retinal vein occlusion and uveitis, and more recently DMO. Iluvien® is a non-erodible intravitreal device releasing 0.2μg fluocinolone acetonide daily for about 36 months, which is injected into the vitreous cavity through a 25G applicator. It has recently been approved in England for the treatment of refractory DMO by NICE but only for use in eyes which have already undergone cataract surgery because cataract is an otherwise inevitable consequence. Like other intravitreal steroids, raised intraocular pressure may occur and nearly 5% of Iluvien treated eyes may need glaucoma surgery over three years.

Intravitreal anti-VEGF therapy for DMO and PDR
Pegaptanib was the first intravitreal anti-VEGF agent to be shown to be effective for DMO, and was quickly followed and replaced by bevacizumab, ranibizumab, and aflibercept as they became available and proved to be more clinically effective. Only ranibizumab and aflibercept have been licensed for intraocular injection, but bevacizumab has been used extensively throughout the world ‘off-label’ and shown to be as clinically effective as ranibizumab and significantly cheaper.

Repeated treatment with these agents is necessary because of the shorter duration of action than intravitreal steroids, but long-term visual results are better than for laser treatment alone or combined with anti-VEGF therapy, and without the risks of raised intraocular pressure or cataract associated with steroids. The number of treatments reduces over time, the DRCR.net reporting nine, three, and two injections in the first, second, and third years respectively in patients allocated to deferred laser treatment.

There are no published studies to date of ‘head to head’ randomised clinical trials of Ozurdex® or Iluvien with intravitreal anti-VEGF therapy, although Ozurdex/Lucentis® and
Ozurdex/Avastin\textsuperscript{45} trials\textsuperscript{55,56} are in progress. These trials will be essential to determine the most appropriate treatment for DMO, in terms of visual recovery, complications, overall cost, and acceptability to patients.

### Revascularisation of the retina: intravitreal activated protein C

Retinal neovascularisation which results from retinal ischaemia can currently be successfully treated by laser photocoagulation, but this is a destructive process which may compromise peripheral vision. The intriguing possibility of stimulating retinal revascularisation using intravitreal activated protein C has been recently reported in two cases of central retinal vein occlusion but further evaluation is clearly required.\textsuperscript{57}

### Drug licensing, treatment options, and personalised health budgets

The modern era of intravitreally injected drug therapy has been plagued by the dilemma of the availability of drugs licensed to be used in this way. Ranibizumab is licensed for intravitreal administration whereas bevacizumab, a much cheaper but almost equally effective alternative,\textsuperscript{46} is not. In the UK, doctors are obliged by the GMC to use licensed drugs where available and not to choose a drug primarily because of its lower cost. As a result, the cumulative drug cost of these new and effective therapies threatens to burgeon out of control. Intravitreal therapy is more effective in treating DMO than laser with better visual outcomes, so who should determine which treatment option is selected? From October 2014, anyone receiving NHS continuing health care in England will have a right to have a personal health budget, and potentially the choice of therapy.

#### Optimising the management of PDR and macular oedema

Panretinal laser photocoagulation remains the cornerstone of management of proliferative diabetic retinopathy, and the innovations in laser delivery described earlier have made this a little more comfortable for patients although doubling the cost of the hardware.

Treatment of DMO requires a more selective and individualised patient approach, which has been greatly assisted by OCT retinal imaging. All patients need to be reminded of the importance of good diabetes, blood pressure and lipid control, implementation of which may lead to regression of sight-threatening retinopathy without the necessity for specific eye treatment.

Engaging patients with OCT images of their retinal changes and subsequent progress has, in the author’s experience, been very helpful in encouraging patients to address control issues without the need for hectoring. It is essential that patients appreciate that their long-term contribution to the control of their diabetes and contributory risk factors is as important as any treatment which their ophthalmologist can provide.

Focal DMO in eyes with good visual acuity and no foveal thickening on OCT should be treated with focal laser photocoagulation which is effective, safe, economical, and with good long-term results particularly where improved diabetes control is achieved.

Diffuse macular oedema associated with reduced visual acuity ideally requires intravitreal therapy, which may be augmented by macular grid laser to reduce the need for additional drug injections. Intravitreal anti-VEGF therapy appears to be slightly more clinically effective in improving visual acuity than intravitreal steroids, without the complications of cataract or raised intraocular pressure.

#### Table 1. Intravitreal drugs for treating diabetic oedema in the UK

<table>
<thead>
<tr>
<th>Generic name (proprietary name)</th>
<th>Mechanism of action</th>
<th>Licensed for IVT?</th>
<th>Effective for DMO?</th>
<th>Effective for PDR?</th>
<th>Duration of effect (weeks)</th>
<th>BNF cost/ volume</th>
<th>Potential doses</th>
<th>Potential minimum unit cost</th>
<th>Dose wasted</th>
<th>Three-year drug cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>Blocks VEGF-A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>£742.17 230µl</td>
<td>3</td>
<td>£247.39</td>
<td>66%</td>
<td>£10 390.38 (£3463.46)</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Blocks VEGF-A</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>£242.66 4ml</td>
<td>40</td>
<td>£6.07</td>
<td>50%</td>
<td>£3397.24 (£84.98)</td>
</tr>
<tr>
<td>Afibercept (Eylea)</td>
<td>Blocks VEGF-A and VEGF-B</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6–8</td>
<td>£816.00 250µl</td>
<td>4</td>
<td>£204.00</td>
<td>75%</td>
<td>£11 424.00 (£2856.00)</td>
</tr>
<tr>
<td>Triamcinolone (Kenalog)</td>
<td>Steroid</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>16–18</td>
<td>£1.49 1ml</td>
<td>1</td>
<td>£1.49</td>
<td>90%</td>
<td>£13.41</td>
</tr>
<tr>
<td>Dexamethasone (Ozurdex)</td>
<td>Steroid</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>16–18</td>
<td>£870.00 solid</td>
<td>1</td>
<td>£870.00</td>
<td>0%</td>
<td>£7830.00</td>
</tr>
<tr>
<td>Fluocinolone (Iluvien)</td>
<td>Steroid</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>150</td>
<td>£5500.00 solid</td>
<td>1</td>
<td>£5500.00</td>
<td>0%</td>
<td>£5500.00</td>
</tr>
</tbody>
</table>

*Based on 14 anti-VEGF injections from DCRC.net or 9 triamcinolone or Ozurdex injections, with potential minimal drug cost shown in parentheses.

IVT = intravitreal therapy; DMO = diabetic macular oedema; PDR = proliferative diabetic retinopathy; BNF = British National Formulary; VEGF = vascular endothelial growth factors.
pressure, but requiring more frequent injections over a period of years. Anti-VEGF therapy has the additional benefit of inhibiting retinal and iris neovascularisation. The longer duration of effect of intravitreal steroids is, however, more attractive to patients.

The higher affinity of aflibercept to VEGF extends its therapeutic effect, and the da Vinci trial showed that, after the first three one-monthly injections, reducing the injection frequency to every two months was as clinically effective as monthly treatment, requiring seven injections over the year compared with 11 monthly injections. In comparison, nine ranibizumab injections were utilised in the first year of the DR CR.net study which would appear to make aflibercept the more cost effective although price discounting through confidential NHS patient access schemes makes direct price comparisons unreliable. Utilising RNF prices, the drug cost of aflibercept is nearly £1000 cheaper over one year when used in this way, with further significant savings accruing from fewer clinic attendances and investigations.

The specific choice of intravitreal agent should be determined primarily by clinical effectiveness, notwithstanding licensing issues. Although trials in neovascular AMD have shown that bevacinumab is not inferior to ranibizumab in clinical effectiveness, there may be individual patients who respond to one agent better than another, so it is important that clinicians can switch to an alternative agent without delays imposed by cost considerations alone.

As in AMD treatment, the drug costs of treating DMO are beginning to escalate and clinicians are not immune to the impact of this on overall health budgets. There is considerable wastage in the administration of ranibizumab and aflibercept, whose unit costs could be significantly reduced (Table 1) if aliquotted under appropriate aseptic conditions as employed for bevacinumab. Adoption of bevacinumab as a first-line anti-VEGF agent would have an even greater impact in reducing costs, although this has the potential to lead to legal challenge by the pharmaceutical industry as a consequence.
of current drug licensing advice by the GMC.

**Illustrative cases**

**Case 1.** (Figure 2.) A 62-year-old woman with type 2 diabetes of 13 years duration presented to her optometrist with reduced visual acuity of 6/30 in both eyes. Significant diabetic retinopathy was detected and she was immediately referred for further management.

Retinal examination and photography showed microvascular changes with dot haemorrhages and microaneurysms at both maculae but very little lipid exudate (Figure). Slit lamp biomicroscopy showed macular oedema, confirmed by OCT scan with central macular thickness of >400μm (Figure). An incidental finding of shallow anterior chambers with narrow drainage angles but normal intraocular pressures was also made.

In view of the extensive and diffuse bilateral macular oedema, poor visual acuity, and concerns about glaucoma, intravitreal therapy with ranibizumab was undertaken, with three injections at monthly intervals to both eyes resulting in improvement in the clinical features of retinopathy, a 50% reduction in macular thickness but deterioration in visual acuity to 6/48 right eye and no improvement in the left acuity. Treatment was then switched to intravitreal triamcinolone in the right eye, with further reduction in macular thickness and improvement in acuity of two lines to 6/30. In view of the better clinical response to intravitreal steroid than ranibizumab, intravitreal fluocinolone (Iluvien) injection was subsequently undertaken in the left eye, with visual acuity improving to 6/19 three months after injection. Right intravitreal fluocinolone injection is planned when the triamcinolone effect has dissipated.

**Lesson:** a poor or modest response to one intravitreal agent does not preclude a good response to an alternative even if the clinical situation appears hopeless – ‘try, try, try again!’

**Case 2.** (Figure 3.) A 64-year-old man presented with a non-ischaemic left central retinal vein occlusion and macular oedema reducing visual acuity to 6/19. The right eye was normal with visual acuity of 6/9. Risk factor investigations revealed hypertension and type 2 diabetes, control of the latter proving less than ideal. The left macular oedema was treated successfully with intravitreal anti-VEGF (bevacizumab or ranibizumab) therapy over the next two years, during which he was observed to develop non-proliferative diabetic retinopathy followed by diabetic macular oedema in the right eye, the latter also treated successfully with intravitreal ranibizumab.

Laser photocoagulation was undertaken after two years to reduce the frequency of intravitreal injections. Visualy significant cataracts developed in both eyes, which were treated successfully by phacoemulsification and intraocular lens implants combined with intravitreal triamcinolone to prevent recurrence of macular oedema.

The macular oedema in both eyes resolved completely one month after the intravitreal triamcinolone injections, so when the oedema recurred intravitreal fluocinolone implants were administered to both eyes. No oedema has recurred yet in the right eye but has reappeared in the left eye one month after the fluocinolone implant injection, which may reflect the additional vascular damage from the original vein occlusion.

**Lesson:** poor diabetes control can confound the best attempts to arrest the progression of the ocular complications of diabetes despite innovations in therapy.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available online at www.practicaldiabetes.com.
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References


20. Tight blood pressure control and risk of macrovascu-