

The management of retinal vein occlusions: a summary

Retinal vein occlusions (RVO) are the most common cause of visual loss from retinal vascular disease second to diabetic retinopathy. Vision is lost due to ischaemia, macular oedema and / or haemorrhage which ultimately effects a patient's quality of life [1].

Classification

RVO can be classified according to findings on fundus examination. The distribution of haemorrhages generally lies in the quadrant supplied by the occluded vein, see Figure 1. Thrombotic occlusion of the central retinal vein running through the optic nerve at the level of the lamina cribrosa would cause haemorrhages distally in all four quadrants. If the central retinal vein has a physiological bifurcation, and one arm becomes occluded with a thrombus then you can class it as a hemiretinal vein occlusion (HRVO). Haemorrhages would either be distributed along the superior or inferior half of the retina. Essentially, the pathophysiology of a central retinal vein occlusion (CRVO) and HRVO are similar, therefore, the natural progression is assumed to be the same and in studies they tend to be grouped together as one. A branch retinal vein occlusion (BRVO) can involve the macular manifesting with visual symptoms. Haemorrhages along a branch of the central retinal vein occur typically at sites of arteriovenous (AV) crossing where the retinal arteriole compresses and occludes the underlying vein [2-4].

RVO can be sub-classified into ischaemic or non-ischaemic based on clinical findings, this is important as it hints to the future visual prognosis. Ischaemic RVO are likely to develop severe sight-threatening complications such as neovascular glaucoma. Signs associated with an ischaemic RVO will be discussed later.

Epidemiology

The prevalence of RVO increases with increasing age with the highest prevalence seen in >80 year olds (4.6%). The prevalence gleaned from published

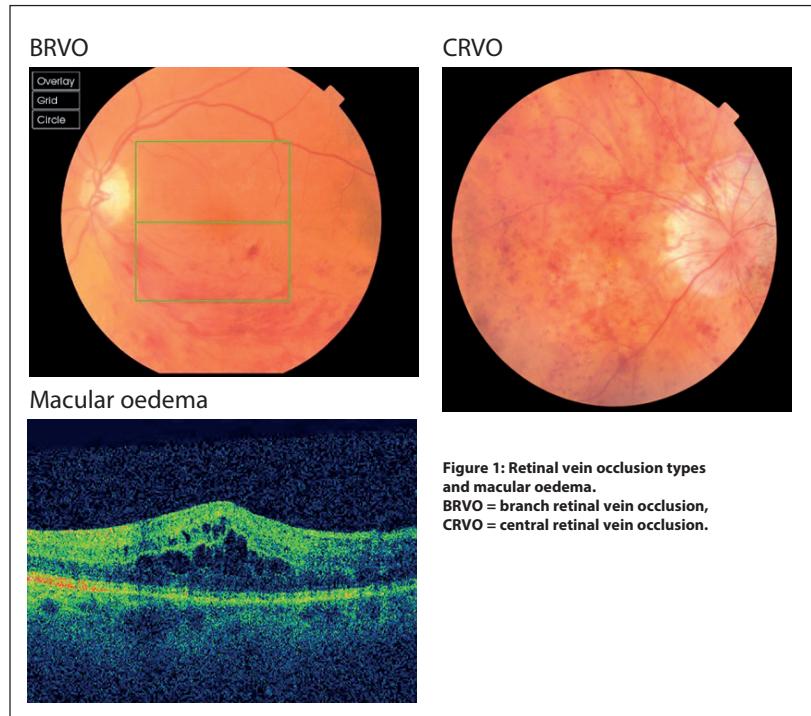


Figure 1: Retinal vein occlusion types and macular oedema.
BRVO = branch retinal vein occlusion,
CRVO = central retinal vein occlusion.

population studies of BRVO, CRVO and HRVO are 0.6-1.1%, 0.1-0.4% and <0.1% respectively. The worldwide estimated prevalence of RVO is approximately 16 million. No gender differences have been found, however, racial differences occur with higher numbers seen in Hispanics and Afro-Caribbean patients compared to Caucasian patients [5-7].

RVO generally present as a unilateral disease. BRVO are three times more common than CRVO. Ten percent of CRVO cases tend to be bilateral, 20% are ischaemic on presentation and 30% of initially non-ischaemic cases eventually develop ischaemia [7].

Risk factors

RVO are associated with increasing age and cardiovascular disease risk factors such as hypertension, hypercholesterolaemia, smoking and obesity [8], or thrombophilia (such as antiphospholipid syndrome and hyperhomocysteinaemia) in patients under 50. Ocular factors such as

hypermetropia (short eyes), raised intraocular pressure and vasculitis are additional risks for RVO [3,4,9].

Presentation

Visual complaints of patients presenting with RVO can vary from asymptomatic to profound visual loss. Patients with CRVO notice a painless, sudden, blurred vision or central scotoma. Reduced vision and pain in a red eye may, however, signify neovascular glaucoma in an eye with raised intraocular pressure (IOP) and neovascularisation of the iris and angle. Visual symptoms of a BRVO would manifest with macular involvement. Otherwise they would be picked up as an asymptomatic incidental finding, especially a nasal BRVO [3,4].

Examination findings

Visual acuity (VA) and pupil response to light in all patients with a RVO should be checked. BRVO not involving the macula would be expected to maintain good VA. A poor presenting VA and the presence

Laser photocoagulation

Settings

- Argon laser machine.
- 1500 – 2000 of 500-micron burns to the retina.
- 0.05-0.1 second applications one burn width apart.
- Energy titrated to a level producing pale retinal burns.

Intravitreal Lucentis 0.5mg/0.05ml



Figure 2: Treatments for complications secondary to retinal vein occlusion.

Intravitreal Ozurdex



Intravitreal Aflibercept



no effect on eyes with ME secondary to CRVO [11]. It is typically administered with the argon laser avoiding the foveal avascular zone and collateral vessels. Uses in ischaemic eyes with neovascularisation are discussed later.

With the emergence of intravitreal treatments, macular grid laser for ME secondary to BRVO has reduced in favour, however, in resistant cases of ME following anti-VEGF treatments, laser can be tried.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is increased in eyes with significant ischaemia including CRVO. When present, VEGF increases vascular permeability and formation of new fragile blood vessels. Treatment with an anti-VEGF treatment should be implemented within six months for a better visual outcome [12].

Steroids

A sustained release implant or short acting Triamcinolone are two intravitreal injections of glucocorticoids that have been trialled to treat ME. Famous trials include the GENEVA Ozurdex studies and the range of SCORE trials [13,14,15]. Both treatments have anti-inflammatory and anti-angiogenic properties. However, they have a greater associated side-effect profile such as cataract progression and raised IOP, compared to anti-VEGF treatments. Such steroid treatments are seen to be more beneficial in pseudophakic patients, and should be avoided in eyes with uncontrolled glaucoma.

The National Institute for Health & Care Excellence (NICE) has approved a list of treatments for the treatment of macular oedema (Table 1).

The COPERNICUS and GALILEO trials found improved vision-related quality of life (NEI-VFQ25) in aflibercept groups compared with sham injection, even in the delayed treatment group. Similarly the CRUISE trial also found an improved vision-related quality of life (NEI-VFQ) in ranibizumab groups compared to the sham group at six months [17,18] (Table 2).

Systemic investigations

Royal college guidelines for systemic investigations for RVO risk factors include [10]: serum blood tests, full blood count, ESR, urea and electrolytes, creatinine, random blood glucose, random cholesterol, plasma protein electrophoresis, thyroid function and blood pressure. Thrombophilia screen for younger patients and specialist investigations in the presence of vasculitis. Any positive findings should be communicated to the patient's general practitioner for monitoring and management.

Treatment

Treatment of cardiovascular disease risk factors should be under the guidance of the patient's general practitioner. Treatment of causes of visual loss secondary to RVO are described briefly above – see Figure 2.

Macular oedema (ME)

ME is a cause of visual loss in patients with RVO. Medical treatments exist targeting intra-retinal fluid resolution and stabilisation of visual function. Several treatments now exist to treat ME secondary to B/CRVO, however, a percentage of patients may see spontaneous resolution.

Argon photocoagulation

Retinal argon laser is the treatment of choice for macular oedema secondary to BRVO, but famously the CVOS trial showed

of an relative afferent pupillary defect (RAPD) signifies significant ischaemia and is associated with a poor prognosis. IOP should be checked and treated medically if raised. VA can also be used to monitor for progression and treatment effect [3,4].

The retina will have scattered retinal haemorrhages in various distributions for which the classification of RVO type can be made, as mentioned earlier. Other retinal features of a RVO include: dilated, tortuous retinal veins, cotton wool spots, macular oedema, retinal and optic disc oedema. The presence or absence of neovascularisation on the iris, disc or elsewhere on the retina should also be documented as this signifies significant ischaemia. Other signs of ischaemia include multiple dark, deep intra-retinal haemorrhages and cotton wool spots. Signs of chronicity include the presence of collateral vessels [3,4].

Investigations

Imaging

Optical coherence tomography (OCT) aids in the diagnosis of macular oedema – see Figure 1. The presence and amount of intraretinal fluid can be measured and used to monitor changes with treatment and progression.

Fundus fluorescein angiography (FFA) aids identification of a RVO in chronic cases. Leaky new vessels and areas of capillary non-perfusion and ischaemia can also be identified.

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Neovascularisation

Neovascularisation occurs in approximately 20% of eyes within six to 12 months commonly in eyes with greater than 10 disc diameters of retinal capillary non-perfusion. This level of ischaemia gives rise to development of these freely growing blood vessels that are at risk of causing sight-threatening vitreous haemorrhage and neovascular glaucoma [3,4].

Retinal neovascularisation should be treated with pan-retinal photocoagulation

Table 1: NICE approved treatments for macular oedema.

Drug	Studies	Summary of study	Results CRVO	Results BRVO
Ozurdex	Geneva trial (2010) Treatment of macular oedema secondary to CRVO [13,14].	Population 154 eyes Treatment dexamethasone intravitreal implant. Groups 0.35 mg (n=136) vs. 0.7mg vs. sham treatment (n=147). Study period Six months, plus six-month open label extension.	BCVA 0.7mg 0.1 letter gain, loss of 1.8 in the sham group ($p<0.001$). Persisted in extension. Peak effect at 90 days. CRT No significant difference was found in the reduction of CRT after six months with 0.7mg compared with sham.	
Lucentis	Central Retinal Vein Occlusion (CRUISE 2010) [12] BRAVO [16].	Population 392 Treatment Ranibizumab Groups Monthly 0.3 or 0.5mg of ranibizumab (n=132 and 130) for six months. Sham injection (n=130). Study period Six months. Six to 12 months all patients received PRN ranibizumab (previously assigned dose or 0.5 mg for the sham group) if they met pre-defined criteria. 12 months (HORIZON) extension 0.5 mg ranibizumab if they fulfilled criteria.	BCVA At six and 12 months Significant increase compared with sham group (12 letters gained vs 7.6 in the sham group). CRT Significant reduction. Significantly more patients achieved CRT $< 250\mu\text{m}$ compared to sham at six months. Delayed treatment (after six months) no difference.	Six months. BCVA Ranibizumab improved by at least 15 letters (55/61% vs. 29%) 6/9 or better (68/65% vs. 42%), up to 49 months.
Aflibercept	Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS [17] 2012) intravitreal injections of 2mg of aflibercept (GALILEO [18] 2012).	Population 114 Treatment Aflibercept Every four weeks for 24 weeks. Groups Aflibercept Sham injection (n=75). Study period Up to 24 weeks. Weeks 24–52, all patients received aflibercept if they met retreatment criteria or sham if retreatment was not indicated. One-year extension GALILEO trial (2012). (3.9 SE 0.3 injections in the sham group and 2.7 SE 0.2 injections in the aflibercept group); Patients continued in a phase with as needed dosing. In the 36, 37 intervention patients also received intravitreal injections of 2mg of aflibercept (n=103) every four over 24 weeks, while the comparison group was given sham injections (n=71). During weeks 24–52, patients remained in their original treatment groups but received their allocated treatment as needed; beginning from weeks 52 to 76, both groups received the study drug every eight weeks.	Significant improvement in BCVA at six months aflibercept group 18 and 17.3 letters (compared with four letters loss and 3.3 letter gain in sham groups, respectively) maintained at 12 months significantly greater than the improvements in the sham groups. >15 letter gain 56.1% compared with 12.3% and 60.2% compared with 22.1%, respectively). Early treatment better. CRT Significantly greater reduction at six months in the aflibercept group. Maintained with retreatment up to 12 months. Delayed treatment similar decrease in CRT as in the original intervention group.	

(PRP) to reduce the risk of vitreous haemorrhage. The aim of laser treatments is to balance out the unbalanced supply and demand of oxygen, with the aim of preserving flow to the macula, i.e. sacrificing peripheral function. In the absence of rubeosis, PRP can be applied in a sectoral pattern to the area of retinal haemorrhages, area of capillary non-

perfusion in eyes with BRVO and to the whole peripheral retina in CRVO [3,4]. Neovascular glaucoma develops in eyes with significant levels of retinal ischaemia. Neovascularisation develops on the iris and within the angle obstructing the flow of aqueous, formation of synechial closure, raises intraocular pressure. IOP should also be addressed initially by

medical means or surgical interventions if not maintained thereafter in eyes with visual potential. Repeatable PRP laser in combination with an anti-VEGF treatment are used to treat new vessel formation, performed urgently to preserve vision. In eyes with no vision, topical steroids and mydriatic agents can be used, or cyclodiode laser for pain management.

Table 2: Side-effects.

Drug	Trial	Results
Intravitreal implant dexamethasone (Ozurdex)	GENEVA 2010 [13]	Increased IOP 30.1% vs. 1.4% sham treatment Moderate or severe increases cataract Higher in the dexamethasone
Aflibercept (Eylea)	COPERNICUS and GALILEO trials [17,18]	No increased incidence of ocular or non-ocular adverse events compared with sham in both
Ranibizumab (Lucentis)	CRUISE trial [12]	No difference in ocular or systemic adverse events between the intervention groups up to 24 months

Intravitreal Avastin and Triamcinolone are not licensed for treating ME / neovascularisation for RVO in the UK. Moreover, in the absence of neovascularisation, treatment with prophylactic laser has not been shown to be beneficial. Currently there is no treatment to reverse capillary non-perfusion.

Surgical treatments

Surgical treatments for RVO have been tried, albeit in small non-randomised clinical trials. Sheathotomy involves separating the retinal artery from the vein at areas of compression in order to improve blood flow [19]. Radial optic neurotomy involves the performance of a radial cut using a microvitreoretinal blade through the lamina cribrosa, with the goal of 'decompressing' the scleral outlet (space confined by the scleral ring and containing the lamina cribrosa, the central retinal artery, central retinal vein and the optic nerve). The ROVO trial found radial optic neurotomy to be more effective than sham [20]. Vitrectomy for vitreous haemorrhage or tractional retinal detachment can be used in advanced cases.

Summary and recommendations

RVO cause significant visual loss in some cases. Identification of RVO type and level of ischaemia is an important prognostic indicator. NICE approved treatments for ME exist, but may not work in clinical practice for all eyes. Anti-VEGF treatments are more favourable due to a better side-effect profile than steroid equivalents albeit with more frequent injections. Future research should focus on comparing all available treatments and long-term need for recurrent injections. But still, poor prognosis is associated with ischaemia for which there is no treatment.

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TAKE HOME MESSAGE

- Management of RVO aims to stabilise or improve vision through early identification and treatment of complications.
- Document symptoms, onset, duration and past medical history.
- Measure: visual acuity, presence of a RAPD, intraocular pressure and central macular thickness by OCT.
- Investigate: systemic risk factors including: BP and serum blood tests.
- Treat macular oedema: intravitreal anti-VEGF or Ozurdex initially, change treatment if no effect with the first, option of macular laser for BRVO.
- Treat neovascularisation with Argon laser (sectoral or PRP) with an adjunctive anti-VEGF injection.

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