The ROYAL COLLEGE of OPHTHALMOLOGISTS

Clinical Guidelines

Retinal Vein Occlusion (RVO) Consultation Document

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Executive Summary

1. Introduction

Retinal vein occlusion occurs when there is an obstruction to the outflow of blood from the retina. This can occur in a branch resulting in a branch retinal vein occlusion or centrally resulting in a central retinal vein occlusion. This condition can occur at any age or gender but is more prevalent in the older age groups. The severity of the impact it can have on vision is a spectrum, with some mild cases with minimal visual disturbances while some can be very significant with marked irreversible damage to the retina and vision loss. This condition can be associated with risk factors such as high blood pressure, high cholesterol and diabetes and management is usually targeting at these risk factors to avoid a further episode or a cardiovascular event to another part of the body.

Macular oedema or fluid leakage within the centre of the retina is a common complication of this condition and can result in poorer vision. This can be improved with treatment and the first line of treatment are injections of a drug into the eye at regular intervals. Some patients can experience growth of new blood vessels in the eye as a complication of this condition and this will require retinal laser treatment to regress the development of these vessels. If left untreated, this can result in worsening of vision and discomfort. Regular monitoring in hospital is recommended for several years to manage any complication that can arise.

2. Key recommendations and Good Practice Points for Implementation

Central retinal vein occlusion (CRVO)

Non-ischaemic CRVO may resolve without any complications. Macular oedema (MO) is the most common complication from CRVO and anti-VEGF treatment is successful at improving vision in eyes with MO secondary to CRVO.

However, 30% of eyes with non-ischaemic CRVO may convert to an ischaemic CRVO over three years. Prompt anti-VEGF therapy does not completely prevent worsening of retinal nonperfusion in eyes with CRVO.[1] Anti-VEGF therapy in eyes with an ischaemic CRVO retains the risk of neovascularisation and will need close monitoring following cessation of anti-VEGF therapy.

Branch retinal vein occlusion (BRVO)

For patients presenting with recent onset mild visual impairment due to MO secondary to BRVO, it may be reasonable to observe the progress of the condition over the first three months of follow-up. However, presentation may be delayed in some patients and in others with significant visual impairment at presentation, only 18 to 41% of eyes improve spontaneously with visual acuity not improving to 6/12 on average, suggesting early treatment may be appropriate in these cases.

Associations and risk factors

The most common associations of Retinal Vein Occlusion (RVO) are related to the raised risk of atherosclerosis and not significantly associated with systemic venous occlusions or their known risk factors. The main associations of RVO can therefore be defined as risk factors for atherosclerosis, and the remainder are conditions that cause hyperviscosity or slow or turbulent flow through retinal veins.

Therefore, diabetes is no more common in patients with RVO than the general population. However, the testing for diabetes at diagnosis of RVO is useful in detecting undiagnosed diabetes. The target HbA1C recommended by NICE for type 2 diabetes is 53 mmol/mol (7.0) (NICE NG28, 2015, updated 2020).

The testing for anti-phospholipid antibodies (aPL) is not recommended for a RVO occurring in isolation of other recognised anti-phospholipid syndrome (APS) clinical associations. There is currently no high quality evidence to support the use of anticoagulation or antiplatelet drugs in the management of RVO.[2] The finding of a thrombophilic abnormality in a patient presenting with a RVO does not alter management options or predict prognosis.

Cardiovascular morbidity and mortality

The systemic conditions for which a patient with RVO may be at greater risk are:

- Stroke: conflicting reports on associations have been noted (see below)[3-6]
- Cardiovascular disease under age 70 was noted in one study[5] but not in another report[7]
- Peripheral venous disease (13/439) 3% pre diagnosis of CRVO.[8]

This does not necessarily mean that CRVO is a risk for these conditions, but rather that RVO and these conditions share underlying risk factors such as hypertension and diabetes. There is no clear evidence that a different therapeutic approach for medical risk factors is warranted following a retinal vein occlusion than would be recommended anyway.

RVO in younger patients (less than 50 years of age)

RVO can occur in young patients with an estimated global prevalence of 0.26% in people age 30-39 years and 0.44% in people age 40-49 years.[28] The need for intravitreal anti-VEGF for macular oedema is less in young patients with CRVO.[63,65] However, at least 20% of patients develop poor visual outcome with severe neovascular complications.[66]

Medical investigations in retinal vein occlusions

The main benefit of medical tests in RVO is to improve health by treating the commonly associated risk factors of atherosclerosis, hypertension, diabetes and lipid abnormalities.

Summary of recommended medical investigations in the eye clinic:

- Medical History
- BP measurement
- Serum glucose estimation
- Request laboratory investigations for FBC and ESR

Further assessment of potential associated conditions, including further medical tests, are probably best performed by the patient's physician who can then organise further management and supportive measures such as smoking cessation.

The decision about whether to continue these oestrogen containing therapies in a woman with retinal vein occlusion should be made on a case by case basis.

Retinal imaging in RVO

- Optical coherence tomography (OCT) is recommended in the diagnosis, monitoring and assessing treatment response of macular oedema secondary to RVO
- Fluorescein angiography (FA)/Optical coherence tomography angiography (OCTA) is recommended to assess retinal nonperfusion to aid the identification of eyes with ischaemic CRVO

Ophthalmological Management of CRVO

- Anti-VEGF agents are the first-line choice for treatment of Macular Oedema due to CRVO.
- Just over a third of patients will require only 3 injections to reach maximum visual acuity (VA) while another third will require 6 consecutive injections. It is recommended to initiate treatment as the posology suggests which is monthly treatment until maximum stable VA is achieved.
- In a PRN regimen, it is recommended that these patients are monitored monthly for optimal visual outcomes.
- a delay in initiating treatment up to six months resulted in fewer visual gains compared to immediate initiation of treatment. It is therefore imperative that patients are initiated on treatment as soon as the diagnosis is established unless the treating physician and/or the patient decide on deferred treatment.
- For patients presenting with a VA of less than 6/96, careful consideration should be given to further therapy in such eyes that do not improve in terms of Snellen visual acuity or OCT central subfield thickness after three loading injections at monthly intervals and treatment is not recommended if no response occurs after six injections. Multiple factors such as degree of macular ischaemia, structural damage at the fovea and other confounding factors should be taken into account to decide continuation of treatment in this group of patients after initial therapy.
- Intravitreal steroids – NICE TA 229 has recommended the use of Ozurdex in the treatment of MO secondary to CRVO
- Laser photocoagulation There is also no evidence to suggest any benefit from a combination of macular grid laser and intravitreal anti-VEGF or steroids for MO secondary to CRVO.

Management of macular oedema in ischaemic central retinal vein occlusion

- Eyes with >10DA of posterior pole nonperfusion should not be excluded from anti-VEGF therapy.
- Eyes with a presenting vision of 6/96 or worse (eyes that were excluded from clinical trials), anti-VEGF should still be considered if there is presence of significant MO as reasonable improvements in vision may still occur. However, if oedema resolve with no improvement in visual acuity following a trial of anti-VEGF, cessation is recommended after three injections.
- 1-2 monthly observation for neovascularisation is recommended in the first year following cessation of anti-VEGF therapy in eyes with ischaemic CRVO.

Management of ischaemic central retinal vein occlusion and anterior segment neovascularisation

- Monitor Ischaemic CRVO monthly for new vessels of the iris and/ or the angle[9] unless there are particular risk factors.
- Inhibitors of vascular endothelial growth factor (anti-VEGF agents) may be used as adjuvants to pan-retinal photocoagulation in patients with anterior segment neovascularisation secondary to ischaemic CRVO.[10]
- Commence anti-VEGF therapy at the earliest sign of iris or angle new vessels followed by sufficient panretinal photocoagulation either on the same day (prior to anti-VEGF therapy) or within 1-2 weeks.

Management of established neovascular glaucoma

- If the eye has any visual potential, intraocular pressure should be controlled with topical pressure-lowering agents, surgical intervention or cyclo-ablative procedures. In addition, regression of iris new vessels (NVI) and angle new vessels (NVA) seem to offer a long-term chance of maintaining ocular comfort.

Further follow-up in eyes that have significant ischaemia

- monthly follow-up is recommended in the first 6 months and follow-up after six months should be every three months for one year.
- Subsequent follow-up for all patients will depend upon treatment given and complications within the earlier period but will not normally be required after three years in uncomplicated cases.
- The development of disc collaterals + spontaneous resolution of MO indicates a good outcome and should lead to discharge from clinical supervision after 6 months provided no other complications.

Ophthalmological Management of BRVO

- Recommended treatment guideline for MO due to BRVO is that if laser photocoagulation is contemplated, it should be performed in those eyes with MO secondary to BRVO of at least three months' duration with visual acuity of 6/12 or worse and without significant macular haemorrhage and with a fluorescein angiogram showing capillary perfusion in the absence of blood involving the fovea. However, only a minority of patients in clinical practice are eligible for this treatment option based on these recommendations.
- Treatment of neovascularisation:
    - Disc or retinal neovascularisation is an indication for photocoagulation to the ischaemic retina (sector photocoagulation), although available evidence suggests that waiting until vitreous haemorrhage occurs before laser treatment does not adversely affect the visual prognosis.[17]

- Follow-up visits at three to four monthly intervals are recommended in patients with one quadrant or more retinal ischaemia.
- Apply sector laser photocoagulation once retinal or optic disc neovascularisation occur.
- Fluorescein angiography is not usually necessary prior to laser because the area of ischaemia is visible clinically.

- Photocoagulation for retinal neovascularisation in BRVO is applied to the sector of retinal capillary closure. An adequate number of laser spots using a single spot or multisport laser should be applied in the affected sector, one shot width apart with sufficient energy to create a mild grey-white laser discoloration of the retina. A quadrant usually requires at least 500 shots of 500µm diameter.

RVO Service Specifications

- Time from referral from the primary source to initial evaluation and treatment by the ophthalmologist at the eye clinic is not more than 2 – 4 weeks from presentation.
- Minimum clinical services required for effective management
  - Best corrected visual acuity assessments by optometrist or certified VA examiners
  - Colour Fundus photographs and Fundus Fluorescein angiography (FFA) / OCTA by trained technical staff
  - Optical coherence tomography (OCT) with the Spectral domain OCT (SD-OCT) by trained technical staff
  - Treatment initiated within one to two weeks of assessment by the attending ophthalmologist
  - Appropriate facilities for IVT injection
  - Appropriate capacity for follow-up, monitoring and re-treatment
- Referral Pathways:
  - All patients suspected to have RVO by the optometrist, general practitioner, or other health workers should be referred directly to the nearest Eye Centre with pathways set up to allow urgent access.
  - Optometrists may be used for 'screening' or first examination of patients suspected of having RVO.
  - Fast track clinics collecting imaging in the community or hospital can help triage to find those who are symptomatic with reduced vision and centre involving macular oedema.[11]
- Low Vision and Living with RVO:
  - Patients with reduced best-corrected visual acuity secondary to RVO should be offered the access to low vision support and advice at an early stage.
  - Do not to wait until all treatment options have been explored or until an individual's vision deteriorates to a level that merits registration as visually impaired/severely visually impaired before referring an individual to low vision and rehabilitation services.

Guideline Development Group

Membership

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Declaration of interest

- Prof Sobha Sivaprasad has received an honorarium for advisory board meetings and speaker fees from Allergan, Boehringer Ingleheim, Novartis, Bayer, Optos, Heidelberg Engineering, Oxurion, Ophthea, Oculis, Apellis and Roche. Been awarded institutional research grants by Novartis, Bayer, Allergan, Boehringer Ingleheim. Received support from industry towards publication for the AURA and RELIGHT, and research grants from Research Grants: Novartis, Bayer, Allergan, Boehringer Ingleheim.
- Mr Luke Nicholson has received speaker fees from Allergan and Bayer.
- Mr Winfried Amoaku has received research funding from Allergan, Bausch and Lomb, Novartis and Pfizer, is on an Advisory Board for Alcon, Allergan, Novartis, Bayer, Alimera, Roche and Thrombogenics, has received educational travel grants from Bayer, Novartis and Pfizer, speaker honoraria from Alimera, Allergan, Bausch and Lomb, Bayer, Novartis and Pfizer. He has been involved with Pharma-sponsored Clinical Trials: Allergan, Bausch and Lomb, Novartis, Pfizer2009 – 14. Clinical Trials: i) National CI (and PI, Nottingham) Pfizer. Case-Crossover Study of PDE5 Inhibitor as factor in AION; ii) PI- Novartis. REPAIR Phase 2, Protocol CRFB002AGB10. Multicentre; iii) PI- Novartis. COMRADE B and C. Phase 3, Protocol CRFB002 EDE17 and CRFB002 EDE18. Multicentre trial ranibizumab vrs dexamethasone in BRVO and CRVO; iv) PI- Phase 4 Observational Constance. He is also a member of the Macular Society Scientific Committee.
- Mr James Talks has attended Advisory Boards for Bayer, Novartis, Alimera and Allergan. He has participated in Pharma-sponsored Clinical Trials for Bayer, Novartis, Roche and Boehringer Ingelheim. He has also received educational travel grants from Bayer.
- Dr Katherine Talks has received educational travel grants from CSL-Behring, Pfizer & Sobi.

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