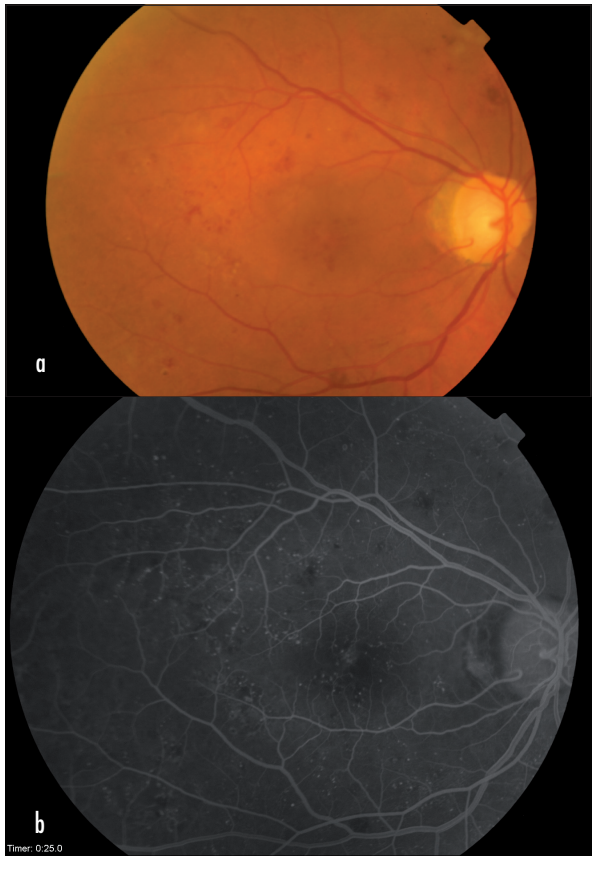
Treatment of diabetic maculopathy

Diabetic maculopathy is an important cause of severe sight impairment. There has been a significant evolution in its treatment over the past decade and laser treatment is now largely being superseded by intravitreal injections of anti-vascular endothelial growth factor agents or corticosteroids.

Diabetic maculopathy is a common and potentially blinding microvascular complication of diabetes mellitus. It is characterized by macular hard exudates, microaneurysms, haemorrhages (*Figure 1*), macular ischaemia and retinal thickening as a result of macular oedema (*Figure 2*). Diabetic macular oedema accounts for more visual loss among people under 50 years of age in the western world than any other eye disease (Luttrull and Dorin, 2012).

An estimated 347 million people worldwide were affected by diabetes in 2011 (Danaei et al, 2011), and its incidence is consistently increasing in developed and developing countries alike, making diabetes mellitus a global pandemic. Within 10 years, 20% of people with type 1 and 25% of people with type 2 diabetes mellitus will develop diabetic macular oedema (Klein et al, 1995). Diabetic maculopathy therefore represents a great cost to both quality of life and the economy. This has driven the investment of significant resources into the development of effective therapies for diabetic macular oedema. Management has evolved rapidly over the last 5 years, with laser therapy, once the cornerstone of treatment, having been largely replaced by emerging pharmacotherapies. This article provides an update on current treatment modalities and major new additions, with a glance at some promising future therapies.

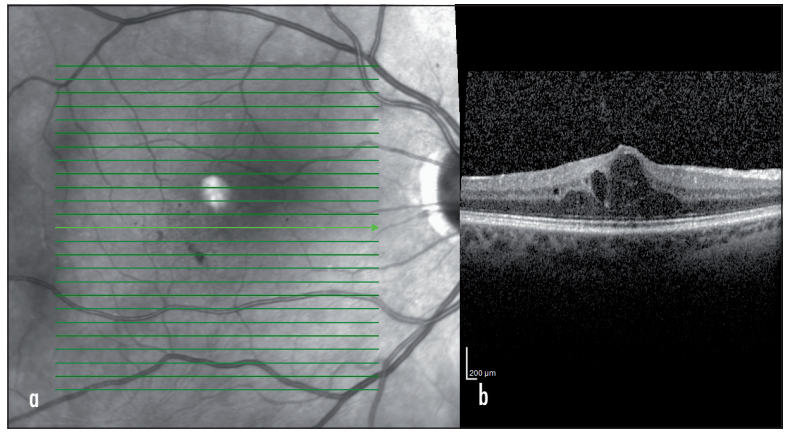
Figure 1. a. Colour fundus photograph and (b) mid-phase fluorescein angiogram demonstrating diabetic maculopathy, with hard exudates, microaneurysms and haemorrhages all visible.



Screening and diagnosis

Recognizing the cost of diabetic eye disease to individuals and society prompted the launch of screening programmes across the world aimed at early detection and intervention. Patients in the UK with diabetes mellitus aged 12 years and over have been systematically screened on an annual basis using digital fundus photography for over 10 years (Peto and Tadros, 2012). Some 2.3 million patients were offered screening in 2011–12, with a nationwide uptake of 81% (NHS Diabetic Eye Screening

Figure 2. Optical coherence tomography image demonstrating diabetic macular oedema. a. Multiple cross-sectional images are taken through the retina at the positions indicated by the green lines. b. One of those central images is shown, and large cystic spaces are immediately visible in the central retina.



Dr Gemma SL Manasseh *is FY1 in the Department of Medicine, Imperial College Healthcare NHS Trust, London,* **Dr Emily Han Shao** *is ST3 in the Department of Ophthalmology, Royal Surrey County Hospital NHS Foundation Trust, and* **Mr Simon RJ Taylor** *is Clinical Senior Lecturer and Consultant Ophthalmic Surgeon, Imperial College London Faculty of Medicine, Hammersmith Hospital, London W12 0NN*

Correspondence to: Mr SRJ Taylor (s.r.taylor@imperial.ac.uk)

Programme, 2013). Strict grading criteria for diabetic maculopathy have been defined alongside criteria for referral to the hospital eye service (*Table 1*).

Within the hospital eye service there are a number of techniques available to ophthalmologists to visualize and assess diabetic macular oedema. Clinical ophthalmoscopy with a slit lamp and biomicroscopic lenses is a subjective and qualitative method routinely used (Virgili et al, 2011). Fluorescein angiography can be useful in identifying treatable lesions and areas of leakage. However, optical coherence tomography has become the key imaging technique. It produces three-dimensional and cross-sectional images of the central retina, based on optical reflectivity (*Figure 2*). This provides valuable information on retinal structure and thickness (Virgili et al, 2011) and is used as an objective and quantitative assessment of macular oedema, both for initial evaluation and, importantly, in monitoring response to treatment.

Pathophysiology of diabetic macular oedema

Diabetic macular oedema can be focal or diffuse. Focal oedema typically surrounds clusters of microaneurysms, which have been demonstrated by fluorescein angiography as being a major cause of leakage (Ahmadi and Lim, 2009). Diffuse diabetic macular oedema results from general breakdown of the blood–retinal barrier, which can be induced by chronic hyperglycaemia (Ahmadi and Lim, 2009). Chronic hyperglycaemia leads to accumulation of abnormal metabolites from multiple overactive biochemical pathways, inducing oxidative stress and causing vascular endothelial growth factor production to be upregulated. Vascular endothelial growth factor is a potent endothelial-specific mitogen that induces vasodilatation, endothelial cell proliferation, production of pro-inflammatory cytokines and increased vascular permeability (Ferrara et al, 1992), which ultimately results in breakdown of the blood–retinal barrier with extravasation of fluid that accumulates as macular oedema. This process is often further compounded by associated conditions such as hypertension, dyslipidaemia and vascular inflammation (Bloomgarden, 2007; Morello, 2007).

Table 1. English National Screening Committee Maculopathy Grading Standard

Maculopathy (M)	Features	Action
M0 No visible maculopathy	Absence of any M1 features	Annual rescreen
M1 Maculopathy	Exudate within 1 disc diameter (DD) of the centre of the fovea, group of exudates within the macula, retinal thickening within 1DD of the centre of the fovea, any microaneurysm or haemorrhage within 1DD of the centre of the fovea only if associated with a best visual acuity of ≤ 6/12	Refer to eye clinic to be seen within 13 weeks

From NHS Diabetic Eye Screening Programme (2013)

Management of diabetic macular oedema

As chronic hyperglycaemia initiates and propagates the succession of pathogenic events, the ultimate management of diabetic macular oedema is strict glycaemic control (Turner et al, 1998). Microvascular damage is compounded by hypertension, thus tight control of blood pressure is essential (UK Prospective Diabetes Study Group, 1998). An emerging body of evidence also supports a role for lipid-lowering agents in the management of diabetic macular oedema, by reducing the severity of hard exudates and leakage of fluid (Panagiotoglou et al, 2010). However, despite efforts aimed at early identification and aggressive treatment of diabetes mellitus and these associated risk factors, around a quarter of patients will develop diabetic macular oedema within 10 years (Klein et al, 1995). Therefore, in addition to these systemic modifications an array of intraocular treatment modalities have been developed.

Laser photocoagulation

Macular laser photocoagulation has been the unequivocal gold standard of treatment for diabetic macular oedema since publication of the Early Treatment Diabetic Retinopathy Study in 1985. This large multi-centre, randomized trial of nearly 4000 patients showed that focal application of laser to leaking aneurysms and grid treatment of diffuse macular leakage provided a 50% reduction in moderate visual loss after 3 years compared with untreated patients (Early Treatment Diabetic Retinopathy Study, 1985) (*Figure 3*). This study, which predates optical coherence tomography imaging, recommended laser photocoagulation for all patients with clinically significant macular oedema, as defined by the following criteria: retinal thickening within 500 μm of the macula centre, hard exudates with associated retinal thickening within 500 μm of the macula centre, or a zone of retinal thickening one disc area in size within one disc diameter of the macula centre (Early Treatment Diabetic Retinopathy Study, 1985, 1991).

Unlike panretinal photocoagulation, which treats proliferative diabetic retinopathy by reducing oxygen requirements of the retina through tissue destruction, the precise mechanism by which macular photocoagulation treats diabetic macular oedema remains unknown. It is likely that focal laser occludes leaking microaneurysms, contributing in part to its efficacy (Royster et al, 1988). Grid laser treatment is thought to work through the influence of macular tissue damage on autoregulation of retinal blood flow, reducing it and consequently any associated fluid shift (Wilson et al, 1988).

Although effective at slowing or preventing further loss of vision, laser photocoagulation is not effective at restoring vision. Potential complications include visible scars that can enlarge and encroach towards the fixation point (Bailey et al, 1999), reduced contrast sensitivity and colour vision (Morgan and Schatz, 1989), as well as complications such as choroidal neovascularization (Roider et al, 2000) and subretinal fibrosis (Stanga et al, 1999).

Efforts to reduce the risks associated with thermal laser have led to the development of the micropulsed diode laser that delivers laser energy in short pulses rather than as a continuous wave. The relative absorption of diode laser is 40% of that of conventional argon lasers, yet it remains therapeutically effective (Ohkoshi and Yamaguchi, 2010) and with fewer side effects. Nevertheless, it still produces its clinical effect by causing iatrogenic retinal damage, and is still associated with visual stabilization rather than improvement.

Corticosteroids

Corticosteroids are anti-inflammatory agents effective at reducing the permeability of retinal capillaries by enhancing endothelial cell tight junctions and downregulating the vascular endothelial growth factor metabolic pathway (Sears and Hoppe, 2005). This reduces leakage of plasma proteins into the interstitial space, helping to restore the osmotic gradient and resolve the oedema (Sivaprasad et al, 2006).

The first intravitreal corticosteroid to be widely used in the treatment of diabetic macular oedema was triamcinolone acetonide. Its benefits in treating diabetic macular oedema refractive to laser photocoagulation and as primary therapy have been well documented (Sutter et al, 2004). Intravitreal triamcinolone provided greater short-term improvements in visual acuity than laser photocoagulation, but this was not sustained beyond 16 months (Beck et al, 2009). In practice, patients require re-injection every 3–6 months as the effect diminishes.

As with systemic corticosteroids, intravitreal triamcinolone causes both cataract (Beck et al, 2009) and glaucoma (Beck et al, 2009), and with each subsequent injection the risk increases. Furthermore, intravitreal injection itself carries risk of endophthalmitis, retinal detachment and vitreous haemorrhage. Therefore the need for regular repeat injections is a major drawback of intravitreal triamcinolone therapy.

More recently, sustained-release steroid intraocular implants have been developed that lengthen the reinjection interval and reduce side effects. Ozurdex is a sustained-release dexamethasone injectible device currently licensed for use in macular oedema following retinal vein occlusion and uveitis. Its short-term benefits in the management of diabetic macular oedema are well documented, but effects are rarely sustained beyond 3–4 months (Pacella et al, 2013). A multi-centre randomized controlled trial comparing laser plus Ozurdex with laser plus sham in patients with diffuse diabetic macular oedema found that although a significant improvement in visual acuity was reported for the first 9 months in those treated with Ozurdex, this was not maintained and significance was lost at 12 months (Callanan et al, 2013). Rates of raised intraocular pressure and cataract were higher in eyes receiving Ozurdex, but lower than that associated with intravitreal triamcinolone.

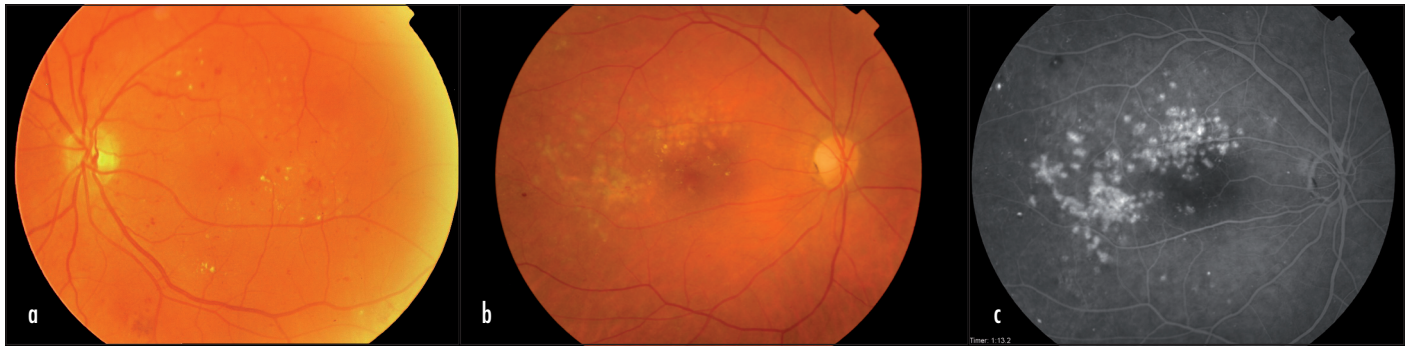
Iluvien is a second-generation injectable fluocinolone acetonide device that has entered phase III trials for diabetic macular oedema. In patients with diabetic macular oedema previously treated with laser photocoagulation, a maxiumum of one Iluvien insert per year provided greater improvement in visual acuity after 3 years when compared with sham. Rates of adverse effects were high; almost all phakic eyes developed cataract after 3 years, and incisional glaucoma surgery was required in 8.1% of the high dose group (Campochiaro et al, 2012). Iluvien is currently approved by the National Institute for Health and Care Excellence for use in pseudophakic patients with diabetic macular oedema refractive to other therapies.

Together, these trials demonstrate a valid role for steroid therapy in diabetic macular oedema, with well-documented improvements in vision. However, despite the development of sustained delivery systems the duration of effect is limited. With the risk of side effects being high, a more effective and safer treatment modality is required.

Vascular endothelial growth factor inhibitors

As previously discussed, vascular endothelial growth factor plays a central role in the pathogenesis of diabetic macular oedema and is therefore a key therapeutic target. Indeed, multiple drugs that target vascular endothelial growth factor have been developed and tested in large

Figure 3. Applying macular laser treatment requires a reasonably high skill level. a. Light grid laser treatment is apparent as faint grey spots within the macula. b. Much heavier laser treatment is visible, and indicates how inexperienced operators can cause significant scarring, especially as scars tend to enlarge and coalesce over time. c. Fluorescein angiography of the same patient highlights the confluent laser scars.



phase III randomized trials for safety and efficacy in treating diabetic macular oedema. These drugs are effective at reducing diabetic macular oedema and restoring vision, but require regular intravitreal injection. This exposes patients to higher risk of injection-related adverse events and places a strain on both eye clinics and budgets.

Ranibizumab (Lucentis) is a humanized monoclonal anti-vascular endothelial growth factor antigen binding fragment specifically designed for use in the eye. It potently inhibits the activity of all known isoforms of vascular endothelial growth factor. There is a large body of robust evidence from multiple large phase III trials demonstrating its efficacy in reducing diabetic macular oedema, and three major trials have demonstrated its superiority over laser therapy (Nguyen et al, 2012). The 3-year results of one trial highlight the importance of early treatment with ranibizumab (Brown et al, 2013). To maintain these effects, patients required an average of seven injections with 12 monitoring visits in year one and three injections with ten monitoring visits in year two, with a total cost of around £10 000 per patient (Mitchell et al, 2012).

Bevacizumab (Avastin) is a monoclonal anti-vascular endothelial growth factor antibody that binds and inhibits all isoforms of vascular endothelial growth factor-A. Ocular use is currently unlicensed, yet numerous randomized trials have demonstrated its superiority over laser therapy, intravitreal steroids and combinations of these, in treating diabetic macular oedema (Rajendram et al, 2012). Again, regular repeat injections of bevacizumab were required for maintenance of effect.

Aflibercept (Eylea) is a fusion protein of human immunoglobulin and vascular endothelial growth factor receptors that binds multiple isoforms of vascular endothelial growth factor with high affinity. A major benefit of aflibercept is its longer duration of action meaning fewer injections and monitoring visits are required. In the phase II clinical trial, laser therapy was compared with an aflibercept dosing regimen consisting of monthly injections for 3 months followed by 2-monthly injections. After 6 months, patients treated with aflibercept demonstrated a significantly greater improvement in mean visual acuity and retinal thickness. One year follow up demonstrated that 2-monthly injections were sufficient to maintain these effects, with seven injections required in total (Do et al, 2012). Although this initial study is promising, further data are required before drawing conclusions on aflibercept.

Pegaptanib (Macugen) is PEGylated aptamer that potently bind vascular endothelial growth factor-165. When compared with sham injection, pegaptanib showed only weak efficacy in treating diabetic macular oedema and no further comparative trials were commenced (Sultan et al, 2011).

These trials also demonstrated the safety of anti-vascular endothelial growth factor agents for intraocular use. The frequency of reported adverse events was low, with raised intraocular pressure being the only consistently reported side effect in a small proportion of patients across all anti-vascular endothelial growth factor therapies, excluding bevacizumab in which rates were comparable with laser. As a result, anti-vascular endothelial growth factor agents are now considered first-line management for patients with diabetic macular oedema.

Enzymatic vitreolysis

The observation that patients with spontaneous or surgical posterior vitreous detachment had significantly reduced rates of diabetic macular oedema or improvement of already established diabetic macular oedema (Tachi and Ogino, 1996) led researchers to believe that vitreoretinal relationships at the macula play a key role. Plasmin is a protease active against fibronectin and laminin, the proteins responsible for vitreous attachment to the retinal surface. Researchers using intravitreal plasmin, either in autologous or recombinant forms (Ocriplasmin), to induce posterior vitreous detachment in patients with diabetic macular oedema found that it effectively reduced macular thickness and improved vision (Diaz-Llopis et al, 2013). When compared to intravitreal triamcinolone, plasmin had a more sustained effect on both macular thickness and visual acuity without the concomitant rise in intraocular pressure (Elsawy, 2012). These therapies represent a promising new approach to treating diabetic macular oedema.

Discussion

The past decade has seen a significant evolution in the treatment of diabetic macular oedema. Laser was once the gold standard therapy, but now its role is debatable. A robust evidence base supports anti-vascular endothelial growth factor drugs as primary therapy for diabetic macular oedema. Both ranibizumab and bevacizumab are superior to laser, and adding laser confers no benefit. However, laser may still be used to treat very focal areas of leakage.

There are no direct head-to-head trials of ranibizumab and bevacizumab, therefore choice is at the ophthalmologist's discretion. Bevacizumab is currently unlicensed for intraocular use, but is considerably cheaper than licensed ranibizumab. Anti-vascular endothelial growth factor drugs represent a significant advance, but they are not the solution; only half of patients gain ≥10 letters in visual acuity following treatment (Mitchell et al, 2011), and regular injections are required to maintain effect.

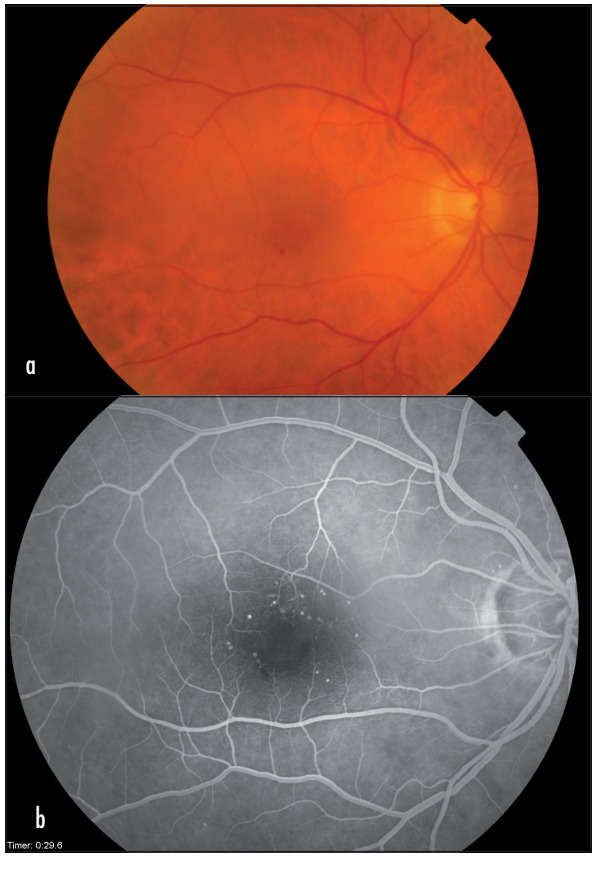
Studies investigating the efficacy of steroid have mixed results, but the association with cataract and raised intraocular pressure is consistent. The effects of dexamethasone implants peak at 3 months and then diminish, requiring retreatment. Each retreatment increases the risk of complications. Fluocinolone requires fewer administrations, potentially one every 3 years, but rates of cataract are high. Some patients may opt for infrequent steroid injections, accepting the considerable risk of cataract

and small risk of glaucoma, over frequent anti-vascular endothelial growth factor injections, despite the difference in potential acuity gain. There also remains a place for steroids in patients not responding to anti-vascular endothelial growth factor drugs. Furthermore, cataract is very common in diabetes, and many patients are pseudophakic when treatment for diabetic macular oedema is required.

As research continues, the management for diabetic macular oedema will constantly evolve. A range of promising new treatment modalities is currently under development that target various elements of the cascade leading to diabetic macular oedema. Some are topical agents (Callanan and Williams, 2008), which may play a major role in the future.

The pathogenesis of diabetic macular oedema is multifactorial, so a combination of therapies working synergistically to target multiple pathways is likely to be needed. The presence of macular ischaemia, as evidenced by an enlarged foveal avascular zone on fluorescein angiography (*Figure 4*), is thought to contribute to poor visual outcomes following treatment (Chung et al, 2008). In the absence of an effective therapy for macular ischaemia, complete resolution of visual loss is unlikely to be achievable. Diabetic macular oedema is an ongoing global problem, and although recent years have seen a number of significant advances, the problem is far from solved. **BJHM**

Figure 4. Ischaemia maculopathy forms a subset of diabetic maculopathy that is very difficult to treat. a. The macular appearance is often featureless, but (b) fluorescein angiography demonstrates an enlargement of the central avascular zone with drop-out of capillaries.



Financial support: Mr SRJ Taylor is supported by the UK National Institute of Health Research. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the UK Department of Health. Conflict of interest: Mr SRJ Taylor has received advisory board fees from Novartis, Allergan and Santen, and grant support from Novartis and GSK; Dr GSL Manasseh and Dr E Han Shao: none.

Ahmadi MA, Lim JI (2009) Update on laser treatment of diabetic macular edema. *Int Ophthalmol Clin* **49**(2): 87–94 (doi: 10.1097/IIO.0b013e31819fd6b2)

Bailey C, Sparrow J, Grey R, Cheng H (1999) The national diabetic retinopathy laser treatment audit III. Clinical outcomes. *Eye* **13**(2): 151–9

Beck RW, Edwards AR, Aiello LP et al (2009) Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* **127**(3): 245–51 (doi: 10.1001/archophthalmol.2008.610)

Bloomgarden ZT (2007) Screening for and managing diabetic retinopathy: current approaches. *Am J Health Syst Pharm* **64**(17 Suppl 12): S8–S14

Brown DM, Nguyen QD, Marcus DM et al (2013) Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* **120**(10): 2013–22 (doi: 10.1016/j.ophtha.2013.02.034)

Callanan DG, Williams P (2008) Topical nepafenac in the treatment of diabetic macular edema. *Clin Ophthalmol* **2**(4): 689

Callanan DG, Gupta S, Boyer DS et al (2013) Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology* **120**(9): 1843–51 (doi: 10.1016/j.ophtha.2013.02.018)

Campochiaro PA, Brown DM, Pearson A et al (2012) Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* **119**(10): 2125–32 (doi: 10.1016/j.ophtha.2012.04.030)

Chung EJ, Roh MI, Kwon OW, Koh HJ (2008) Effects of macular ischemia on the outcome of intravitreal bevacizumab therapy for diabetic macular edema. *Retina* **28**(7): 957–63 (doi: 10.1097/IAE.0b013e3181754209)

Danaei G, Finucane M, Lu Y et al (2011) National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: Systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* **378**(9785): 31–40 (doi: 10.1016/S0140-6736(11)60679-X)

Diaz-Llopis M, Udaondo P, Millán JM, Arevalo JF (2013) Enzymatic vitrectomy for diabetic retinopathy and diabetic macular edema. *World J Diabetes* **4**(6): 319–23 (doi: 10.4239/wjd.v4.i6.319)

Do DV, Nguyen QD, Boyer D et al (2012) One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular

KEY POINTS

- Diabetic eye disease is the leading cause of visual impairment in the working age population and accounts for a significant personal and economic burden.
- Diabetic macular oedema typically affects the central vision.
- Traditional treatment involves gentle laser therapy, but intraocular injections of anti-vascular endothelial growth factor agents or corticosteroids are becoming more commonly used.
- Despite these new treatment options, ischaemic maculopathy remains a difficult clinical problem.

edema. *Ophthalmology* **119**(8): 1658–65 (doi: 10.1016/j.ophtha.2012.02.010)
Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. *Arch Ophthalmol* **103**(12): 1796–806
Early Treatment Diabetic Retinopathy Study Research Group (1991) Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* **98**(5 Suppl): 766–85
Elsawy MF (2012) Intravitreal autologous plasmin as a therapeutic modality for diffuse diabetic macular edema. *Clin Ophthalmol* **6**: 2063–8 (doi: 10.2147/OPTH.S36609)
Ferrara N, Houck K, Jakeman L, Leung DW (1992) Molecular and biological properties of the vascular endothelial growth factor family of proteins. *Endocr Rev* **13**(1): 18–32
Klein R, Klein B, Moss SE, Cruickshanks KJ (1995) The Wisconsin epidemiologic study of diabetic retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology* **102**(1): 7–16
Luttrull JK, Dorin G (2012) Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: A review. *Curr Diabetes Rev* **8**(4): 274–84
Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K, Knudsen M, Onwordi H (2012) Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol* **96**(5): 688–93 (doi: 10.1136/bjophthalmol-2011-300726)
Morello CM (2007) Etiology and natural history of diabetic retinopathy: An overview. *Am J Health Syst Pharm* **64**(17 Suppl 12): S3–7
Morgan CM, Schatz H (1989) Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. *Ophthalmology* **96**(1): 96–103
Nguyen QD, Brown DM, Marcus DM et al (2012) Ranibizumab for diabetic macular edema: Results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* **119**(4): 789–801 (doi: 10.1016/j.ophtha.2011.12.039)
NHS Diabetic Eye Screening Programme (2013) NHS National Eye Screening Programme. http://diabeticeye.screening.nhs.uk/statistics (accessed 17 September 2014)
Ohkoshi K, Yamaguchi T (2010) Subthreshold micropulse diode laser photocoagulation for diabetic macular edema in Japanese patients. *Am J Ophthalmol* **149**(1): 133–9 (doi: 10.1016/j.ajo.2009.08.010)
Pacella E, Vestri AR, Muscella R et al (2013) Preliminary results of an intravitreal dexamethasone implant (Ozurdex®) in patients with persistent diabetic macular edema. *Clin Ophthalmol* **7**: 1423–8 (doi: 10.2147/OPTH.S48364)
Panagiotoglou TD, Ganotakis ES, Kymionis GD et al (2010) Atorvastatin for diabetic macular edema in patients with diabetes mellitus and elevated serum cholesterol. *Ophthalmic Surg Lasers Imaging* **41**(3): 316–22 (doi: 10.3928/15428877-20100430-04)
Peto T, Tadros C (2012) Screening for diabetic retinopathy and diabetic macular edema in the United Kingdom. *Current Diabetes Reports* **12**(4): 338–45 (doi: 10.1007/s11892-012-0285-4)
Rajendram R, Fraser-Bell S, Kaines A et al (2012) A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: Report 3. *Arch Ophthalmol* **130**(8): 972–9
Royster AJ, Nanda SK, Hatchell DL, Tiedeman JS, Dutton JJ, Hatchell MC (1988) Photochemical initiation of thrombosis. fluorescein angiographic, histologic, and ultrastructural alterations in the choroid, retinal pigment epithelium, and retina. *Arch Ophthalmol* **106**(11): 1608–14
Sears JE, Hoppe G (2005) Triamcinolone acetonide destabilizes VEGF mRNA in Müller cells under continuous cobalt stimulation. *Invest Ophthalmol Vis Sci* **46**(11): 4336–41
Sivaprasad S, McCluskey P, Lightman S (2006) Intravitreal steroids in the management of macular oedema. *Acta Ophthalmol Scand* **84**(6): 722–33
Sultan MB, Zhou D, Loftus J, Dombi T, Ice KS ; Macugen 1013 Study Group (2011) A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* **118**(6): 1107–18 (doi: 10.1016/j.ophtha.2011.02.045)
Sutter FK, Simpson JM, Gillies MC (2004) Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: Three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology* **111**(11): 2044–9
Tachi N, Ogino N (1996) Vitrectomy for diffuse macular edema in cases of diabetic retinopathy. *Am J Ophthalmol* **122**(2): 258–60
Turner R, Holman R, Cull C et al (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**(9131): 837–53
UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**(7160): 703–13
Virgili G, Menchini F, Murro V, Peluso E, Rosa F, Casazza G (2011) Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database Syst Rev* **7**: CD008081 (doi: 10.1002/14651858.CD008081.pub2)
Wilson DJ, Finkelstein D, Quigley HA, Green WR (1988) Macular grid photocoagulation. An experimental study on the primate retina. *Arch Ophthalmol* **106**(1): 100–5