Management of branch retinal vein occlusion

This article addresses advances in the management of branch retinal vein occlusion – a common retinal vascular disorder in elderly patients which is a significant cause of ocular morbidity. New intravitreal therapies have improved the prognosis for patients, albeit with significant cost implications.

Branch retinal vein occlusion is a retinal vascular disorder that frequently causes significant visual loss (Mitchell et al, 1996). The Beaver Dam study reported a 15-year cumulative incidence of branch retinal vein occlusion of 1.8% and over half of cases are found in people over 65 years of age (Klein et al, 2008). Prevalence varies with race or ethnicity, but not with sex. The management of branch retinal vein occlusion has changed significantly in recent years, and the introduction of novel intravitreal therapies has greatly improved the visual prognosis, but led to an increasing burden on ophthalmic services.

History and examination

The manner of presentation typically depends on whether the macula is involved, as this is responsible for most visual symptoms. Symptomatic patients often present with a sudden painless decrease in vision, worse in the mornings, or with visual field defects (Oh et al, 2007); the visual acuity is often poor (from 6/12 to 6/60 or worse). This is most common with superotemporal branch retinal vein occlusion – inferotemporal or nasal branch retinal vein occlusions are more often asymptomatic and often detected by optometrists on routine refraction, although these patients may have arcuate, central or paracentral scotomas and segmental reduction in peripheral vision.

The diagnosis is essentially clinical, and fundal signs include: dilated, tortuous retinal veins or focal venous constriction in non-hypertensive patients, deep and superficial haemorrhages, cotton wool spots, capillary non-perfusion, disc and retinal oedema, all confined to one section of the retina (*Figure 1*). Occlusions occur frequently in areas of high arteriovenous crossing sites (artery over vein), especially in the superotemporal quadrant.

Fluorescein angiography can be useful to illustrate the extent of macula oedema, ischaemia and peripheral capillary non-perfusion (*Figure 2*). Optical coherence tomography is a non-invasive, high-resolution imaging technique that can quantify macular oedema and provide a tool for monitoring response to treatment (Domalpally et al, 2009) (*Figure 3*).

Figure 1. A superotemporal branch retinal vein occlusion, showing a characteristic distribution of retinal haemorrhages and exudates.

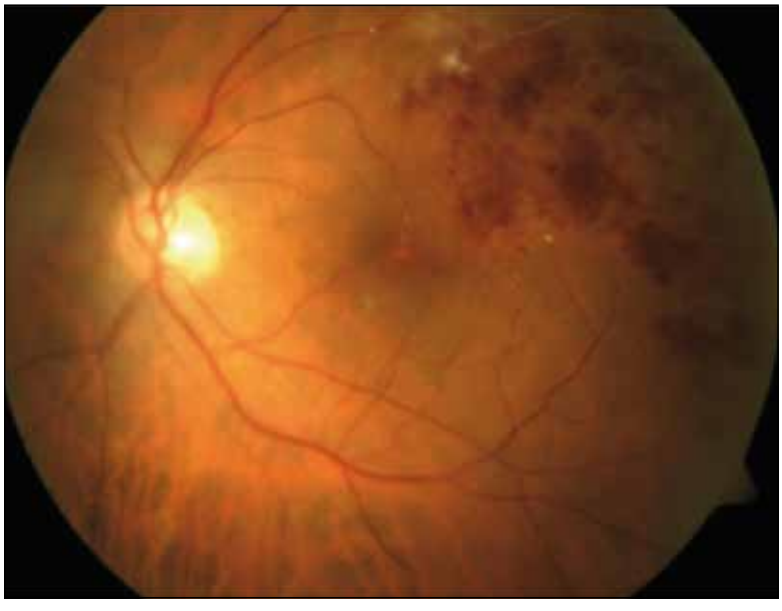
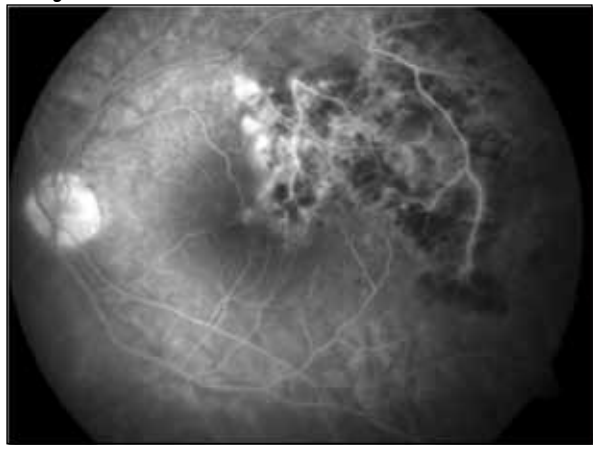


Figure 2. Fluorescein angiography of a branch retinal vein occlusion demonstrating masking by retinal haemorrhage and macular leakage.



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Complications of branch retinal vein occlusion affect visual prognosis and include macula oedema in 60% of eyes, as well as pre-retinal or optic disc neovascularization less commonly (*Figure 4*) (Rogers et al, 2010). Neovascularization can develop up to a year after the initial event and leads to recurrent vitreous haemorrhages and consequent visual loss.

Risk factors for the development of branch retinal vein occlusion

Mechanisms known to be involved in the development of branch retinal vein occlusion include thrombus formation, external vessel wall compression and vasculitis, but the interaction between diseased vessel walls and abnormal blood constituents and viscosity is complex (Cheung et al, 2008). About 90% of occlusions involve temporal retinal veins at artery over venous crossings (Hamid et al, 2008). The two vessels share a common sheath at this point, predisposing the vein to occlusions as a result of atherosclerotic changes to the artery which compress the vein, causing endothelial damage and encouraging thrombus formation (Kumar et al, 1998). Other haematological risk factors include increased plasma viscosity and reduced retinal blood flow (Noma et al, 2009). Ocular risk factors include glaucoma (Klein et al, 2008) and hypermetropia, presumably for structural anatomical reasons (Di Capua et al, 2009; Noma et al, 2009).

Half of branch retinal vein occlusions are associated with hypertension (Appiah and Trempe, 1989; Simons and Brucker, 1997). Diabetes mellitus is also more common in patients with branch retinal vein occlusion when compared to controls (18% *vs* 8%; Di Capua et al, 2009), but branch retinal vein occlusion is not linked to the presence of diabetic vessel disease (Dodson et al, 1993). Hypertension and hyperlipidaemia are common associations with diabetes and their control should be maintained to lower the risk of disease recurrence and visual loss (Dodson et al, 1993). Recurrence of disease is higher in patients who display a high cardiovascular risk profile (Di Capua et al, 2009). When cardiovascular risk factors are within the normal range, screening for coagulation disorders is warranted, especially in the young (in 51% of younger patients a thrombophilic disorder is the cause), those with bilateral disease, history of previous thrombosis or a similar family history (Kuhli-Hattenbach et al, 2009).

Patients should be examined to prevent recurrence and further non-ocular target organ damage. Upon diagnosis appropriate tests for cardiovascular disease, diabetes and glaucoma (Sperduto et al, 1998) and medical referral should be made as required. The Royal College of Ophthalmologists (2009) recommend that this is performed within 2 months of diagnosis. The Framingham algorithm can accurately determine cardiovascular risk to aid initiation of treatment in high-risk patients (Martin et al, 2002).

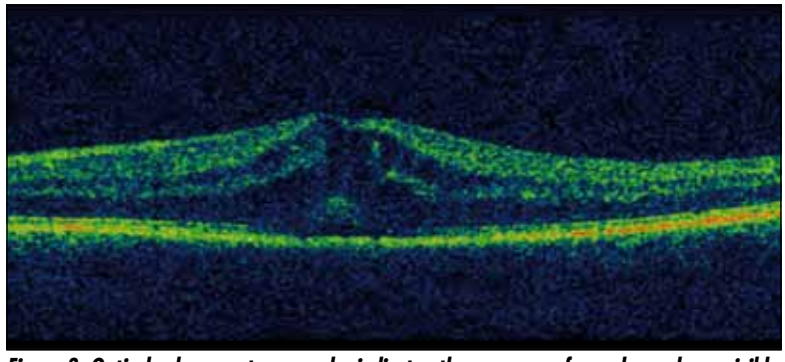


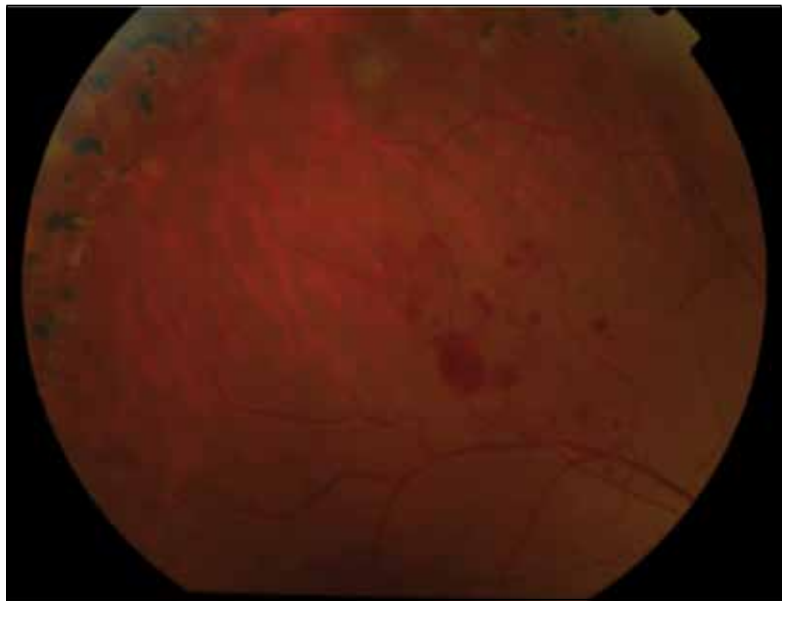
Figure 3. Optical coherence tomography indicates the presence of macular oedema visible as cysts within the central retina.

Risk factors in those under 45 years of age include: resistance to activated protein C, antiphospholipid antibodies, deficiency of the anticoagulant proteins and factor XII deficiency (Kuhli-Hattenbach et al, 2010), but factor V Leiden and prothrombin 20210A mutations have not been found to be risk factors for branch retinal vein occlusion (Aras et al, 2001).

Management

Patients presenting with good visual acuity have a favourable prognosis, but the prognosis is less good in other cases: the natural history is for 50% of eyes to retain 6/12 or better, but for 25% to deteriorate to vision of 6/60 or worse (Rogers et al, 2010). Argon laser treatment was first introduced in the 1970s, and can be used to treat both neovascularization and macular oedema (*Figure 4*). The Branch Retinal Vein Occlusion Study showed that scatter laser photocoagulation can effectively treat retinal and optic disc neovascularization (McIntosh et al, 2007). Grid macular laser

Figure 4. Retinal neovascularization can occur following branch retinal vein occlusion. Some scars of peripheral scatter laser photocoagulation are visible on the periphery of this figure, but more laser is required.



can be used to treat macular oedema, and is usually carried out following fluorescein angiography to identify leaking capillaries and the degree of any macula ischaemia. Laser is usually started 3 months after onset to allow for any spontaneous resolution and reduction in haemorrhage.

Novel intravitreal therapies

The first intravitreal therapy for branch retinal vein occlusion was intravitreal steroid in the form of triamcinolone acetate (Kenalog). This proved effective at restoring visual acuity in the short term, but the side-effect profile was less than ideal, with some 40% of patients developing raised intraocular pressure and cataract within a year (Cekic et al, 2005; Chen et al, 2006; Scott et al, 2009). Newer drugs include anti-vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab (Avastin, Genentech/Hoffman-La Roche AG, Basel, Switzerland) and ranibizumab (Lucentis, Genetech/Novartis AG, Basel, Switzerland), which were originally introduced for 'wet' age-related macular degeneration, and of which only ranibizumab is licensed for ophthalmic indications.

Ranibizumab is a fast, effective, well-tolerated, safe treatment for macular oedema secondary to branch retinal vein occlusion and improves both visual acuity and central retinal thickness (Campochiaro et al, 2010). Clinical trials suggest that three injections at monthly intervals are enough to give an 18 letter improvement and reduce macular oedema by approximately 90% (Campochiaro et al, 2008), but repeat monthly injections for up to 2 years are required to maintain this benefit. Macular oedema also responds quickly to bevacizumab, but multiple injections are still required to maintain significant short- and long-term gains in vision (Hoh et al, 2008). Longer studies are still required to determine how bevacizumab and ranibizumab can benefit patients with branch retinal vein occlusion in the long term and ophthalmologists and commissioning bodies are in a quandary as the drugs are broadly equivalent, bevacizumab is much cheaper, but ranibizumab is licensed (Martin et al, 2011; Rosenfeld, 2011).

Ozurdex (Allergan Inc., Irvine, California) is an intravitreal dexamethasone implant that has also been shown to be effective in the treatment of visual loss from macular oedema in branch retinal vein occlusion (*Figure 5*) (Haller et al, 2010). One implant gives a significant improvement in vision for up to 6 months, but approximately 80% of patients required reinjection at the end of this time period (Haller et al, 2010). Data from both the Ozurdex and ranibizumab trials suggests that early treatment provides increased visual benefit (Campochiaro et al, 2008, 2010; Haller et al, 2010).

Figure 5. The sustained release intravitreal dexamethasone implant (Ozurdex, Allergan Inc., Irvine, California).

Researchers have recently started looking at intraocular cytokine levels in an attempt to explain why some patients respond better to one particular treatment modality than another. It has been suggested that IL-12 production may be linked to failure to respond to anti-VEGF agents (Kaneda et al, 2011), and that longer-acting compounds may carry some advantage in reducing rebound increases in cytokine levels, but further research is required. Unfortunately, the construction of the clinical trials for ranibizumab and Ozurdex differ significantly in terms of inclusion criteria such that it is difficult to compare the efficacy of these drugs without a formal head-to-head trial. Head-to-head trials are now underway but, interestingly, the National Institute for Health and Clinical Excellence (2011) recently appraised Ozurdex in the treatment of branch retinal vein occlusion and gave it a positive final appraisal determination, finding it more cost effective even than bevacizumab, despite the ten times increased cost of the licensed drug, mainly as a result of the reduced frequency of injections required.

Conclusions

Branch retinal vein occlusion is a significant ophthalmic problem in elderly patients, but new treatment options have become available in recent years, improving the prognosis for patients with visual impairment as a result of macular oedema. The National Institute of Health and Clinical Excellence has recently supported the use of Ozurdex, but head-to-head trials with ranibizumab are currently underway and should provide interesting data as to their relative efficacy. The role of bevacizumab remains unclear, but cost pressures are likely to promote its use where funding for more expensive drugs remains difficult. BJHM

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Conflict of interest: Mr SRJ Taylor and Professor S Lightman have received advisory board fees from Allergan, Inc. Mr SRJ Taylor is a principal investigator for the Novartis-funded COMRADE study comparing Ozurdex and Lucentis in branch and central retinal vein occlusion at the Royal Surrey County Hospital NHS Foundation Trust.

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KEY POINTS

- Branch retinal vein occlusion is a common cause of visual loss in elderly patients.
- Management is of both the retinal vascular problem and of any risk factors that render repeat episodes more likely.
- The major cause of visual loss is macular oedema, but new intravitreal therapies are now available.
- Anti-vascular endothelial growth factor agents such as ranibizumab have been shown to be effective, but the National Institute for Health and Clinical Excellence has recently issued a positive final appraisal determination for the long-acting intravitreal steroid implant Ozurdex, mainly on the grounds of its reduced injection frequency.
- The role of bevacizumab, which is not licensed for ocular use and probably never will be, remains uncertain in branch retinal vein occlusion as it does in other ocular conditions.