Retinal vein occlusions are important causes of loss of vision; indeed, they are the second most common retinal vascular disease, following diabetic retinopathy. For this reason alone, primary eye-care providers must be well versed in diagnosis and management. Risk factors, though not universally agreed upon, include but are not limited to advancing age, systemic hypertension, arteriolar sclerosis, diabetes, hyperlipidaemia, blood hyperviscosity, thrombophilia, ocular hypertension and glaucoma. Typically, visual loss is secondary to macular oedema and/or retinal ischaemia. Treatment modalities have included observation, systemic thrombolysis and haemodilution, radial optic neurotomy, chorioretinal anastomosis, vitrectomy, laser photocoagulation and intravitreal injection of anti-inflammatory and, most recently, anti-vascular endothelial growth factors.

Key words: aflibercept, bevacizumab, macular oedema, pegaptanib, ranibizumab, retinal vein occlusion, sheathotomy, vascular endothelial growth factor, vitrectomy

In the realm of retinal vascular disease, retinal vein occlusion (RVO) trails only diabetic retinopathy as a cause of visual loss, with an incidence estimated to be as high as 2.6 per cent and a prevalence of one to two per cent in patients over the age of 40.1–3 This extrapolates to nearly 200,000 cases of RVO in North America annually.4 RVO may account for as much as 12 per cent of severe visual loss, exhibiting no significant gender or ethnic disparity.5 First described as retinal apoplexy and haemorrhagic retinitis in the late 1800s, RVO has been categorised anatomically as central or branch RVO, the latter being four to six times more common.6 Central RVO blocks all venous outflow, whereas branch RVO may be occlusion of a first-order (hemispheric or quadrantic) or second-order (macular or twig) tributary. A hemi-central RVO involves blockage of one of two central retinal vein trunks within the optic nerve head, an anatomical variation found in only 20 per cent of the population, making hemi-central RVO the least common form of RVO.7,8 Whether hemi-central RVO is best classified as a variant of central or branch RVO has yet to be agreed upon.9 The term venous stasis retinopathy and the modifiers impending, incipient, partial or incomplete have been used in describing asymptomatic yet at-risk patients.10 Differential diagnoses include but are not limited to ocular ischaemic syndrome, papilloedema and diabetic and radiation retinopathies.11

**CLINICAL FEATURES**

A patient with RVO typically presents with symptoms that include a painless and unilateral reduction in central vision and visual field of variable severity. Prodromal symptoms such as amaurosis fugax that are common in arterial occlusive disease are rare in RVO.12 Initially, symptoms depend primarily upon the severity of macular oedema and retinal haemorrhaging, later upon the complications of prolonged retinal oedema and ischaemia, including secondary neovascularisation.13 Visual acuity (VA) at presentation tends to be 6/15 to 6/18 in both ischaemic and non-ischaemic branch RVO.14 As many as 99 per cent of eyes with ischaemic central RVO present with VA of 6/60 or worse and nearly half show significant restrictions in peripheral visual field. Most also demonstrate a relative afferent pupillary defect, perhaps the most sensitive and specific predictor of ischaemic central RVO.

The ophthalmoscopic appearance of central RVO has been described poetically and accurately as a blood and thunder or ‘tomato ketchup’ fundus (Figure 1). Central RVO exacerbates venous stasis, increases the intraluminal pressure by up to 24 times, up-regulates inflammatory mediators, including vascular endothelial growth factor (VEGF) and compromises the inner blood-retinal barrier.15 This leads to transudation of blood and plasma from the dilated and tortuous retinal veins, producing optic nerve head oedema, and intraretinal haemorrhages and oedema through all four quadrants of the retina, including the macula. The appearance of hemi-central RVO is similar but confined to one retinal hemisphere. Chronic macular oedema may damage glial and retinal pigment epithelial cells, further reducing retinal fluid clearance. Aqueous flare may be noted, evidence of the inflammatory nature of RVO.16 The presence or absence of retinal ischaemia is an important consideration, particularly in central RVO, although it has been suggested that all central RVOs demonstrate ischaemia to some degree. Ischaemic central and hemi-central RVO (representing 20 to 30 per cent of both diagnoses) exhibit all retinal morphological alterations to a more severe extent and are further typified by retinal nerve fibre layer haemorrhages and numerous cotton wool spots.17 Ischaemia is thought to result from both inflammation and the oedema-mediated increase in interstitial pressure physically compressing capillaries and compromising perfusion. Pre-existing
Atherosclerosis causing arteriolar insufficiency exacerbates the hypoxia. Reduced blood flow in macular capillaries is worsened by hyperviscosity, causing further ischaemic damage to the vascular endothelium. Ischaemic central RVO may also involve occlusion of the central retinal artery at the level of the lamina cribrosa. It has been hypothesised that the obstruction in non-ischaemic central RVO is posterior to the lamina cribrosa, allowing anterior central retinal vein tributaries within the optic nerve to develop collateral channels, improving drainage and perfusion.

The retinal appearance of branch RVO is similar to that of central RVO but confined to the sector drained by the affected vessel and the absence of optic nerve head oedema. Four out of five branch RVO are found at arterio-venous crossings and as many as two in three are found in the temporal retina due to the high number of such crossings. In nearly two-thirds of arterio-venous crossings in controls, the relatively thick-walled arteriole lies superficial to the venule, while in cases of branch RVO, a more superficial arteriole is essentially universal. In addition to mechanically compressing the vein against the retina, a damaged arteriole may trigger venous constriction through the release of endothelin-1. Depending upon severity and proximity to the macula, patient symptoms vary, with superior temporal branch RVO tending to be accompanied by macular oedema twice as often as those in other quadrants.

RVO is a very elegant example of a red (haemorrhagic) infarct, whereas retinal arterial occlusion typifies a white (ischaemic) infarct. Regardless of mechanism, unresolved infarction results in tissue death; tissue death results in visual loss. Over time, as many as 77 per cent of patients presenting with RVO will develop collateral vessels, alternate pathways of venous outflow that arise as a compensatory response to the obstruction. This percentage seems to rise with severity of occlusion. Collateral formation in central RVO occurs at the optic nerve head, whereas that in branch RVO is most often temporal to the macula (Figure 2). Should venous outflow improve naturally or through prompt treatment, collateralisation may become unnecessary. While many clinicians consider collateralisation to be beneficial, it may not serve to expedite the resolution of macular oedema despite reducing interstitial hydrostatic pressure within the retina. In fact, final VA may be worse in the presence of collaterals, perhaps testament to the severity of the initial occlusion.

The ophthalmoscopic assessment of RVO can be complemented through a number of ancillary investigations. In the presence of extensive haemorrhaging, as many as one in three intravenous fluorescein angiographies may be difficult to interpret at presentation, making fluorescein angiography of strong predictive value no earlier than three months. Choroidal filling is normal, while the amount of perifoveal perfusion and macular oedema are strong prognostic indicators of the final VA. Late-phase fluorescein angiography will show variable staining of the optic nerve head and retinal veins. Typically, ischaemic central RVO will show poor perifoveal perfusion and 10 to 30 plus disc areas of peripheral capillary non-perfusion. An ischaemic branch RVO will

Figure 1. Central retinal vein occlusion. (Image courtesy of Jason Calhoun, Mayo Clinic, Jacksonville, Florida, USA)

Figure 2. Branch retinal vein occlusion. (Image courtesy of Maria Whitman, Carolina Eye Associates, Southern Pines, North Carolina, USA)
demonstrate five or more disc areas of non-perfusion.\textsuperscript{29} In central RVO, ischaemia predisposes to neovascularisation of the iris and/or the angle. Therefore, although RVO is characterised as a retinal disease, careful non-dilated anterior segment biomicroscopic and gonioscopic examination is essential, with particular attention paid to the pupillary margin. Neovascularisation of the iris is noted in 16 to 21 per cent of all central RVO but 35 to 85 per cent in the presence of ischaemia, typically within the first six months. The risk of anterior segment neovascularisation increases from 16 per cent in eyes with less than 30 disc areas of non-perfusion to 52 per cent in eyes with more than 75.\textsuperscript{30} Neovascular glaucoma develops in eight per cent of all central RVO but as many as 82 per cent of ischaemic central RVO. Intraocular pressure (IOP) must be carefully monitored and if left untreated, neovascular glaucoma can be devastating, leading to blindness in three of four cases and phthisis bulbi in one of four. Anterior segment neovascularisation is rare in hemi-central and branch RVO but posterior segment neovascularisation may arise due to the preservation of viable retinal vasculature supporting new vessel growth. This neovascularisation elsewhere typically arises at the junction of perfused and non-perfused retina.

Given that macular oedema is a common cause of visual loss, optical coherence tomography is helpful in documenting its extent upon presentation and in follow-up. Cystic intraretinal oedema, diffuse retinal thickening and subretinal fluid may be observed. Cystic oedema appears to be more disruptive than diffuse thickening or subretinal fluid. Preservation of both the photoreceptor integrity line (the junction between inner and outer photoreceptor segments or IS/OS line) and the external limiting membrane are important prognostic indicators of good post-event VA.\textsuperscript{31–33} Thinning of the retinal nerve fibre layer may indicate more significant retinal ischaemia. Fundus autofluorescence is increased in the presence of macular oedema and photoreceptor loss.\textsuperscript{34} These observations may help explain persistent poor VA following near-complete resolution of macular oedema and guide treatment toward those eyes most likely to realise improvement.

Strong prognostic indicators of poor outcome include older age, duration and degree of VA reduction, and duration and amount of macular oedema, haemorrhaging and ischaemia at presentation.\textsuperscript{35,36} In general, visual outcome is good in non-ischaemic RVO, where the primary source of poor vision is macular oedema but poor in ischaemic RVO, where macular oedema is a relatively minor factor.

Prompt resolution of macular oedema is desirable given that permanent photoreceptor damage can occur within three months.\textsuperscript{37} Such resolution does not lead to a linear improvement in VA. In the case of central RVO, patients with initial VA of 6/12 or better retain that in 65 per cent of cases and 90 per cent remain better than 6/60. Conversely, 79 per cent of those presenting with VA of 6/60 or less do not show significant improvement and demonstrate a six times greater likelihood of developing neovascular complications. Using a relative afferent pupillary defect in concert with analysis of the amplitude of the b-wave electroretinogram, investigators were able to correctly identify 97 per cent of ischaemic central RVO. A definitive and prompt differential diagnosis at presentation is critical. In non-ischaemic central RVO, the average patient will lose 10 letters of acuity at six months but only three at 12 months; however, in ischaemic central RVO an average loss of 15 letters at six months becomes 35 by 12 months. Indeed, only 10 per cent of patients presenting with ischaemic central RVO maintain a final VA better than 6/120.\textsuperscript{38} Continued vigilance is required as conversion to ischaemic central RVO heralded by acuity dropping to 6/60 or less occurs in up to 34 per cent of initially non-ischaemic cases within three years, albeit most rapidly in the first four months.\textsuperscript{39} That being said, given that much of our knowledge of the natural history of central RVO has been derived from post-hoc analyses, any prognostication must be taken with a grain of salt.\textsuperscript{40}

\textbf{PATHOPHYSIOLOGY AND RISK FACTORS}

While the pathogenesis of RVO has yet to be fully elucidated, it appears multifactorial and different for central versus branch RVO, although arterial disease is felt to be the primary aetiology in both presentations. Studies have suggested a common systemic cardiovascular risk profile, more so for ischaemic RVO, consistent with diffuse disease of the vascular endothelium.\textsuperscript{41} RVO may be categorised as primary in the absence of contributing systemic disease and secondary in its presence.\textsuperscript{42,43} Several mechanisms have been proposed, at least in part dependent upon the anatomical location of the occlusion.\textsuperscript{44} Shortly after its initial identification, some attributed central RVO to thrombosis within the central retinal vein at or posterior to the lamina cribrosa, while others blamed intimal wall thickening and dissection. Arteriolar/sclerotic thickening of an arterial wall where artery and vein share a common adventitial sheath may cause compression of either the central or a branch retinal vein. This may ‘pinch off’ the lumen of the vein at the level of the lamina cribrosa, where the central retinal vein naturally narrows in healthy aging eyes, disrupting laminar flow and increasing the likelihood of thrombus formation. Akin to other venous occlusive processes, the Virchow triad of hypercoagulability, vascular turbulence and stasis and endothelial injury can explain the pathophysiology of RVO.\textsuperscript{45}

Peripheral arterial disease, coagulopathies, particularly in younger individuals, complicated diabetes with end-organ damage, associated with a two-fold increase in risk of central RVO and hypertension and hyperlipidaemia, two critical systemic risk factors for RVO, must be considered.\textsuperscript{46–48} Diabetes appears to be of more significance in central RVO, whereas hypertension is more prevalent in branch RVO.\textsuperscript{49} Carotid artery disease is an important comorbidity requiring investigation.\textsuperscript{50} Increased blood viscosity may exacerbate stasis of venous flow and, in fact, hyperviscosity syndromes may cause retinopathy clinically indistinguishable from central RVO.\textsuperscript{51} Dehydration and smoking both increase blood viscosity leading to stagnation of microcirculation, one of the principle causes of capillary non-perfusion.

Thrombophilia is the propensity to develop venous thrombosis due to abnormal coagulation. It may be congenital or acquired and has long been an area of interest, particularly in younger patients, among whom the pathogenesis of RVO may differ from that of older patients with coexisting atherosclerosis. An imbalance in clot formation versus clot breakdown (increased coagulation and decreased fibrinolysis) has been reported in patients with central RVO and predisposes to neovascularisation.\textsuperscript{52} A meta-analysis of nearly one-half million patient files indicated a relative risk for central retinal vein occlusion of nearly 2.5 times in the presence of a hypercoagulable
state, including hyperhomocysteinaemia, a recognised risk factor for both arterial and venous thrombosis.\textsuperscript{53} There is an increased risk of RVO in otherwise healthy young women using oral contraceptive medications, known to increase thrombus formation.\textsuperscript{43,50} Conversely, the risk of RVO is 70 per cent lower in post-menopausal women being treated with exogenous estrogen, consistent with the reduced cardiovascular risk profile associated with hormone replacement therapy.\textsuperscript{54} The factor V Leiden mutation may increase the risk of RVO through its effects on activated protein C (an inhibitor of clot formation).\textsuperscript{55} Some young patients presenting with RVO demonstrate significantly increased resistance to activated protein C and should be counselled on their increased risk of deep vein thrombosis and pulmonary embolism, cautioned against smoking and carefully monitored if using oral contraceptives or undergoing surgery.

Obstructive sleep apnoea (a disorder characterised by intermittent cessation of breathing during sleep) is estimated to affect one in four middle-age men and may independently double the annual incidence of RVO.\textsuperscript{56} Patients with RVO and obstructive sleep apnoea share a number of common risk factors, including hypertension and tendencies to hypercoagulate, and hypoxia-mediated dilation of the central retinal artery may compress the central retinal vein at the lamina cribrosa.

Systemic vasculitis, as evidenced by elevated C-reactive protein and erythrocyte sedimentation rate, may predispose to RVO. Erythrocyte sedimentation rate seems more important in females and less important in branch RVO. While matrix metalloproteinase 2 gene variants appear to increase susceptibility to RVO, pro-atherosclerotic inflammation-related gene polymorphisms at the interleukin and tumour necrosis factor alleles have not been confirmed as independent risk factors.\textsuperscript{59-61} Treatment with systemic anti-inflammatory agents has been inconclusive.\textsuperscript{62}

Ocular hypertension is an important ophthalmic consideration in RVO. Ocular hypertension may cause physical compression of the central retinal vein as it passes through the lamina cribrosa, which itself may be anatomically altered by increased IOP. This may lead to disturbed laminar fluid flow and thrombus formation. In the presence of glaucoma, the incidence of central RVO may be as high as 4.5 per cent. Studies have found an odds ratio of 5.4 for a history of glaucoma in patients with central RVO and glaucoma may be found in as many as 29 per cent of cases of central RVO.\textsuperscript{63} In patients with central RVO, fellow eyes demonstrate a statistically higher IOP than in controls. It has been suggested that the unique anatomy of the central retinal vein characterising hemi-central RVO may predispose to concurrent open-angle glaucoma.\textsuperscript{64} IOP-lowering therapy helps improve perfusion in the presence of RVO and may be considered in the fellow eye, which has a 10 per cent risk of RVO development. Indeed, nine per cent of contralateral eyes may show evidence of prior or concurrent RVO. Despite lacking elevated IOP, eyes with normal-tension glaucoma also demonstrate an increased risk of RVO.\textsuperscript{65} In such cases, the risk of permanent VA reduction seems higher, perhaps due to the pre-existing vascular insufficiency that may accompany normal-tension glaucoma and the fact that branch RVO seems to occur closer to the optic nerve head, causing more retinal ischaemia.

Although central retinal vein occlusion tends to be a disease of the elderly, one in six is found in patients younger than 55 years. The clinical course of this subgroup is more variable and presenting VA does not seem to be as important a prognostic indicator as in older patients. Presenting VA tends to be slightly better at 6/15 versus 6/24, although final VA is statistically more likely to drop precipitously, secondary to macular oedema or vitreous haemorrhage, often within the first several months. Interestingly, there is also a greater likelihood of initial poor acuity improving in younger patients, albeit slowly. The typical systemic vascular profile is observed, with two in three having a history of hypertension, diabetes and/or hyperlipidaemia. Bilateral central RVO in a young patient is strongly suggestive of a haematologic or coagulation disorder.\textsuperscript{66} The risk of anterior segment neovascularisation is comparable, while posterior segment neovascularisation is more common in younger individuals. Both may occur late in the clinical course, necessitating vigilant monitoring.

**TREATMENT**

Regardless of age, treatment of contributing systemic vascular conditions is important to prevent both life- and sight-threatening complications, including involvement of the fellow eye.\textsuperscript{67} RVO may be independently associated with increased cardiovascular mortality.\textsuperscript{68} In male smokers, the 10-year relative risk of developing cardiovascular complications after RVO is more than four-fold that of controls. Increased physical activity and, interestingly, moderate alcohol consumption decrease the risk of central RVO.

Treatment of the RVO itself may be directed at the aetiology or the sequelae of the occlusion. Reduction of blood viscosity through haemodilution leads to increased blood velocity in areas of compromised retinal microcirculation and improves the visual prognosis of some patients with central RVO.\textsuperscript{69} Due to the risk of increasing ischaemia, this treatment may be best avoided in patients with concurrent cardiovascular, renal or pulmonary comorbidities, describing the majority of patients with RVO. More targeted treatment early in the course of moderate non-ischaemic central RVO, selectively reducing red blood cell count alone, may improve VA, reduce central retinal thickness and prevent conversion to ischaemic central RVO, while maintaining a more favourable systemic safety profile.\textsuperscript{70}

Systemic heparin, streptokinase and tissue plasminogen activator have been used (heparin as early as 1938) to ‘tip the balance’ from thrombogenesis to thrombolysis. Although decreased systemic coagulability seemed universal after treatment, improvement in vision was not, supporting a multifactorial aetiological hypothesis of central RVO being due to more than thrombus formation alone. Particularly with streptokinase, secondary and immediate vitreous haemorrhage exacerbated visual loss in a number of patients. Building upon its long track record in the treatment of cardiovascular and cerebrovascular disease, the use of systemic tissue plasminogen activator in concert with acetylsalicylic acid, a platelet aggregation inhibitor, was viewed with optimism; however, a prospective study over nearly 40 years suggested that patients taking anticoagulants and/or aspirin at presentation with central RVO consistently showed more retinal haemorrhaging, poorer VA and more visual field loss than patients who were not.\textsuperscript{71} There may be an important distinction between the aetiology and treatment of central RVO versus deep vein thrombosis based upon the role of the adjacent central retinal artery. It is also important to note that patients taking such medications may be doing so as a result
of systemic risk factors that predispose to central RVO. Some authors have gone as far as to suggest that warfarin and acetylsalicylic acid are independent risk factors for central RVO and advise against their use in treatment. Conversely, others believe that acetylsalicylic acid increases optic nerve head blood flow and leads to more rapid resolution of macular oedema associated with non-ischaemic central RVO. Retinal endovascular fibrinolysis, the direct injection of tissue plasminogen activator into an occluded central retinal vein post-vitreectomy with or without ancillary intravitreal steroid or scatter laser, promotes visual recovery superior to natural history, while mitigating the potential side effects of systemic tissue plasminogen activator. Prompt administration of treatment prior to thrombus organisation appears to improve success.

Creation of a therapeutic chorioretinal anastomosis, an alternative drainage pathway bypassing the site of obstruction by directly connecting venous outflow to the choroidal bed, may be considered for perfused RVO. Successful laser anastomosis creation appears possible in three of four cases, particularly with direct venous puncture in younger patients with better baseline VA. This results in a relative VA advantage of eight to 12 letters versus control over 18 months of follow-up. Conversion to ischaemic RVO may be prevented. Complications including vitreous haemorrhage and choroidal neovascularisation seem more frequent with high-intensity laser treatment and physical incisional surgery and in the presence of systemic hypertension and retinal ischaemia.

Arteriovenous sheathotomy, the surgical separation of retinal artery and vein through cutting the common adventitial sheath, may be employed in conjunction with vitrectomy to relieve venous compression in branch RVO. While reduction of macular oedema and prevention of neovascularisation are often achieved, VA improvement is more equivocal. In some cases, resolution of macular oedema occurs despite sheathotomy being anatomically impossible, raising questions about the relative contributions of decompression versus stand-alone vitrectomy.

Given the above and the fact that vitreomacular traction may exacerbate macular oedema, vitrectomy alone has been studied as a means to release traction, remove angiogenic agents and improve oxygenation to the inner retina. A number of inflammatory mediators, including VEGF and agents within the interleukin and C-reactive protein families have been isolated and directly correlated with increased macular oedema in eyes with RVO. Conversely, the anti-inflammatory activity of pigment epithelium derived factor appears to be down-regulated. Given the increasing popularity of intravitreal injections in the treatment of macular oedema and the potential reduction in their efficacy post-vitrectomy, this approach is likely to face continued scrutiny.

The theory of neurovascular compression within the optic nerve at the level of the lamina cribrosa birthed radial optic neurotomy as a treatment modality. Radial optic neurotomy involves a radial incision made parallel to the retinal nerve fibre layer on the nasal aspect of the optic nerve head to the level of the lamina cribrosa/scleral ring, sparing the temporal papillomacular retinal nerve fibre bundle. In theory, this decompresses the central retinal artery and vein at an anatomical bottleneck, alleviating a potential ‘compartment syndrome’. Individual variations, including smaller than average scleral ring or thickening of the adventitia, may predispose some patients to neurovascular compression, further narrowing the lumen of the central retinal vein, increasing turbulence and the potential for thrombus formation. In an initial case series, 90 per cent of patients with severe central RVO experienced anatomical resolution and rapid clearing of haemorrhaging, with 73 per cent ultimately improving in VA by an average of five Snellen lines. Subsequent randomised prospective studies and anatomical rationalisation of the role of compartment syndrome have been equivocal. It has been hypothesised that at least part of the success of radial optic neurotomy is attributable to the accompanying vitrectomy or the induction of an opticociliary anastomosis. Given the potential for serious complications, including neovascularisation, globe perforation and catastrophic intraocular haemorrhage due to laceration of the central retinal artery and vein and/or the Zinn-Haller arterial circle, radial optic neurotomy requires an experienced surgeon exercising great care.

Laser photocoagulation was long considered the gold standard for the treatment of RVO sequelae despite rather modest functional (VA) improvement. The Branch Vein Occlusion Study concluded that macular grid photocoagulation is indicated for the reduction of persistent macular oedema secondary to branch RVO when VA is less than 6/12. While treatment should be deferred for three months to allow for the spontaneous improvement that characterises the natural history of branch RVO, greater VA improvement was noted when laser treatment was initiated within 12 months. Treatment must be deferred in the face of significant haemorrhaging and is not helpful in the presence of macular ischaemia. Unlike branch RVO, visual loss in central RVO is not responsive to grid laser therapy even in the face of intravenous fluorescein angiographic evidence of a significant reduction in macular oedema. In fact, following the Central Vein Occlusion Study, observation remains the standard of care for central RVO-associated macular oedema. This difference likely reflects the diffuse capillary leakage characterising central RVO as opposed to the more focal nature of branch RVO. While preventative peripheral scatter photocoagulation may be considered in ischaemic branch RVO, panretinal photocoagulation is only indicated in ischaemic central RVO in the presence of, but not for the prevention of, anterior segment neovascularisation. Panretinal photocoagulation is often successful in inducing regression of the neovascularisation of the iris and angle and preventing neovascular glaucoma through the deliberate destruction of retina and reduction in stimulus for neovascularisation. Neovascularisation shows two to four times the post-treatment regression in panretinal photocoagulation-naïve eyes than in repeat treatment.

Over the past decade, the use of anti-VEGF agents has revolutionised the treatment of retinal vascular disorders, from age-related macular degeneration (AMD) to proliferative diabetic retinopathy to RVO. The VEGF family was identified in 1989, although the presence of an angiogenic ‘factor X’ responsible for anterior segment neovascularisation was proposed 40 years earlier. VEGF-A through to F and placental growth factor regulate angiogenesis and vascular permeability, VEGF-A, initially known as vascular permeability factor, has emerged as the isomer primarily responsible for ocular angiogenesis, and is generally abbreviated simply as VEGF. Low levels of systemic VEGF are critical for normal physiologic function and tissue maintenance. The primary producers of intraocular VEGF are the retinal ganglion cells, Müller cells.
and retinal pigment epithelium. VEGF is up-regulated by ischaemia and inflammatory mediators and evidence of its pivotal role in ocular angiogenesis accumulated rapidly. Intraocular administration of VEGF increased retinal ischaemia and vascular permeability and elevated intraocular levels of VEGF were found in many neovascular syndromes including RVO, which demonstrates concentrations up to 33 times that observed in healthy eyes. VEGF increases vascular permeability by loosening tight junctions between endothelial cells, breaks down the inner and outer blood-retinal barrier and promotes endothelial cell migration and proliferation leading to neovascularisation. In cases of ischaemic central RVO, intraocular levels of VEGF are driven by severity of ischaemia and are strongly correlated with future neovascularisation. There is a direct correlation between VEGF levels and macular thickness, and an inverse relationship with VA. While the pathogenesis of vascular disease is multifactorial, the inhibition of VEGF alone is sufficient to inhibit neovascularisation.

Steroids prevent breakdown of the blood-retinal barrier by, among other mechanisms, indirectly inhibiting VEGF and other inflammatory mediators, including interleukins and prostaglandins, critical protagonists in the final pathway to retinal ischaemia. Intravitreal injection or implantation of steroid allows for high intraocular concentrations, while minimising systemic absorption and side effects. Over the last decade, several studies, including the SCORE Series, have shown intravitreal preservative-free triamcinolone acetonide to be nearly five-fold superior to standard care (observation as per the Central Vein Occlusion Study) with respect to VA improvement in non-ischaemic central RVO. Eyes with branch RVO did not respond better to intravitreal triamcinolone acetonide than to standard care (grid laser when VA was less than 6/12 as per the Branch Vein Occlusion Study). In fact, grid laser proved beneficial across a wide range of visual acuities and remained standard care. Intravitreal triamcinolone acetonide may be effective as an adjunctive treatment to grid laser. Eyes with hemi-central RVO appear to respond to intravitreal triamcinolone acetonide in a manner akin to branch RVO, suggesting that the two occlusions share clinical similarities. There was no statistically significant reduction in macular oedema or long-term neovascular events in the treatment groups when compared to standard care. Therefore, the significant improvement in VA in central RVO was not secondary to a simple reduction in central retinal thickness, emphasising the importance of inflammation. Microperimetry demonstrates improved macular sensitivity in non-ischaemic central RVO after intravitreal triamcinolone acetonide. The response to intravitreal triamcinolone acetonide is short-lived, necessitating administration every four months for persistent macular oedema and may demonstrate tachyphylaxis, losing effectiveness beyond one year despite repeated injections. Dose-dependent steroid-specific side effects include cataract formation and ocular hypertension, the latter in 30 to 50 per cent of cases. Use of the lowest effective steroid dose provided an adverse event profile similar to that of observation alone.

It has been suggested that the risks of repeated intravitreal triamcinolone acetonide may be addressed through the use of sustained-release steroid liquid or implant. Due to its relatively short intravitreal half-life but anticipated longer duration of effect, the injectable Ozurdex biodegradable dexamethasone insert may prove to be the steroid of choice. Through the GENEVA trials investigating both central and branch RVO, Ozurdex proved safe and effective in improving VA and reducing central retinal thickness at 90-days after initial and repeat treatments. A mean 10-letter improvement occurring within 90 days wanes to three letters at day 180, meaning that more frequent injection may be necessary but does appear successful. Duration of macular oedema at initiation of treatment was a strong independent predictor of post-treatment VA improvement and macular oedema reduction. Intraretinal haemorrhage improves and active neovascularisation stabilises more rapidly in treated eyes. Ocular hypertension proved relatively rare, peaking at day 60, typically responding to topical treatment and normalising by day 180 after initial and repeat treatment. Cataract progression was more common following repeat treatment.

Fluocinolone acetonide implants have shown near-universal cataract formation and IOP increase to greater than 30 mmHg in two-thirds of eyes, necessitating filtration surgery in one-third and explant of the insert in several. Still, regulators have granted approval for the treatment of inflammatory and neovascular syndromes not adequately addressed by other therapies.

Research around specific therapeutic inhibition of the four principle VEGF isoforms containing 121, 165, 189 and 206 amino acids led to the development of aptamers (oligonucleotide ligands that selectively bind to molecular targets), fusion proteins and antibodies and antibody fragments. Pegaptanib sodium is an RNA aptamer with a molecular weight of 40 kDala (kDa) that binds selectively to VEGF, the most prevalent isoform in ischaemia-mediated macular oedema and ocular angiogenesis. Ranibizumab is a 48 kDa antibody fragment that binds to all VEGF isoforms. Aflibercept is a 115 kDa pan-VEGF receptor decoy that also binds placental growth factor. These ophthalmic agents are complemented by bevacizumab, a 149 kDa full-length antibody with two binding sites for all VEGF isoforms approved for systemic treatment of advanced carcinoma in 2004. Pegaptanib sodium (Macugen) became the first aptamer approved for human use in 2004. Its intravitreal use has been evaluated in diabetic macular oedema, AMD and central RVO. Specific to the last, intravitreal pegaptanib at six-week intervals provided a relative improvement in mean VA of 10 to 12 letters, greater mean decrease in central retinal thickness and less neovascularisation than observation alone. Studies again confirmed that decreased macular oedema does not directly correlate with improved VA. Intravitreal pegaptanib may be an effective alternative to intravitreal triamcinolone acetonide and/or non-selective anti-VEGF agents. It has been suggested that non-selective or pan-VEGF blockade may be detrimental due to blocking neuroprotective isoforms of VEGF essential in retinal homeostasis, adaptive response to ischaemic insult and prevention of apoptosis. Further, anti-VEGF mediated decreases in nitrous oxide production by endothelial cells may exacerbate macular ischaemia and reduce collateral formation.

Ranibizumab (Lucentis) and off-label bevacizumab (Avastin), both non-selective pan-anti-VEGF agents, have taken the retinal world by storm. Intravenous bevacizumab at the oncologic dosage of 5.0 mg/kg reduces macular oedema and improves VA in neovascular AMD. In 2005, intravitreal bevacizumab was first administered to a patient with AMD refractory to all other treatments. Studies indicated that
intravitreal bevacizumab is as efficacious as intravenous administration, while mitigating the risk of transient ischaemic attacks, stroke and myocardial infarction. Subsequently, intravitreal bevacizumab was considered in a number of ocular neovascular syndromes, including but not limited to proliferative diabetic retinopathy, pathologic myopia, angioid streaks, peripapillary choroidal neovascularisation and RVO. Retinal penetration was good despite its molecular weight being above the retinal exclusion limit of 76 kDa. No retinal toxicity was noted even at intravitreal bevacizumab doses of 5.0 mg, four times the customary dose. Given its indications for systemic use, bevacizumab is supplied in either four or 16 ml vials with a concentration of 25 mg/ml. Compounding pharmacies must partition it using aseptic techniques to allow for more typical 1.0 to 1.25 mg off-label intravitreal bevacizumab dosages. Despite the risk of contamination associated with compounding, there is significant economic incentive to continue this practice: intravitreal bevacizumab can be one-fortieth the price of intravitreal ranibizumab. Incidents of endophthalmitis have led some to suggest compounding single rather than multiple doses of intravitreal bevacizumab, increasing costs but minimising risks.

Eyes with central RVO treated with intravitreal bevacizumab tend to demonstrate significant decreases in central retinal thickness within two weeks, preceding peak improvement in VA (Figure 3). VA improvement was greatest in patients symptomatic for less than three months, while central retinal thickness decrease was independent of symptom duration. Although treatment of central RVO may lead to greater relative reduction in central retinal thickness, treatment of branch RVO tends to yield more improvement in VA. Intravenous fluorescein angiography demonstrates a marked reduction in dye leakage within one week of treatment (Figure 4). Intravitreal bevacizumab is also efficacious in reducing or inducing regression of neovascularisation of the iris and angle and neovascular glaucoma, often dramatically within days of administration. Benefits tend to be sustained at 12 months providing treatment is continued at intervals no less frequent than every 12 weeks. Early initiation of treatment proved important, particularly for patients over the age of 70, who showed a mean VA gain of 21 additional letters with early versus delayed treatment despite equivalent central retinal thickness reduction. Patients not responsive to initial therapy do not show an enhanced response to more intensive treatment. Unlike intravitreal triamcinolone acetonide, intravitreal bevacizumab shows no tendency toward expedited cataract formation. A mild anterior chamber reaction has been reported in approximately 20 per cent of cases. Electrophysiological testing shows no retinal toxicity and no local or systemic adverse effects are consistently reported; however, isolated cases of post-intravitreal bevacizumab ‘rebond’ macular oedema more severe than that noted pre-treatment, perhaps due to up-regulation of VEGF receptors, have been documented. Early growth of an epiretinal membrane has also been noted after intravitreal bevacizumab, although eyes with chronic macular oedema are already prone to epiretinal membrane formation, albeit not typically as early as several months.

Despite being first-line RVO therapy for a slim majority of retinal specialists, intravitreal bevacizumab is being used off-label, whereas intravitreal ranibizumab has been approved for a number of ocular neovascular syndromes, including RVO in 2009. Intravitreal ranibizumab inhibits all isoforms of VEGF, binding with an affinity of 100 to 140 times that of intravitreal bevacizumab. Clinical efficacy appears equivalent to intravitreal bevacizumab with a comparable administration schedule. The CRUISE and BRAVO studies indicated that monthly intravitreal ranibizumab in both central and branch RVO yields an improvement in Early Treatment Diabetic Retinopathy Study (ETDRS) acuity after six months of nine to 14 letters above sham treatment, with the majority of that gain occurring by day seven. The speed of improvement suggests that the bulk of RVO-induced macular oedema is VEGF-mediated, rather than the result of increased venous pressure. In central more so than branch RVO, early response to intravitreal ranibizumab, defined as central retinal thickness of 250 μm or less at month three, was a reliable predictor of longer-term treatment success. Maintenance of the central retinal thickness reduction at month six was two to three times as common with monthly intravitreal ranibizumab as with sham treatment: three of four patients with central RVO and five of six with branch RVO showed no residual macular oedema after intravitreal ranibizumab. As-needed dosing for a subsequent six to 18 months maintained both VA improvement and central retinal thickness reduction and this emphasised the importance of regular follow-up and individualised treatment, particularly for patients with central RVO. Control patients who received intravitreal ranibizumab beginning at month six showed comparable mean central retinal thickness reduction but less VA improvement than those treated earlier—more evidence of the indirect relationship between reduced macular oedema and improved VA and an argument in favour of early treatment.

Intravitreal ranibizumab speeds the resolution of intra-retinal haemorrhage, theoretically allowing for earlier concomitant grid
laser in cases of branch RVO. While CRUISE and BRAVO suggested that intravitreal ranibizumab appears to slow the progression of retinal non-perfusion and may improve reperfusion in RVO, eyes with significant pre-existing ischaemia may respond quite differently to anti-VEGF therapy. As with intravitreal bevacizumab, weaning patients off treatment altogether has proven difficult.154

Interestingly, one of the purported advantages of intravitreal bevacizumab or ranibizumab versus intravitreal triamcinolone acetonide and steroid implants is IOP stability; however, a statistically significant and sustained elevation of IOP after intravitreal bevacizumab or ranibizumab may be noted, not attributable to the addition of volume alone, and more so in patients already diagnosed with glaucoma.156,157 Proposed mechanisms include pharmacologic increase, trabeculitis or physical trabecular meshwork blockade. The latter may explain the slightly greater rate of IOP elevation with the larger molecular weight bevacizumab, although the compounding required for intravitreal bevacizumab or ranibizumab may be contributory. Given that the number of patients receiving intravitreal bevacizumab or ranibizumab is only likely to increase, more investigation is necessary.

Afibercept (Eyelea or VEGF Trap-Eye) binds both VEGF and placental growth factor, another mediator of retinal vascu-

In the GALILEO study, intravitreal aflibercept proved superior to sham in the treat-
maintenance of central RVO-associated macular oedema, providing a mean VA gain of 18 ETDRS letters and a near 450 µm reduction in central retinal thickness following six monthly injections.161 Similar efficacy was demonstrated through the COPERNICUS study, with a mean 17 letter gain in VA and 413 µm central retinal thickness reduction was main-
tained after six more months of careful as-needed dosing. For patients initially assigned to sham treatment, as-needed dosing beginning at six months produced impressive reductions in central retinal thickness but limited improvement in VA. Again, this implicates chronic macular oedema as a source of irreversible photoreceptor damage and supports prompt intervention. Based on these results, FDA approval for intravitreal aflibercept treatment of central RVO was granted in late 2012.164

While significant differences between study designs and populations make direct comparison of RVO treatments difficult, there may be advantages to exploit and syn-

In some trials, ischaemic complications were investigated intravitreal bevacizumab appears amenable to combination of bevacizumab plus triamcinolone acetonide in both primary and repeat treatment.166 Others have investigated intravitreal bevacizumab plus Ozurdex and conclude that combination therapy may be synergistic in improving VA and lengthening the time required between treatments, particularly after central RVO.167 In the case of central RVO, it may be reasonable to consider a ‘loading dose’ of six-monthly intravitreal ranibi-
zumab injections followed by ongoing monthly follow-up with treatment dictated by VA and/or central retinal thickness. In the case of branch RVO with macular oedema, anti-VEGF treatment for the first six months could be followed by grid laser, should macular oedema persist or recur.168 In some trials, ischaemic complications were experienced despite anti-VEGF treatment, prompting investigators to suggest that con-
current laser treatment may be necessary for ischaemic central RVO. Panretinal photocoagulation and peripheral scatter laser remain the most effective treatments for permanently reducing VEGF expression and ischaemic complications following RVO.\textsuperscript{166} Although laser may lessen the future anti-VEGF treatment burden, it does not guarantee visual improvement beyond that attributed to injection in isolation.

A number of questions remain around the use of anti-VEGF agents in patients with RVO:

1. What is the role of intravitreal bevacizumab, ranibizumab or aflibercept in patients with initial VA better than 6/12?
2. What is the role of intravitreal bevacizumab, ranibizumab or aflibercept in patients with severely reduced VA, likely secondary to advanced macular ischaemia?
3. How long can or should initial intervention be deferred in RVO, realising that spontaneous improvement is possible in up to one in three patients but recognising the detrimental effects of prolonged macular oedema?
4. Can a loading dose followed by a ‘treat and extend’ philosophy adequately address persistent or recurrent macular oedema?
5. Are intravitreal bevacizumab, ranibizumab and aflibercept equivalent in treating RVO?

A partial answer to the last question may be alluded to in the results of the CATT study comparing intravitreal bevacizumab and ranibizumab in the treatment of neovascular AMD.\textsuperscript{170,171} After one year, bevacizumab and ranibizumab administered at the same schedule had equivalent effects on VA, although mean central retinal thickness was reduced slightly more effectively through monthly ranibizumab. At the beginning of year two, some patients initially treated monthly were switched to as-needed dosing but all patients retained their original drug assignment. Such a ‘treat and extend’ or ‘treat and observe’ strategy is the pattern of many retinal specialists. After two years, a small difference in mean VA gain was noted favouring ranibizumab, with the greatest difference between ranibizumab monthly and bevacizumab as-needed. The bevacizumab as-needed group also showed a slightly greater prevalence of residual subretinal fluid. Similar results were found in the IVAN trial. There were inconclusive differences in VA between bevacizumab and ranibizumab and between continuous and discontinuous treatment at one year, although retinal morphologic status favoured continuous treatment.\textsuperscript{172} An accompanying meta-analysis of clinical trials concluded that the two drugs have equivalent effects on VA but that intravitreal ranibizumab and continuous treatment result in greater reduction in central retinal thickness.

However, neovascular AMD and RVO are very different disease processes, making extrapolation difficult if not ill-advised. The dramatically elevated VEGF levels that typify RVO may favour the higher binding affinity of ranibizumab over that of bevacizumab in the immediate reduction of central retinal thickness.\textsuperscript{173} The CRAVE trial, currently underway, has been designed to provide more conclusive answers to this important question.

There is systemic absorption and distribution following intravitreal bevacizumab, which has a serum half-life of 20 days, more so than following ranibizumab with its serum half-life of only six hours. In fact, a therapeutic effect has been noted in an untreated eye with branch RVO following conteralateral intravitreal bevacizumab injection for AMD.\textsuperscript{174} Systemic VEGF levels are reduced 117-fold at day one and four-fold at month one after intravitreal bevacizumab administration, changes comparable to those observed with systemic administration.\textsuperscript{175} Comparative and individual evaluation of systemic thromboembolic events associated with intravitreal anti-VEGF treatment has provided equivocal conclusions. Investigators demonstrated that use of intravitreal bevacizumab and ranibizumab for AMD conferred no increased risk of stroke in patients with no prior cerebrovascular history.\textsuperscript{176}

Meta-analyses of major clinical trials indicated that ophthalmic anti-VEGF therapy did not significantly increase the risk of systemic adverse events.\textsuperscript{177} The overall relative risk of systemic adverse events was slightly greater in the bevacizumab group at both years one and two of the CATT study (1.3 risk ratio), although major adverse events appeared to be of equal frequency in this and other studies.\textsuperscript{178} A 57 per cent increased risk of haemorrhagic stroke has been reported with intravitreal bevacizumab as compared to ranibizumab, while CATT sub-analysis suggested the risk of systemic thromboembolic events was 1.15 per cent with bevacizumab versus 0.15 per cent with ranibizumab.\textsuperscript{179} An Australian population-based study showed no significant difference in systemic adverse events for patients treated with bevacizumab or ranibizumab; however, while myocardial infarction remained rare, it was 2.3 times more likely in the treatment group.\textsuperscript{180} Systemic risks do not appear to be dependent upon frequency of dosing, and it is important to note that patients receiving ophthalmic anti-VEGF therapy often suffer from systemic comorbidities that may predispose them to thromboembolic complications.

The future of retinal vascular disease management seems likely to include nanomedicine gene therapy and targeted drug-delivery systems directed against integrin peptides and non-VEGF mediators of angiogenesis.\textsuperscript{181,182} While initially still requiring intravitreal injection, albeit with potentially reduced frequency and improved target specificity, nanoparticle technology may eventually lend itself to topical drug delivery. Very recently, systemic minocycline has been investigated for its neuroprotective activity in an animal model of branch RVO.\textsuperscript{183} Macular oedema is reduced, inflammatory mediators are down-regulated, microglial activation is prevented and apoptotic pathways are inhibited. While promising, further investigation is pending.

CONCLUSION

Retinal vein occlusion is a relatively common and frequently devastating cause of visual loss primarily as a result of macular oedema and retinal ischaemia and has deservedly received a great deal of attention. First recognised over a century ago, its pathogenesis remains uncertain, although a variety of systemic and ophthalmic risk factors have been identified. For many years, the standard of care remained observation for central RVO and grid laser for branch RVO, as despite the efforts of many investigators, no predictably more effective interventions were identified.

That changed with the advent of intravitreal injections of anti-inflammatory and anti-angiogenic agents, beginning with corticosteroids and evolving to include VEGF antagonists, including pegaptanib, bevacizumab, ranibizumab and aflibercept. Much work remains, including the identification of the most effective single treatment or treatment combination to minimise risk and health-care costs, while optimising patient outcomes in the face of this debilitating condition.
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ACKNOWLEDGEMENTS
The author is indebted to Dr Thomas Freedo and Dr Catherine Chiarelli for their invaluable review and commentary.

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