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SAVRS Clinical Practice Guideline for the management of Retinal Vein Occlusion

This is a revised Clinical Practice Guideline – Reviewed May 2024 (Dr RD Viljoen)

Main Changes:

- Update in treatment regime/ medication
- Re-formatting of article in accordance with new OSSA guidelines for society document publications

Key Points:

- Clinical examination
- Diagnostic tests
- Intravitreal therapy

Scope and purpose:

- To describe the work-up and management of Branch Retinal Vein Occlusion (BRVO) and Central Retinal Vein Occlusion (CRVO)
- To discuss the indications for intravitreal therapy in Retinal Vein Occlusion (RVO)
- The guideline applies to health professionals and funders

Stakeholder involvement:

- The guideline development group includes individuals from the SAVRS Academic Advisory Committee (AAC)
- The AAC includes Ophthalmologists from both the public and private sector

Editorial Independence:

- No funding or sponsorship was received for the publication of this clinical guideline
- The views of medical aids, government bodies and manufacturers of therapeutic agents have not influenced the content of this guideline
- No competing interests from guideline development group members were present

Adoption of recommendations from other guidelines:

- Recommendations were adopted from the following existing international guidelines
    - The Royal College of Ophthalmologists – Clinical guidelines, Retinal Vein Occlusion, Jan 2022

- American Academy of Ophthalmology – Preferred Practice Patterns for Retinal Vein Occlusion, 2019

Evidence-based methods:

- A systematic internet search for evidence on the management of RVO was performed
- Evidence was selected based on peer reviewed publications and guidelines from international ophthalmology groups[1,2]
- There is an explicit link between the recommendations and the supporting evidence
- The guideline has been externally reviewed by the SAVRS Academic Advisory Committee
- Suggested future complete document revision: 2029

CLINICAL ASPECTS and KEY RECOMMENDATIONS

Background:

- Retinal vein occlusion (RVO) is the second most common retinal vascular disorder following diabetic retinopathy and affects about 0.5% in the 2008 general world population aged 30yrs or older, and is often associated with vision loss.
- The patient population includes people over 40 years of age, with the most common age range from the 6th to the 7th decade.
- RVO occurs when there is a partial or complete obstruction of a retinal vein by a thrombus, and is classified by the location of the occlusion:
  - Central retinal vein occlusion (CRVO) is an obstruction of the retinal vein at or posterior to the optic nerve head.
  - Branch retinal vein occlusion (BRVO) is an obstruction at a branch or tributary of the central retinal vein.
  - Hemi-retinal vein occlusion (HRVO) affects either the superior or inferior retinal hemisphere.
- The two main complications of RVO are macular oedema (MO) and retinal ischaemia leading to iris and /or retinal neovascularization.
- Macular oedema is the most common cause of visual impairment in RVO, followed by foveal ischaemia.
- Both CRVO and BRVO can broadly be classified into ischaemic and non-ischemic types based on the area of capillary non-perfusion, and this distinction is useful for clinical management.

Associations and risk factors

- The main risk factor for both CRVO and BRVO is older age.
  - RVO can however occur in young patients with an estimated global prevalence of 0.26% in people aged 30-39 years and 0.44% in people aged 40-49 years.
- The most common associations of RVO are related to the raised risk of atherosclerosis (arterial hypertension, hyperlipidaemia, diabetes) and not significantly associated with systemic venous occlusions or their known risk factors.

Diagnosis

The initial examination of a patient with a RVO includes all relevant aspects of the comprehensive adult medical eye evaluation, with particular attention to those aspects related to retinal vascular disease.

- **History**
  - Location and duration of vision loss
  - Current medications
  - Medical history (e.g. systemic hypertension, diabetes, hyperlipidaemia, cardiovascular disease, sleep apnoea, coagulopathies, thrombotic disorders, pulmonary embolus)

- Ocular history (e.g. glaucoma, previous surgery)

- **Examination**
  - Visual acuity (VA)
  - Pupillary assessment for an RAPD
  - Slit lamp biomicroscopy, looking carefully for fine, abnormal, new iris vessels
  - IOP
  - Gonioscopy prior to dilatation – important in cases of an ischaemic CRVO, when there is an elevated IOP or when iris neovascularization risk is high
  - Binocular fundoscopic evaluation of the posterior pole
  - Examination of the peripheral retina and vitreous

  Because treatment is effective in reducing the risk of vision loss, a detailed examination is indicated to asses for the following features that often lead to visual impairment:

  - Macular oedema, detected both clinically and/or by using OCT
  - Signs of ischaemia, including neovascularization of the disc or elsewhere, presence of a RAPD, extensive haemorrhages, venous dilatation and tortuosity, and cotton wool spots
  - Optic nerve head neovascularization and/or neovascularization elsewhere
  - Vitreous or preretinal haemorrhage

- **Diagnostic tests**

  A number of imaging tests may enhance the clinical examination and optimize patient care. The most common tests include the following:

  - ***Optical coherence tomography (OCT)***
    - Provides high-resolution imaging of the macula and is extremely useful to detect the presence and extent of any associated macular oedema, vitreoretinal interface changes, and subretinal fluid.
    - In clinical practice, treatment decisions are commonly based on OCT measurements. For example, the decision to repeat anti-VEGF injections, change therapeutic agents, initiate laser treatment, or even consider vitrectomy surgery is frequently based on both visual acuity and OCT findings.

  - ***Optical Coherence Tomography Angiography (OCTA)***
    - Several studies have demonstrated that in eyes with RVO, non-invasive OCTA is similar to fluorescein angiography in detecting capillary nonperfusion, enlarged foveal avascular zone, and vascular abnormalities.

  - ***Colour and Red-Free Fundus Photography***
    - Useful for documenting the severity of the retinal findings, the extent of intraretinal haemorrhages, the presence of NVD and NVE, the response to treatment and the need for additional treatment at future visits.

  - ***Fluorescein angiography (FA)***
    - FA is used to evaluate the extent of the vascular occlusion, the degree of ischaemia (ischaemic vs non-ischaemic), and the extent of macular ischaemia. It is a useful technique to distinguish collateral vessels, from retinal neovascularization. Recent advances in widefield FA (wfFA) have enabled its use to evaluate peripheral non-perfusion, helping to guide effective laser treatment.

  - ***Ultrasonography***
    - Ultrasonography is an extremely valuable diagnostic tool that enables assessment of the anatomic status of the retina in the presence of a vitreous haemorrhage or other media opacity.

Medical Investigations for RVO

- 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.
- The recommended medical investigations in the eye clinic are:
    - 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 oestrogen containing therapies in a woman with retinal vein occlusion should be made on a case-by-case basis.

Management (General)

- A comprehensive ocular examination and retinal imaging should do the following:
    1. Distinguish RVO as either BRVO or CRVO
    2. Evaluate for macular oedema
    3. Estimate the degree of ischaemia
    4. Evaluate for retinal and/or iris neovascularization

- **Non-ischaemic CRVO**

    - Non-ischaemic CRVO may resolve without complications.
    - Macular oedema is the most common complication from CRVO and intravitreal injections of anti-vascular endothelial growth factor inhibitors (anti-VEGF's) or corticosteroids are successful at improving vision in eyes with MO secondary to CRVO.
    - A delay in initiating treatment up to 6 months resulted in lower 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 patient decide on deferred treatment.
    - There is no evidence to suggest any benefit from a combination of macular grid laser or Pan-retinal photocoagulation (PRP) with anti-VEGF or steroids for MO secondary to CRVO.

- **Ischaemic CRVO**

    - 30% of eyes with non-ischaemic CRVO may convert to an ischaemic CRVO over 3 years. Prompt anti-VEGF therapy does not completely prevent worsening of retinal nonperfusion in eyes with CRVO.
    - The management of macular oedema is similar to non-ischaemic CRVO.
    - Anti-VEGF therapy in eyes with an ischaemic CRVO retains the risk of neovascularization.
    - In eyes with CRVO with retinal and/or iris neovascularization, dense peripheral PRP is indicated. Occasionally, initial treatment with an anti-VEGF agent might be helpful for an immediate but non-sustained benefit and may also improve the ability to deliver a complete laser treatment.

- **BRVO**

    - In eyes with BRVO and MO, anti-VEGF injections, intravitreal steroids and focal laser treatment all have demonstrated therapeutic benefit.
    - In eyes with BRVO and neovascularization of the retina, retinal laser photocoagulation in the area of non-perfusion helps to decrease the risk of a vitreous haemorrhage.

- There is currently no high quality evidence to support the use of anticoagulation or antiplatelet drugs in the management of RVO

Intravitreal injections

- **Anti-VEGF**
  Currently, three anti-VEGF agents are used routinely for the treatment of macular oedema associated with RVO.
  - Ranibizumab (Lucentis®) and Aflibercept (Eylea®) are approved by the FDA and SAHPRA.
  - Bevacizumab (Avastin®) remains off-label for ophthalmologic conditions, although evidence demonstrating its efficacy exists.

  Faricimab (Vabysmo®) has recently (2023) also been approved by the FDA[3]

- **Corticosteroids**
  - Dexamethasone implant (Ozurdex®) has been approved by the FDA and SAHPRA for the treatment of macular oedema.
  - Preservative free Triamcinolone is used off label, although evidence demonstrating its efficacy also exists.
  - The side effect profile for corticosteroids differ from anti-VEGF's, with an increased risk of cataract formation and IOP rise.

TREATMENT ALGORITHM FOR CRVO

- Treatment of risk factors (to be managed by the patient's physician)

Baseline assessment

1. Visual acuity measurement, RAPD, OCT, IOP, and gonioscopy (if ischaemic CRVO suspected).
2. Colour fundus photographs and fluorescein angiography should be performed when the diagnosis is uncertain. Angiography (FA and wfOCTA) is recommended to assess the extent of retinal nonperfusion in suspected ischaemic CRVO cases and this can either be done at baseline or at a later stage if anti-VEGF therapy is commenced. Prophylactic PRP should be considered and discussed in eyes with >10 disc areas (DA) of posterior pole nonperfusion.
3. If no iris (NVI) or angle neovascularization (NVA) and OCT evidence of MO:
   a. If visual acuity is 6/96 or better, commence intravitreal anti-VEGF
   b. If less than 6/96, the potential for significant improvement in visual acuity is guarded and the risk of ocular neovascularization is high. However, eyes with VA < 6/96 with significant macular oedema should be offered treatment as some of the eyes may respond. These patients should be watched for NVI/NVA.
   c. If visual acuity is better than 6/12, it is not unreasonable to observe the patient for spontaneous resolution as per the judgement of the treating ophthalmologist.

Choice of agent

- Ranubizumab and Aflibercept are the 2 anti-VEGF agents recommended by NICE (National Institute of Health and Care Excellence - UK) for MO due to CRVO.
- Ozurdex® is also recommended by NICE for this condition.
- The choice is based on the clinician and patient choice, after discussions considering injection frequency, risk of IOP rise, formation of cataract.
- There is no visual acuity or central macular thickness restriction in the commencement of treatment with any of these agents.

Treatment

- At each follow-up visit, visual acuity, macular thickness and IOP should be assessed, and the presence of neovascularization assessed.

- If ranibizumab or aflibercept are the first line of treatment, monthly intravitreal injections are initiated until maximum stable visual acuity is achieved.
- If no improvement in visual acuity over the course of the first 3 injections is observed, cessation of treatment may be considered, and it is recommended after 6 injections.
- Patients who achieve visual acuity stability can be managed either with a treat and extend regimen or a PRN regimen.
- Patients on the treat and extend regimen may be extended by 2-4 weeks longer than the prior interval if the vision remains stable and there is no recurrence of MO.
- The intervals can be shortened if there is loss of visual acuity due to MO secondary to CRVO.
- Once this interval to recurrence is identified, it is advisable to maintain on this interval for a 6 month period before extending again.
- Patients on a PRN regimen should be monitored at monthly (or bi-monthly) intervals and treatment resumed when there is loss of visual acuity due to MO secondary to CRVO.

- If Ozurdex® is the first line of treatment, re-treatment may be required at 4-6 monthly intervals until visual stability is obtained.
    - The occasional patient may require treatment at 3 months.
    - However, more frequent and repeated treatments with Ozurdex® increase the risk of adverse events and these should be discussed with the patient.
    - Patients should be monitored for raised intraocular pressure (IOP) which peaks at Day 60 and formation or progression of cataract.
    - Intravitreal Ozurdex® does not protect or mask neovascularisation thus eyes judged to be ischaemic will still require monthly assessments.

Stopping treatment

- Consider stopping ranibizumab and aflibercept therapy if after 3 consecutive monthly treatments, visual acuity has not improved and CMT has not reduced from baseline.
- Reduction in MO without VA improvement or deterioration (i.e. stable VA) may be accepted as a favourable, but suboptimal outcome.
- Stopping ranibizumab and aflibercept therapy is recommended if after 6 consecutive monthly treatments, visual acuity has not improved by at least 5 letters and CMT has not reduced from baseline.
    - However, if anti-VEGF is commenced in an eye with very poor presenting vision to assess visual potential, and there is no improvement after 3 loading doses, treatment can be stopped.
    - Consider FA or wfOCTA at this stage if it has not been done to clarify if the visual acuity is poor due to central macular ischaemia alone or widespread retinal ischaemia.
    - If the latter, consider prophylactic PRP.
- In eyes with >10DA of posterior pole nonperfusion, upon cessation of anti-VEGF therapy, 1-2 monthly reviews are recommended in the first year.

Switching agents

- If an anti-VEGF agent is stopped due to lack of efficacy, there are no randomised controlled trials that provide evidence that switching to another anti-VEGF agent may be effective.
- However, given our experience with switching anti-VEGF agents in neovascular age related macular degeneration, it may be worthwhile switching to another anti-VEGF agent and further monthly injections for 3 months may be given to assess the efficacy of the switch.
- In **SCORE2**, there was a favourable improvement in vision following a switch to aflibercept from bevacizumab in poor responders.
- There is a good rationale to switch from Ozurdex® to an anti-VEGF agent and vice versa as the different mode of actions of these agents may aid in resolution of MO. However, the long-term outcomes of sequential or combination treatment of anti-VEGF agents and steroids remain unclear.

Follow-up / discharge

- ***Non-ischaemic CRVO***
    - In eyes not requiring treatment, follow-up every 3 months is recommended in the first 6 months.
    - Discharge from ophthalmologist eye services can be considered after a minimum of 18 months if no intervention is required or 18 months from the last intravitreal therapy.

- ***Ischaemic CRVO or eyes with >10DA of posterior pole nonperfusion***
    - If anti- VEGF therapy is not commenced, monthly monitoring is recommended for 6 months and subsequently every 3 months for a year. This can be extended in the second and third year.
    - In ischaemic CRVO eyes that received anti-VEGF therapy, 1-2 monthly reviews are recommended in the first year.
    - Follow-up is recommended for 3 years from the last intervention, if any.

Anterior segment neovascularization

- ***If iris or angle neovascularization occurs and the anterior chamber angle is open***
    - Urgent intravitreal anti-VEGF is recommended with PRP within the same day (prior to anti-VEGF treatment) or within 2 weeks initially.
    - PRP plus intravitreal bevacizumab (off label) can be repeated if NVI / NVA persist.

- ***If iris or angle neovascularization are present with a closed angle and raised intraocular pressure***
    - Urgent PRP is recommended with cyclodiode laser therapy / tube shunt surgery. The latter is preferable if the angle closure is established.
    - If the intraocular pressure is normal or normalizes with the above therapy, intravitreal bevacizumab can be considered.
    - If the intraocular pressure is significantly elevated it should be managed as above with topical and medical management in addition.
    - Caution is advised if bevacizumab or any anti-VEGF agent is considered in the presence of raised intraocular pressure as this can be exacerbated in the short-term.
    - If vitreous haemorrhage precludes a view of the fundus, transscleral diode therapy and retinal cryotherapy can be used. An early specialist glaucoma opinion should be sought.

TREATMENT ALGORITHM FOR BRVO

- Treatment of risk factors (to be managed by the patient's physician)

Baseline assessment

- Measure visual acuity, OCT, colour fundus photography.
- FFA can help assess the degree of ischaemia as can OCTA, but may be more useful to assess reasons for poor vision after initial anti-VEGF treatment, to distinguish new vessels from collaterals or if laser is planned for new vessels.

Treatment

- For a BRVO with centre involving oedema, intravitreal therapy with anti-VEGF or intravitreal dexamethasone injections can be started, with a similar treatment regime as for CRVO with macular oedema.
- The choice of treatment will be dependent on the clinician and the patient taking into consideration the frequency of treatment, risk of IOP rise and cataract formation.
- For a macular BRVO with no oedema, follow-up with repeat OCT can be performed.
- For a non-macular involving BRVO follow-up may or may not be required depending on the degree of ischaemia.
- Grid laser is an option for BRVO, but the results are not likely to be as good as intravitreal treatment.
    - If contemplated, it should be performed in those eyes with MO secondary to BRVO of at least 3 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.

Ischaemic BRVO

- Watch carefully for NV. Retinal neovascularisation occurs in 36% of eyes with >5 DD.
- If NVE – consider sector laser photocoagulation applied to all ischaemic quadrants. Intravitreal anti-VEGF treatment may also be given in combination with laser.
- Follow-up at 3 monthly intervals for up to 24 months.

RVO service specifications

- The time from referral from the primary source to initial evaluation and treatment by the ophthalmologist at the eye clinic should not more than 2-4 weeks from presentation.

- Minimal clinical services required for effective management
    - Visual acuity assessments.
    - Colour Fundus photographs and Fundus Fluorescein angiography (FFA) / OCTA by trained technical staff.
    - Optical coherence tomography (OCT) with the 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 perform 'screening' or first examination of patients suspected of having RVO.
    - Fast track clinics acquiring imaging in the community or hospital can be set-up to triage those who are symptomatic with reduced vision and centre involving macular oedema.

- Low vision and living with RVO
    - Patients with reduced best corrected visual acuity (BCVA) secondary to RVO should be offered the access to low vision support and advice at an early stage.

REFERENCES:

1. Retinal Vein Occlusion (RVO) Guidelines, The Royal College of Ophthalmologists, January 2022
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