The Royal College of Ophthalmologists

Interim Guidelines for Management of Retinal Vein Occlusion

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3 INTRODUCTION

3.1 Background

Retinal vein occlusion (RVO) is a common cause of visual loss in the United Kingdom.

It is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein.[1-3] Thrombus formation may be the primary cause but other possible causes are external compression or disease of the vein wall e.g. vasculitis. Retinal vein occlusions are the second commonest cause of reduced vision due to retinal vascular disease [4, 5] with BRVO occurring 2-3 times as common as CRVO.[6, 7] In the Australian population study the incidence was 0.7% at 49-60yrs and 4.6% at 80yrs.[7] It is currently estimated from pooled data from 15 population studies from that there are about 520 new cases per million population of RVO.[8] These include 442 and 80 per million of BRVO and CRVO respectively.

It typically occurs in middle aged and elderly patients (i.e. over age of 50 years) with equal sex distribution in both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). CRVO is classically characterised by disc oedema, increased dilatation and tortuosity of all retinal veins, widespread deep and superficial haemorrhages, cotton wool spots, retinal oedema and capillary non-perfusion. In less severe forms the disc oedema may be absent. BRVO has similar features except that they are confined to a portion of the fundus. In view of the significant ophthalmological and medical consequences of retinal vein occlusion, these guidelines promote a good standard of practice and the achievement of best visual and medical outcome.

3.2 Remit of the guidelines

The document aims to provide updated recommendations on the management of RVO in the light of recent developments in both diagnostic tools and treatment options that supersede those in the previous RVO guidelines. It has also reviewed the risk factors for RVOs and included recommendations for investigations and indications for medical management. These guidelines are intended for the use of ophthalmologists, but will also be useful to physicians, general practitioners, and commissioners.

The guidelines are considered interim and will be reviewed in a year (or earlier, as necessary) as new evidence continues to emerge.

The recommendations in this document are based on scientific and medical evidence. The guidelines do not address the NHS funding of its recommendations, which are in the remit of NICE and the NHS.

4 METHODS

4.1 The Guideline Development Group

Three ophthalmologists with expertise in medical retinal diseases, and a medical ophthalmologist constituted the RVO Guidelines Development Group.

4.2 Gathering the evidence

4.2.1 Search methodology

The searches for the evidence base were conducted by the Management Team at NHS Evidence-eyes and vision. Full details of the search methodology and the search strategy are provided in ***Appendix A and Appendix B*** respectively.

(The search output was also used to inform the NHS Evidence Update on Retinal Vein Occlusion March 2010, http://www.library.nhs.uk/eyes/viewResource.aspx?resid=345418).

Period of Search: January 2002 to 15th February 2010

This time interval covered the period since the searches for the 2004 Retinal Vein Occlusion Guidelines had been undertaken.

Databases searched:
NHS Evidence - eyes and vision; PubMed; Medline; EMBASE; CINAHL; AMED; BNI; and PsycINFO

Inclusion criteria:

a) *Publication type –*

- Secondary publications (including Cochrane systematic reviews, systematic reviews, reviews, meta or cost analysis)
- Interventional studies (randomised controlled trials and controlled clinical trials).
- Observational studies (cohort, case control, validation studies, observational or comparative studies, case reports/series, population based cross-sectional and cohort studies and qualitative surveys).

b) *Relevancy to the scope of the Guideline*

In addition references from the *Central Vein Occlusion Study and the Branch Vein Occlusion Study* (trials that reported between 15 and 25 years ago) were identified as seminal research underpinning the evidence base for the current management of retinal vein occlusion in the NHS, and were also included.

4.2.2 Supplemental searches

a) These were conducted by the Guideline Development Group and covered the period from February to August 2010.

b) Citations from the 2004 Guideline were selected by the Guideline Development Group for their relevance to the scope of the guideline and the updated evidence base ***(see 4.2.)***

4.3 Assessing the evidence and forming recommendations

Relevant literature was identified and the level of evidence graded.
Recommendations for a good standard of practice were formed using the following categories (i.e. strength of the evidence) and included in the text of the guidelines.

A	At least one meta-analysis, systematic review, or good quality randomised control trial (RCT) directly applicable to the target population; or a body of evidence consisting principally of RCTs, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including high quality systematic reviews of case-control or cohort studies, directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from RCTs.
C	A body of evidence including studies rated as well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated

evidence from studies rated as high quality systematic reviews of case-control or cohort studies.

D	Evidence from non-analytic studies, e.g. case reports, case series or expert opinion

4.4 Consultation process

The Guideline Development Group invited comments on the draft guideline from all UK consultant ophthalmologists prior to publication over a month consultation period. Two external experts from outside the UK were also invited to evaluate the guidelines. The comments were evaluated, and where appropriate, incorporated into the final version of the guideline.

5 AETIOLOGY AND RISK FACTORS

Retinal vein occlusion is due to thrombosis within retinal veins (central, hemi or branch)[1-3] although it remains unclear whether it is a primary or secondary effect.

Established cardiovascular risk factors are the predominant medical associations for both central and branch vein occlusions and are summarised below and include differentiation by age and ethnic groups. (See table 1) [9,10]

5.1 Strength of evidence

B Hypertension

This is the predominant risk factor with up to 64% of patients having hypertension (Table 1) in the older age group (more than 50 years).[11] This is more prevalent in BRVO than CRVO. A new diagnosis or uncontrolled hypertension is a common finding. Inadequately controlled hypertension is associated with recurrence of RVO in the same eye or fellow eye involvement.

C Hyperlipidaemia

Hyperlipidaemia (cholesterol > 6.5 mmol/l) is the predominant association in the younger age group (< 50 years) of patients with retinal vein occlusion and is associated in up to 50% of older patients.[12]

B Diabetes mellitus

Diabetes mellitus (table 1) is associated with retinal vein occlusion. This may be due to an increase of other cardiovascular risk factors (e.g. 70% of type II diabetics are hypertensive).[11,13,14]

C Glaucoma

Current evidence suggests an association between central retinal vein occlusion and glaucoma.[7, 15] One study suggests that BRVO is associated with glaucoma. [13]

C D Thrombophilia

Antiphospholipid antibody syndrome and hyperhomocysteinaemia are the two haematological factors with the strongest evidence for association with CRVO, although this is not proven. Factor V Leiden, protein S,C, and anti-thrombin 3 deficiency have also been reported.[16] Thombophilia and the other rarer associations e.g. oral contraceptive pill, and optic disc vasculitis assume more importance in younger patients (<50 years).[17, 18]

5.2 Other Important Observations

Myeloproliferative disorders occur in 1% of patients presenting with retinal vein occlusion.[10]

D Other rare associations with retinal vein occlusion include:

- Inflammatory diseases that cause or are associated with retinal vasculitis – Behçets disease, polyarteritis nodosa, sarcoidoisis, Wegener's Granulomatosis and Goodpasture's Syndrome.
- Chronic renal failure and other secondary causes of hypertension and diabetes e.g. acromegaly, Cushing's syndrome.
- Secondary causes of hypercholesterolaemia eg hypothyroidism.

6 NATURAL HISTORY OF RETINAL VEIN OCCLUSIONS, AND LIVING WITH RETINAL VEIN OCCLUSIONS

6.1 CRVO

Natural history data from the CVOS study [19,20], and a systematic literature review[8] demonstrated that visual outcome of CRVO depends on the visual acuity at presentation. Eyes with initial visual acuity of 20/40 (6/12) or better have a better prognosis for retaining good vision than those with worse vision. Only 20% of eyes with initial visual acuity of 20/50-20/200 (6/15 -6/60) improve spontaneously to 20/50 (6/15) while 80% of patients with baseline vision worse than 20/200 (6/60) remain at this level or worsen. Furthermore, the longer the duration of macular oedema, the more the structural damage at the fovea so it is justifiable that early treatment be initiated.

6.2 BRVO

Natural history data from an evidence based systematic review of 24 studies by Rogers et al (2010) [21] indicated that VA was moderately poor (worse than 6/12) at presentation, and that although there may be some improvement in the follow-up period, such improvement was limited such that the average improvement did not result in VA better than 6/12. Macular oedema may develop in 5 to 15% of eyes over a 1 year period; however, of the eyes that had macular oedema at presentation, 18 to 40% may show some resolution. Approximately 20% of untreated eyes experienced significant vision deterioration over time. In the BVOS, approximately 50% of untreated eyes with BRVO retain vision of 6/12 or better whilst 25% will have vision of <6/60.[5] Fellow eye involvement by BRVO may occur in 10% of cases over time.

6.3 Low Vision and Living with RVO

It is known that the sudden onset of visual loss whether unilateral or bilateral results in significant distress. CRVO is reported to be associated with a decreased vision-

related quality of life as measured by the VFQ-25. The decrease in VFQ-25 scores is related to the degree of visual loss in the better-seeing eye and the overall systemic health of the patient. [22] Another study has shown that BRVO is associated with a decrease in vision-related quality of life as determined by the VFQ-25 and that the decrease in VFQ-25 score correlated well with the visual acuity of the involved eye, even when good visual acuity is maintained in the uninvolved eye.[23] Patients with either central or branch retinal vein occlusion with macular oedema have significant impact on their quality of life, and were willing to undergo potentially invasive treatment. [24,25]

7 MANAGEMENT

There are two aims in the management of retinal vein occlusion: the identification of modifiable risk factors and their medical management and the recognition and management of sight-threatening complications.

Although the systemic investigation and treatment in all types of vein occlusion is similar, the ophthalmological management of central (CRVO) and branch retinal vein occlusion (BRVO) differs. These will therefore be considered separately.

7.1 OPHTHALMOLOGICAL MANAGEMENT

7.1.1 Central retinal vein occlusion (CRVO)

The main management problem is to differentiate ischaemic from non-ischaemic central retinal vein occlusion. Patients with ischaemic CRVO are at risk of neovascular glaucoma. This risk of iris neovascularisation is higher if the area of retinal ischaemia (retinal non-perfusion as determined by FFA) is >10 disc diameters.[19] Ischaemic central retinal vein occlusion is associated with one or more of the following characteristics:-

1. Poor visual acuity (44% of eyes with vision of <6/60 develop rubeosis [19]
2. Relative afferent pupillary defect
3. Presence of multiple dark deep intra-retinal haemorrhage
4. Presence of multiple cotton wool spots
5. Fluorescein angiography showing greater than 10 disc areas of retinal capillary non-perfusion (CVOS) [19]
6. Electrodiagnostic tests (ERG): reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time [26-30]
7. Degree of retinal vein dilatation and tortuosity

There is no evidence as to which combination of the above characteristics best defines ischaemic CRVO. It is important to note that up to 30% of patients with initially non-ischaemic central retinal vein occlusion will develop ischaemic transformation.[20,31-33] This is usually heralded by further rapid visual deterioration and requires further assessment. CRVO especially of the non-ischaemic type needs to be differentiated from the ocular ischaemic syndrome and other simulating retinopathies.

7.1.1.1 Management of ischaemic central retinal vein occlusion and anterior segment neovascularisation

An initial evaluation of risk factors and the appropriate treatment of the present risks must proceed alongside management of the ocular findings.

A The evidence supports the use of laser pan-retinal photocoagulation (PRP) when iris new vessels (INV) or angle new vessels (ANV) are visible. [19]

C Recent evidence indicates that intravitreal anti-VEGF agents in combination with PRP results in dramatic regression of the INV/ANV. [34-37] iCRVO should be monitored monthly for new vessels iris and/ or angle. Repeat anti-VEGF and PRP are advocated in case of recurrence of new vessels. In some patients, it may not be logistically possible to review these patients monthly, 2-3 monthly reviews may be sufficient, unless there are particular risk factors. Particular individualized arrangements need to be made for these patients.

C In circumstances when regular follow-up is impractical, prophylactic treatment with PRP and anti-VEGF agent may be appropriate.[38] However, none of the available or commonly used anti-VEGF agents (bevacizumab, ranibizumab, pegaptanib) currently have regulatory approval for such an indication.

D

There is no proven protective effect of intravitreal triamcinolone acetonide on anterior segment neovascularisation and it may exacerbate any pre-existing neovascular glaucoma.This treatment option is not recommended.

7.1.1.2 Posterior segment neovascularisation

This is an uncommon complication following ischaemic central retinal vein occlusion in eyes which have not developed neovascular glaucoma or who have been successfully treated for rubeosis by laser.[39] There is anecdotal evidence that new vessels may be managed with a combination of anti-VEGF and PRP.

D

Pan-retinal photocoagulation for CRVO with INV or ANV requires 1500 – 2000 of 500-micron burns at the retina. This is best applied with 0.05-0.1 second applications one burn width apart with sufficient energy to produce a pale burn in the retina. Treatment is usually placed in the periphery avoiding areas of retinal haemorrhage. Some cases require further treatment if the iris neovascularisation fails to regress.[19]

C

The pan-VEGF A blockers, ranibizumab and bevacizumab have been shown to cause regression of new vessels of the iris, angle and retina when given intravitreally at the dose of 0.5mg/0.05ml and 1.25mg/0.05ml respectively.[34-36] However, the effect is transient and recurrence of new vessels is common so repeated treatment, typically every six weeks with these agents supplemented with PRP may be required.

No anti-VEGF agent (bevacizumab, ranibizumab, pegaptanib) currently has a licensed indication for posterior segment neovascularisation following ischaemic CRVO. As such, GMC Guidelines on “Good Medical Practice” as it relates to the use of both off-label and unlicensed medications and the manufacturer’s advice should guide any physician directed potential intraocular use.

7.1.1.3 Management of established neovascular glaucoma

D

The aim of management of this condition in a blind eye is to keep the eye pain free. This is usually achieved by topical steroids and atropine. However, if the eye has any visual potential intraocular pressure should be controlled with topical pressure-lowering agents,cyclo-ablative procedures or filtering surgery

C

Intravitreal and intracameral bevacizumab has been shown to cause regression of iris new vessels and decrease angle obstruction.[40,41] Comparative case series indicate that iris new vessels regress faster after intravitreal bevacizumab with PRP than with PRP alone.[36,42] The reports also suggest that bevacizumab may reduce the need for surgical interventions and serve as a useful adjunct to filtering surgery. [37,44]

7.1.1.4 Macular oedema

A

Macular oedema following central retinal vein occlusion results from leakage of perifoveal capillaries. It results in visual loss. Randomised controlled trials have failed to indicate benefit with grid laser photocoagulation, although a trend in favour of treatment has been observed in younger patients. [45] Although there was significant reduction in the severity of macular oedema in treated eyes compared to controls there was no visual acuity benefit.[45]

A

Triamcinolone acetonide (TRIVARIS): The rationale for the use of intravitreal triamcinolone acetonide (IVTA) to treat macular oedema is that corticosteroids reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF.

Evidence for the use of a specific preparation of triamcinolone in CRVO is from the SCORE-CRVO Study (SCORE Study Report 5). [46] In this study, a preservative-free form of triamcinolone (TRIVARIS, Allergan) given at different doses, 1mg and 4mg, at four monthly intervals and with pre-defined re-treatment criteria, was compared to observation. Results showed that both

doses of TRIVARIS produced both anatomical and functional improvement of macular oedema due to CRVO, compared to observation. However, at month 12, the 1mg dose had a better safety profile compared to the 4mg dose in terms of a lower incidence of raised intraocular pressure (IOP) >35mmHg (5% vs. 8%), incidence of cataract formation or progression (26% vs. 33%, cf. 18% for observation) and need for cataract surgery (0% vs. 4%). [46]

However, although FDA approved, TRIVARIS is not available for use in clinical practice anywhere in the world and there are significant differences between TRIVARIS and other currently available triamcinolone preparations. Specifically, TRIVARIS is a single-use, pre-filled, preservative free preparation, containing an injectable suspension of triamcinolone acetonide at a concentration of 80mg/mL. This formulation contains hyaluronic acid and a uniform and narrow distribution of triamcinolone particles and is buffered such that the pH is in a narrow range of 7.0-7.4.

In contrast, the triamcinolone preparation that is commonly used in the UK, is 4mg from the KENALOG formulation (Squibb) which is indicated for intra-articular joint use and has a contraindication for ocular use although it has been used widely in Europe and the USA in the last few years. KENALOG is typically presented in 1mL glass vials containing triamcinolone at a concentration of 40mg/mL with a preservative, Benzyl Alcohol at 0.99% w/v, which contains a wide variation in triamcinolone particle size. In addition to the known risks of cataract and raised IOP seen with TRIVARIS, the presence of a preservative may also lead to an increased risk of sterile endophthalmitis.

A preservative-free preparation of triamcinolone TRIESENCE (Alcon) has been produced for use in the USA, but is currently unavailable in the UK, has no ocular license for use in the UK and has no randomised controlled, clinical trial data to support its use.

Therefore, there is no Grade A evidence to suggest that the visual and anatomical responses seen with TRIVARIS in SCORE-CRVO would be replicated with off-label IVTA preparations such as KENALOG or TRIESENCE. [47] As such, GMC Guidelines on “Good Medical Practice” as it

relates to the use of both off-label and unlicensed medications and the manufacturer's advice should guide physician directed intraocular use.

A

Dexamethasone Biodegradeable Implant: The rationale for the use of intravitreal dexamethasone to treat macular oedema is similar to that of IVTA, although dexamethasone has been show to be a more potent corticosteroid that IVTA but also is able to reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF. However, dexamethasone when injected intravitreally in its free form, has a short half-life that limits its clinical utility as an injectable suspension. [48]

A pre-filled applicator single-use, sustained release biodegradeable implant containing 0.7mg of dexamethasone (OZURDEX, Allergan) has been studied in the GENEVA study programme.[49] In this study, OZURDEX and an alternative dose of dexamethasone implant (0.35mg) were compared to a sham injection, in patients with CRVO and BRVO in 2 parallel multicentre studies and published together as the GENEVA study. Re-treatment was possible 6 months after the first injection under pre-specified re-treatment criteria. The first trial did not meet its original primary end-point , namely proportion of eyes gaining 15 letters. The two trials were analysed together and the primary outcome measure for all patients was time to achieve a ≥ 15 letter gain. The percentage of eyes with ≥ 15 letter gain in BCVA was significantly higher in both implant groups compared with sham at days 30 to 90 with a peak effect at 60 days. Subgroup analyses of the BRVO and CRVO subjects showed a significantly greater number achieved ≥ 15 letter gain from 30 to 90 days than sham treated eyes, and that sham treated eyes in the BRVO subgroup were more likely to improve spontaneously than similar managed CRVO eyes

Anatomically, improvements in macular oedema as seen by OCT were also seen. In terms of safety, raised IOP peaked again at month 2 (3.2% of patients had an IOP>35 mmHg), but declined significantly by month 3 and was close to 0% by month 6, with 19% of patients requiring an IOP lowering agent at month 6 and 0.7% of patients requiring any IOP lowering surgical

procedures. Similarly, rates of cataract progression were low with 7% progression at month 6, compared to 4% in the sham group. [49]

Based on the GENEVA study programme, OZURDEX has received FDA and EU approval for the 0.7 mg preparation, and is licensed in the UK for the treatment of adult patients with macular oedema following either BRVO or CRVO.[50] A post hoc analysis suggested that eyes treated within 90 days of CMO being present were more likely to improve than eyes commencing treatment after this time point..

A

Ranibizumab: The pan-VEGF blocker, ranibizumab (LUCENTIS, Novartis) when given in 2 doses (0.3mg and 0.5mg) every month for 6 months, in the CRUISE Trial, was shown to produce a 3-line gain of visual acuity and corresponding anatomical response.[51] The mean gain in VA was 12.7 and 14.9 letters respectively with the 0.3 and 0.5 mg compared to the sham treated group at 6 months. Following the first 6 months, all patients were enrolled into an open-label extension for an additional 6 months and the overall 12 months results suggest that the visual gain established in the first 6 months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.6 injections in 1st 6 months, vs. 3.3 injections in 2nd PRN 6 month phase). These results also show that patients in the usual care group who were subsequently treated with ranibizumab 0.5mg benefited from such treatment. Early treatment may be preferable as confirmed from the earlier smaller observational studies [53-54], and a sham controlled study.[55]

Ranibizumab 0.5mg (LUCENTIS) has subsequently received a license for the treatment of macular edema following retinal vein occlusion (RVO) in the USA, although in the EU, regulatory authorisation is not expected till 2011.

D

Bevacizumab: The pan-VEGF blocker, bevacizumab is unlicensed for intraocular use. Several case series (without controls) indicate that approximately 50% of subjects with non-ischaemic CRVO improve 2 or more lines with intravitreal bevacizumab, whilst 90% of eyes showed vision

stabilization by 12 months.[56-60] However, the dosing schedule is unclear and the long-term outcomes remain unclear. The SmPC for bevacizumab has recently been altered to include cases of severe intraocular inflammation following intravitreal administration of the drug.
(http://www.medicines.org.uk/EMC/medicine/15748/SPC/Avastin)

GMC Guidelines on "Good Medical Practice" as it relates to the use of both off-label and unlicensed medications and the manufacturer's advice should guide physician directed intraocular use.

C

Pegaptanib: A phase II trial, and prospective case series indicate that intravitreal 0.3mg pegaptanib sodium when given every 6 weekly for 6 months improved the visual acuity by approximately 7 letters at 6 months. [61] The reported follow-up periods are short and so the treatment regimen and the response to treatment in the long-run remain unclear.

7.1.1.5 Recommendations for Further Follow-up

D

Follow-up after the initial 6 months of treatment will depend upon initiation of anti-VEGF agent or steroid treatment for macular oedema but will normally be required for up to 2 years in uncomplicated cases. The eyes should be monitored for ischaemia (> 10DD non-perfusion) and for occurrence/recurrence of macular oedema. The development of disc collaterals +/- resolution of the macular oedema should lead to discharge from clinical supervision. Detailed treatment and follow-up algorithms are provided in subsequent sections of this guideline.

7.1.1.6 Experimental treatments

Chorio-retinal anastomosis (C-RA) was recently evaluated in a small (n=113) randomised clinical trial. [62] Of patients in whom the C-RA was patent (76%), VA improved by a mean of 11.7 letters compared to controls. Side effects included

neovascularisation at the site of the anastomosis in18% and vitrectomy was required in 9%, due to macular traction or non-resolving vitreous haemorrhage. The procedure requires a special high power laser and significant operator experience. It is only recommended in the context of prospective data collection by an ophthalmologist specifically trained in its use. An Australian review of the technique concluded that there was only level IV evidence available.[63] The procedure was therefore classified as experimental, with potential to cause serious side effects.

Other studies have reported significant complications associated with the procedure e.g. choroidal neovascularisation[64], retinal and subretinal fibrosis or traction[65], and vitreous haemorrhage.[66]

Trials of other treatments such as radial optic neurotomy (RON) with pars plana vitrectomy, and thrombolytic therapies are under way.[67, 68] RON is essentially a procedure in which a radial incision is made in the nasal segment of the scleral ring in order to decompress the presumed pressure within this compartment so as to relieve pressure on the CRV. These, however, are only experimental at present and are, therefore, not recommended except as part of clinical trials.

7.1.2 Branch Retinal Vein Occlusion

The diagnosis of branch retinal vein occlusion is clinical, as described before. In doubtful cases, especially small BRVO, fluorescein angiography may be indicated to confirm the diagnosis. Fluorescein angiography is particularly useful in determining the extent of macular oedema and ischaemia. In the BVOS, approximately 50% of untreated eyes with BRVO retain vision of 6/12 or better whilst 25% will have vision of <6/60. Macular oedema and neovascularisation of the retina or disc are the two major complications which may require therapy. Retinal neovascularisation occurs in 36% of eyes with >5 DD, and 62% with >4DD area of non-perfusion, as reported in 2 independent studies.[6, 69]

7.1.2.1 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. [6 ,69] New vessels occur only when there is at least a quadrant of capillary closure and commonly after six months following the occlusion.

Follow up visits at 3- 4 monthly intervals are recommended in patients with one quadrant or more retinal ischaemia. It is recommended that sector laser photocoagulation is applied 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 neovascularisation is applied to the sector of retinal capillary closure.[6] 500-micron burns at the retina are used and are applied in a scatter pattern to the affected sector, one burn width apart are appropriate with sufficient energy to create a gentle burn. A quadrant usually requires 400-500 burns.

7.1.2.2 Laser treatments for macular oedema

A

Laser Photocoagulation: Randomised clinical studies in the laser treatment of macular oedema have demonstrated that a grid pattern of photocoagulation in the distribution of leaking capillaries is beneficial but it is recommended only after a period of three to six months following the initial event and following absorption of the majority of haemorrhage.[5, 70].

Fluorescein angiography should be carried out prior to this therapy usually at > 3 months if visual acuity is 6/12 or less. This has two functions. Firstly it identifies the leaking capillaries and secondly will indicate the degree of macula ischaemia, which may limit the value of photocoagulation.[70] It will also help to avoid laser to collaterals.

D

Laser Photocoagulation: Those with severe visual loss (less than 6/60 vision) and those in whom symptoms have been present for more than one year are unlikely to benefit from photocoagulation. [70]

D

Laser Photocoagulation: The optimal technique to administer laser photocoagulation for macular oedema requires gentle burns of 50 to 100um. The power depends on the individual patient. An average of between 20 to 100 applications (depending on the area of vascular leakage) are required in a grid pattern to the areas of vascular leakage but avoiding the foveal avascular zone (i.e. the burns must not approach the foveal centre by less than 1/2 DD). Collaterals should be avoided. [5,70]

Initial follow-up in all patients treated with laser photocoagulation should be at three months following the occlusion. Subsequent follow-up at three to six monthly intervals will depend on complications and laser treatment, and will not normally be required after two years in uncomplicated cases

7.1.2.3 Pharmacologic Treatments

A

Triamcinolone acetonide (TRIVARIS): Evidence for the use of a specific preparation of triamcinolone in BRVO is from the SCORE-BRVO Study (SCORE Study Report 6).[71,72] In this study, a preservative-free form of triamcinolone (TRIVARIS, Allergan) given at different doses, 1mg and 4mg, at four monthly intervals and with pre-defined re-treatment criteria, was compared to laser photocoagulation. Results showed that both doses of TRIVARIS produced both anatomical and functional improvement of macular oedema due to BRVO, but this was similar in magnitude to laser. In addition, at month 12, both the 1mg and 4mg doses had an inferior safety profile compared to laser in terms of a higher incidence of raised intraocular pressure >35mmHg (IOP) (2% and 14%, vs. 1%), incidence of cataract formation or progression (25% and 35%, vs. 13%) and need for cataract surgery (0% and

4%, vs. 3%). As such, laser is considered to have a more favourable benefit:risk profile to TRIVARIS in BRVO.

Similar to the case in CRVO, there is no Grade A evidence to suggest that the visual and anatomical responses seen with TRIVARIS in SCORE-BRVO would be replicated with off-label IVTA preparations such as KENALOG or TRIESENCE.[73-75] As such, GMC Guidelines on "Good Medical Practice" as it relates to the use of both off-label and unlicensed medications and the manufacturer's advice should guide physician directed intraocular use.

A

Dexamethasone Biodegradeable Implant: In the GENEVA study programme[48] (Haller, 2010), OZURDEX and an alternative dose of dexamethasone in an implant (0.35mg) was compared to a sham injection, in patients with CRVO and BRVO in 2 parallel multicentre studies. Re-treatment was possible 6 months after the first injection under pre-specified re-treatment criteria. . The first trial did not meet its original primary end-point , namely proportion of eyes gaining 15 letters. The two trials were analysed together and the primary outcome measure for all patients was time to achieve a ≥ 15 letter gain. The percentage of eyes with ≥ 15 letter gain in BCVA was significantly higher in both implant groups compared with sham at days 30 to 90 with a peak effect at 60 days. Subgroup analyses of the BRVO and CRVO subjects showed a significantly greater number achieved ≥ 15 letter gain from 30 to 90 days than sham treated eyes, and that sham treated eyes in the BRVO subgroup were more likely to improve spontaneously than similar managed CRVO eyes

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Based on the GENEVA study programme, OZURDEX has received FDA and EU approval for the 0.7 mg preparation, and is licensed in the UK for the treatment of adult patients with macular oedema following either BRVO or CRVO.[50] A post hoc analysis suggested that eyes treated within 90 days of CMO being present were more likely to improve than eyes commencing treatment after this time point..

A

Ranibizumab: The pan-VEGF blocker, ranibizumab (LUCENTIS, Novartis) given in 2 doses (0.3mg and 0.5mg) every month for 6 months, was compared with sham, in the BRAVO study. [76] At 6 months, the mean gain in VA was +16.6 and +18.3 letters (0.3 and 0.5 mg respectively) compared to +7.3 letters in the sham injection group. Sixty-one percent of the ranibizumab 0.5mg group achieved a 15 letter gain vrs 29% in the sham treated group. However from months 3-5, a single application of rescue laser photocoagulation was also allowed in all study arms if hemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤20/40 or mean central subfield thickness ≥250 μm, and compared with the visit 3 months before the current visit, patient had a gain of <5 letters in BCVA or a decrease of <50 μm in mean central subfield thickness. Based on these criteria, approximately 20% of patients in both ranibizumab arms received adjunctive laser, versus 55% in the sham injection arm. Following the first 6 months, all patients were enrolled into an open-label extension for an additional 6 months and the overall 12 months results suggest that the visual gain established in the first 6 months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.7 injections in 1st 6 months, vs. 2.7 injections in 2nd PRN 6 month phase).[76] These results also show that patients in the sham injection group who were subsequently treated with ranibizumab 0.5mg benefited from such treatment. However, as seen with the results of GENEVA & CRUISE studies, the visual acuity outcome never caught up in this delayed treated group compared to eyes treated earlier.

Ranibizumab 0.5mg (LUCENTIS) has subsequently received a license for the treatment of macular oedema following retinal vein occlusion (RVO) in the

USA, although in the EU, it has yet to receive regulatory approval. As such, GMC Guidelines on “Good Medical Practice” as it relates to the use of both off-label and unlicensed medications and the manufacturer’s advice should guide physician directed intraocular use.

C

Bevacizumab: Currently, increasing short-term data support the fact that multiple intravitreal bevacizumab injections reduce macular oedema secondary to branch retinal vein occlusion including those that had failed previous laser treatment.[57,59,60,77-79] The most common treatment regimen is two to three injections over the first 5-6 months.

However, further randomized, controlled trials are required to assess long-term safety and efficacy of intravitreal bevacizumab. No recommendations on the use of intravitreal bevacizumab can be made at this time. Due to the unlicensed nature of bevaciumab when compounded and distributed to third parties, GMC Guidelines on “Good Medical Practice” as it relates to the use of both off-label and unlicensed medications and the manufacturer’s advice should guide physician directed intraocular use.

C

Periocular triamcinolone: Periocular (orbital floor or retrobulbar) triamcinolone has been administered as treatment of macular oedema in BRVO.[80, 81] Although both routes of administration demonstrated efficacy, the results are short-lived. [81]

7.1.2.4 Other Treatments

A

The evidence on the efficacy of surgical interventions in BRVO are limited to case reports and case series.[82]

NICE has reviewed the evidence of arteriovenous sheathotomy for this condition and recommended that this procedure be done only as part of a research study. [83]

7.1.3 Hemisphere vein occlusion

The risk of rubeosis in ischaemic hemi-central vein occlusion is greater than that of BRVO but less than that of CRVO. The risk of disc neovascularisation appears greater for hemispheric vein occlusion than either ischaemic CRVO or BRVO.

The management of hemispheric vein occlusion is similar to that described for branch retinal vein occlusion, the guidelines for treatment options being those described above for retinal branch vein occlusion.

7.2 MEDICAL MANAGEMENT

7.2.1 Referral for medical investigation and treatment

IT IS THE RESPONSIBILITY OF THE OPHTHALMOLOGICAL TEAM TO ENSURE MEDICAL INVESTIGATION AND TREATMENT IS INITIATED ON DIAGNOSIS OF RETINAL VEIN OCCLUSION.

Recommended investigations for patients with retinal vein occlusion are listed in Table 2. It is the responsibility of the diagnosing physician or ophthalmologist to:

1. Investigate and interpret results.
2. Refer the patient for appropriate medical advice with urgency according to the severity of underlying risk factor(s).
3. Ensure that specialists in the relevant field should manage the rarer causes of retinal vein occlusion.
4. Ensure that initiation of medical management occurs within 2 months of diagnosis.

The importance of detecting and treating underlying medical conditions lies in the need to prevent further non-ocular target organ damage, as well as to prevent recurrence of venous occlusion particularly in the fellow eye.[68] Two long-term follow-up studies of patients with retinal vascular disease (retinal vein occlusion and retinal arterial occlusion) demonstrate excess cardiovascular morbidity, mortality from stroke, [69, 70] and myocardial infarction over a ten-year period.

7.2.2 Medical Management

Medical management should be targeted at three areas:

7.2.2.1 Restoring venous patency

D

Clinical & Diagnostic Work-up: This is applicable in a limited number of cases. Patients with 'incipient' retinal vein occlusion (consisting of the presence of dilated retinal veins and few widely scattered haemorrhages without any macular oedema in patients who are either asymptomatic or have transient episodes of blurring in the affected eye and may have slight increase in retinal circulation time on fluorescein angiography [88] should have medical investigation for underlying systemic risk factors and treatment urgently as there is the potential to prevent progression, or to reverse the existing occlusion.

The medical therapies explored to improve retinal venous flow include: -

C

Anti-coagulants: heparin

Fibrinolytic agents: streptokinase, tissue plasminogen activator (intravitreal or systemic)

Anti-platelet drugs: aspirin, prostacyclin, ticlopidine

These would seem to be logical treatments, but results from trials using heparin, streptokinase and warfarin have been disappointing with limited evidence of benefit owing to adverse effects of retinal and vitreous haemorrhage. Aspirin is not recommended for primary prevention of cardiovascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors .[89] Given that there is insufficient evidence to suggest that RVO is a risk factor for stroke or vascular mortality, the role of aspirin in RVO remains equivocal.

C

Haemodilution: The effects of haemodilution have been inconsistent in completed control trials in RVO and the treatment may have adverse affects on the patients' general well-being.

7.2.2.2 Ameliorate cardiovascular morbidity and mortality associated with retinal vein occlusion

C

Manage underlying risk factors: Although reports on the association of RVO with cardiovascular morbidity and mortality are conflicting, it is crucial that all cardiovascular risk factors be identified and treated in patients with RVO. [86, 87]

Cardiovascular risk factors identified in patients with retinal vein occlusion should be managed according to the Joint British recommendations on prevention of coronary heart disease and the recent updates on the management of hypertension and the use of statins.[91- 93]

Patients with rarer underlying conditions such as myeloma and inflammatory disorders should be referred and managed by appropriate specialists.

7.2.2.3 To prevent the recurrence of retinal vein occlusion

C

Several series have demonstrated that recurrence of retinal vein occlusion may occur in the affected eye or in the fellow eye in up to 15% of patients over a five year follow up period.[85] Rates vary according to studies in differing countries from 9 to 15%. In view of the poor potential visual outcome of patients with recurrent retinal vein occlusion, this aspect has been studied, but not in controlled trials. Available data supports the concept that recurrence of retinal vein occlusion may be reduced by medical treatments of underlying cardiovascular risk factors.

D

Hormone Replacement Therapy: Although estrogen-containing HRT should not be commenced in those women with retinal vein occlusion, continued use does not appear to be associated with a higher rate of recurrence.[94]

Historically, HRT was contraindicated and discontinued following central vein thrombosis.[13] Following the work of the Eye Disease Case-Control Study Group and Kirwan and associates[17], medical practice showed a trend to continue HRT following retinal vein occlusion due to the epidemiological evidence supporting HRT in the prevention of cardiovascular disease.

This policy has not lead to the potentially disastrous visual outcome of recurrence of retinal vein occlusion in the fellow eye. Currently, the decision about whether to continue HRT in a woman with retinal vein occlusion should be made on a case by case basis. The decision should be based on the woman's individual case history, including the indication for HRT use.

The degree of residual visual impairment may influence the decision as a recurrence in the fellow eye may have a potentially devastating visual outcome. Further guidance may be obtained from the results of thrombophilia screening, as this may provide an indicator of future risk. The current uncertainty about the effects of HRT on cardiovascular risk and recent guidelines for the use of HRT should also be considered.

7.2.3 Management of younger patients (less than 50 years of age)

Central retinal vein occlusion in this age group has been thought to have a more benign outcome in a greater proportion of patients, with spontaneous regression of the central retinal venous occlusive event being more common. However, at least 20% of patients develop poor visual outcome with severe neovascular complications.[95] Some authorities advocate the use of steroid therapy but this has not been tested in controlled trials.

Patients in this age group with BRVO usually have underlying systemic conditions such as hypertension or hyperlipidaemia which should be managed appropriately.[95] Those with CRVO present a particular problem in investigation and management. Many of these patients will have no identifiable underlying cause despite extensive investigation including the specialised investigations listed in Table 2.

In females the contraceptive pill is the most common underlying association, and caution is advised in patients with retinal vein occlusion. There is debate as to the exact prevalence of thrombophilic disorders in this patient group as well as appropriate therapy. Identified inflammatory disease should be treated as appropriate to the condition and referred for specialist medical advice.

7.3 TREATMENT ALGORITHMS

Dexamethasone intravitreal implant (Ozurdex) has received its FDA and EU licenses for treatment of retinal vein occlusions. These were based on the GENEVA Study results.

Clinical trial evidence for ranibizumab's effects in retinal vein occlusion are available from two phase III clinical studies in branch occulsions (BRAVO Study) and central occlusions (CRUISE study). Ranibizumab has recently received FDA approval for the treatment of RVO in the US. It is assumed that the EU licence for ranibizumab in the treatment of retinal vein occlusion will be available shortly.

The GMC Good Medical Practice Guidelines, and the manufacturer's advice should guide the intraocular use of ranibizumab in conditions outside its current indications.

7.3.1 Minimum Service Specifications for retinal vein occlusions

The minimum service specifications include personnel and equipment and are similar to those for neovascular age-related macular degeneration (nAMD). A consultant ophthalmologist with expertise in the management of medical retinal diseases is expected to lead the team. Support would be provided by other ophthalmologists at consultant, middle grade as well as trainees.

It is expected that there will be adequate support from the nurses, ophthalmic photographers/technicians. A clinic coordinator and data entry personnel equipped with an electronic patient record (EPR) system are essential to running an efficient service delivery. LogMAR visual acuity systems, and an OCT (Stratus or higher specification) are required as part of the minimum service requirements. (See RVO Service Provision, below).

7.3.2 Treatment of Risk Factors

It is essential to treat risks known to be associated with all types of RVO. It is the responsibility of the ophthalmological team to ensure that medical investigations and

treatment is initiated on diagnosis of RVO. This ensures that the risk of recurrence of RVO, or the occurrence of new occlusions are reduced. It also improves the chance of reversing the retinal vein occlusion, as well as ameliorate cardiovascular morbidity and mortality associated with RVO.

It is expected that the ophthalmic team will evaluate, or arrange for such evaluation, of the patient for common risk factors of systemic hypertension, diabetes, hyperlipidemia, and glaucoma/ocular hypertension. Referral would be expected to the appropriate physician for optimal management.

Patients should also be referred to the appropriate specialists in the relevant field for investigation and management of the rarer risk factors.

7.3.3 Treatment Algorithm for CRVO

7.3.3.1 Baseline Assessments

The minimum assessments required before commencing treatments for CRVO include:

1. Clinical examination including
    a. Best corrected visual acuity (BCVA)
    b. Pupillary reactions- the presence of a brisk afferent papillary defect (APD)
    c. IOP
    d. Gonioscopy
    e. Slit lamp biomicroscopy of the anterior segment and fundus
2. Retinal Imaging
    a. Colour fundus photographs in all cases
    b. Optical coherent tomography (OCT) with Zeiss Stratus or higher specification OCT

c. Fundus fluorescein angiography (FFA) where the interpretation is not confounded by the presence of marked intraretinal haemorrhage or can be based on clinical judgement.

7.3.3.2 Management at baseline

This depends on whether the CRVO is ischaemic or non-ischaemic. There is no evidence as to which combination of characteristics best defines ischaemic CRVO. It is important to note that up to 30% of patients with initially non-ischaemic central retinal vein occlusion will develop ischaemic transformation. This is usually heralded by further rapid visual deterioration and requires further assessment. CRVO especially of the non-ischaemic type needs to be differentiated from the ocular ischaemic syndrome and other simulating retinopathies.

7.3.3.3 Non-Ischaemic CRVO

By definition, there will be no iris or angle NV

1. If VA is 6/12 or worse +OCT ≥250 microns (Stratus, or equivalent) consider pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust evidence.
2. However, the presence of a brisk APD associated with VA<6/96 indicates potentially poor treatment outcomes.
    a. As such no treatment would be recommended for such cases. Watch for NVI/NVA, and treat as ischaemic CRVO below.

7.3.3.3.1 Management – Subsequent Follow-Up

1. Depending on baseline VA, OCT & FFA findings, and initial treatment options, monitoring will be required at varying frequencies during the first 6 months.

a. Assessments at each visit include VA, IOP, gonioscopy, fundoscopy, and OCT
b. From month 6 to 18 months, monitoring at monthly or 3 monthly, depending on the particular treatment of choice

2. Re-treatment as per the criteria below

7.3.3.3.2 Re-treatment Criteria

1. Based on the results of the clinical trials, treatment may be repeated unless
    a. VA>6/7.5 (84 letters on LogMAR) OR
    b. Central Retina Thickness (CRT) on OCT<250 microns OR
    c. Treatment is discontinued at the clinician's discretion (See below)
2. Re-treatment with dexamethasone implant (OZURDEX) should take place at 4 to 6 month intervals. There is only limited case report data to support dosing intervals less than 6 monthly.
3. Based on the CRUISE study, consider following the monthly injection schedule for the first 6-12 months, and the PRN re-treatment criteria from the study should be used as the basis for a PRN dosing regimen.

7.3.3.3.3 Treatment discontinuation

1. Treatment may be discontinued in the presence of continuing deterioration of vision or morphology of the macula.
2. Criteria for stopping treatment include
    a. No evidence of benefit from treatment, e.g. continued worsening / lack of stabilisation of vision despite an adequate trial of therapy.
    b. Rise in IOP uncontrolled by effective IOP lowering agents when dexamethasone implant (OZURDEX) has been the treatment

c. When using ranibizumab, or off-label agents such as other anti-VEGF agent e.g. bevacizumab, if in the clinician's opinion, the benefit: risk profile of further treatment is unfavourable, e.g. new MI or CVA.

7.3.3.4 Ischaemic CRVO

7.3.3.4.1 Management at baseline

In the presence of significant retinal ischaemia at baseline, regular monitoring is advised.

7.3.3.4.2 Subsequent Management

1. Monitoring should be at monthly intervals wherever possible. Where this is impossible, two monthly monitoring may be acceptable.

   a. **If Iris or angle NV present and anterior chamber angle is open**

      i. There is limited anecdotal evidence for the use of intravitreal bevacizumab in such cases and its use would be considered unlicensed, e.g. Panretinal photocoagulation (PRP), in combination with intravitreal bevacizumab and review 6-weekly.

      ii. Repeat PRP +/- intravitreal bevacizumab if NVI/NVA still persists at follow-up

      iii. Follow-up 3 monthly to up to 12 months. Subsequent follow-up will be guided by the clinical findings and on-going other treatment

   b. **If iris or angle NV and anterior chamber angle is closed**

      i. There is limited anecdotal evidence for the use of intravitreal bevacizumab in such cases and its use would be considered unlicensed, e.g. Advise PRP +/- intravitreal bevacizumab.

ii. Consider specialist glaucoma input and the options of cyclodiode laser therapy or tube/ shunt surgery

c. Where ischaemic CRVO occurs but there is no anterior segment vascularisation (NVI/NVG) as yet, and regular follow-up is impractical, it is reasonable to provide prophylactic treatment with PRP

7.3.4 Treatment Algorithm for BRVO

7.3.4.1 NON –ISCHAEMIC BRVO

7.3.4.1.1 BASELINE ASSESSMENTS

The minimum assessments required before commencing treatments for BRVO include:

3. Clinical examination including
    a. Best corrected visual acuity (BCVA)
    b. Pupillary reactions- the presence of a brisk afferent papillary defect (APD)
    c. IOP
    d. Gonioscopy if clinically indicated
    e. Slit lamp biomicroscopy of the anterior segment and fundus
4. Retinal Imaging
    a. Colour fundus photographs in all cases
    b. Optical coherent tomography (OCT) with Zeiss Stratus or higher specification OCT
    c. Fundus fluorescein angiography (FFA) where the interpretation is not confounded by the presence of marked intraretinal haemorrhage or as per clinical judgement.

7.3.4.1.2 Management of macular oedema secondary to BRVO with no or minimal evidence of macular ischaemia

1. 1. If patients with macular oedema secondary to BRVO are seen within 3 months of onset of BRVO, consider pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust clinical evidence of efficacy.
2. If patients are seen after 3 months from onset of BRVO, consider laser photocoagulation or pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust clinical evidence of efficacy.

*7.3.4.1.3 Management in eyes with evidence of marked macular ischaemia No immediate treatment is recommended. Watch for conversion of the RVO to i*schaemic type and subsequent neovascularisation

7.3.4.1.4 Re-treatment criteria

1. Based on the results of the clinical trials, treatment may be repeated unless.
    a. VA>6/7.5 (84 letters on LogMAR) OR
    b. Central Retina Thickness (CRT) on OCT<250 microns
    c. Treatment should be discontinued (See below)
2. Re-treatment with dexamethasone implant (OZURDEX) should take place with 4-6 months after first treatment.
3. Re-treatment with ranibizumab injections should occur monthly for the first 6 months followed by a PRN schedule based on re-treatment criteria from the BRAVO study
4. Re-treatment with modified Grid Laser Photocoagulation should be considered at 4 monthly intervals

7.3.4.1.5 Discontinuation of treatment

1. Treatment may be discontinued in the presence of continuing deterioration of vision or morphology of the macular
2. Criteria for stopping treatment include
    a. No evidence of benefit from treatment, e.g. Continued worsening / lack of stabilisation of vision despite treatment on 2 consecutive treatment visits
    b. Rise in IOP uncontrolled by effective IOP lowering agents when dexamethasone implant (OZURDEX) has been the treatment
    c. When using ranibizumab, or off-label agents such as other anti-VEGF agent e.g. bevacizumab, if in the clinician's opinion, the benefit: risk profile of further treatment is unfavourable, e.g. New MI or CVA.

7.3.4.2 Unlicensed and Contraindicated pharmacological agents - Considerations

1. Triamcinolone
    - There are no randomised controlled trials for any clinically available triamcinolone preparation, in retinal vein occlusion.
    - Clinical trial evidence for the use of triamcinolone in retinal vein occlusion comes from the SCORE Study and involves a single-use, preservative free preparation, using a triamcinolone concentration of 80mg/mL and of a narrow particle size distribution (TRIVARIS).
    - This TRIVARIS preparation is not currently available for clinical use anywhere in the world and is different from the commonly available Kenalog which is formulated in large vials with a preservative (BAK), has a triamcinolone concentration of 40mg/mL and has a wide variation in triamcinolone particle size.
    - The manufacturer of Kenalog (Bristol Myers Squibb) has specifically advised against its intraocular use and the product license in the UK specifically states that it is contraindicated for use intraocularly.

- The GMC Good Medical Practice Guidelines, and the manufacturer's advice should guide the intraocular use of Kenalog.

2. Anti-VEGF - Bevacizumab
    - Bevacizumab received its initial UK product license for the management of metastatic colorectal cancer in combination with 5-FU, a chemotherapeutic agent
    - Bevacizumab does not have a license for the management of any ocular conditions.
    - However, it has been used extensively in clinical practice with some success, for the management of many retinal conditions that have a VEGF driven pathophysiology, despite a lack of randomised controlled, clinical trial evidence.
    - The MHRA has recently confirmed that the license status in the UK for bevacizumab for the management of any retinal disease including retinal vein occlusion when compounded in a pharmacy and distributed to a third party in single dose pre-filled syringes, is "unlicensed", since its formulation is different from that used in the oncology setting.
    - The GMC Good Medical Practice Guidelines, and the manufacturer's advice should guide the intraocular use of bevacizumab.

7.3.4.3 Ischaemic BRVO

7.3.4.3.1 Management

1. Watch carefully for NV
2. Perform 3 Monthly follow, especially if the area of retinal ischaemia is > 4DD, and treatment is not required for macular oedema.
3. If NVE occurs, there is limited anecdotal evidence for the use of intravitreal bevacizumab in such cases and its use would be considered unlicensed, e.g.
    a. PRP+/- intravitreal bevacizumab 4-6 weekly until quiescent.
    b. The use of bevacizumab must be guided by the GMC Good Medical Practice Guidelines on the use of unlicensed products.
4. Follow-up 3 monthly to up to 12 months. Subsequent follow-up will be guided by the clinical findings and on-going treatment.

7.3.4.3.2 Other Options

All other treatments for BRVO, including A-V sheathotomy currently remain investigative, and as such are not recommended as part of routine clinical practice.

7.3.5 Hemispheric Vein Occlusion Algorithm

1. The management of hemispheric vein occlusion is similar to that described for branch retinal vein occlusion. Particularly, macular oedema secondary to hemi-vein occlusion is managed similarly to than in BRVO.
2. The risk of rubeosis in ischaemic hemi-central vein occlusion is greater than that of BRVO but less than that of CRVO. Assessment for anterior segment neovascularisation, including gonioscopy is therefore indicated. The management of NVI/NVG is the same as that secondary to CRVO.

7.4 RVO SERVICE PROVISION

Patients with retinal vein occlusion have previously been evaluated and followed up in eye clinics. Essentially, these clinic visits were aimed at identifying modifiable risk factors and managing the sight threatening complications of the vein occlusion. A few patients benefited from laser treatment. Recent large controlled clinical trials have unequivocally demonstrated the clinical efficacy for intravitreal injections of ranibizumab (Lucentis) and dexamethasone implants (Ozurdex) in preventing visual loss, and improving vision in all types of RVO.

7.4.1 Burden of disease due to RVO

There are currently no UK based studies on the prevalence of RVO. It is currently estimated from pooled data from 15 population studies from that there are about 520 new cases per million population of RVO.[8] These include 442 and 80 per million of BRVO and CRVO respectively. However, only 200-260/million will require treatment as some patients with RVO retain good vision and do not require any treatment.[8,19,20,21] BRVO occurs 2-3 times as common as CRVO.

7.4.2 Existing service provision and referral pathways

The management of an individual patient depends on the type of RVO and complications. Until recently, the management of retinal vein occlusion has been retinal laser photocoagulation for macular oedema (in BRVO), retinal or iris neovascularisation. Some cases of iris neovascularisation require cyclodiode laser or cyclocryotherapy. With the introduction of intravitreal delivery of dexamethasone and anti-VEGF treatments, the management of RVO is undergoing significant change as indicated in other parts of this guideline.

7.4.3 Anticipated workload

Given the effectiveness of intravitreal steroid injections and anti-VEGF therapies in all types of RVO, the number of patients eligible for treatment, and treatment frequency will increase significantly.

Patients receiving anti-VEGF therapy will require 4 - 6 weekly visits whilst those receiving dexamethasone may require injections every 4-6 months, but require monitoring visits as well at 4-6 weeks intervals. It will not be feasible to ask these patients to travel long distances for repeat treatments at these intervals. It is therefore essential to provide comprehensive treatment in the local hospital eye unit.

As these patients already attend the different local eye clinics for diagnosis and investigation, it is only the frequency of attendances and provision of injections that will alter. It is expected that clinic attendances will increase, probably to as much as 4-6 times the current attendances for RVO in the first 12 months following diagnosis. In addition, the times required for administering treatments have to be allowed for.

7.4.4 RVO Service Specifications

7.4.4.1 Early access

It is recommended that the time from referral from the primary source to initial evaluation and treatment by the retinal specialist at the eye clinic is not more than 2-4 weeks from presentation. This recommendation is based on reports from the CVOS that reported that the final visual acuity depends on the visual acuity at presentation.[19,20] More recently, the GENEVA Study [49] also suggested that visual recovery is better for eyes that are treated early after the onset of RVO.

7.4.4.2 Geographical equity of access to all regions within the UK

There needs to be immediate access to retinal specialists with expertise in the management of RVO for all patients, irrespective of geographic location. Referral pathways of RVO to treating specialists may vary but must be appropriate for different regions, as there may be several variations in geographic population distribution, logistics, expertise, and physician workload. The guiding principle is that no particular patient or region should be disadvantaged.

7.4.4.3 Minimum clinical services required for effective management

These include

1. Best corrected visual acuity assessments by optometrist or certified VA examiners
2. Colour Fundus photographs and Fundus Fluorescein angiography (FFA) by trained technical staff
3. Optical coherence tomography (OCT) with the Stratus or higher specification equipment by trained technical staff
4. Treatment initiated within 1-2 weeks of assessment
5. Appropriate facilities for IVT injection
6. Appropriate capacity for follow up, monitoring and re-treatment

7.4.5 RVO 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 Casualty, or Eye Clinic. Optometrists may be used for ‘screening’ or first examination of patients suspected of having RVO. Referrals from the optometrist should be sent directly to an ophthalmology department, and should not necessarily pass through the general practitioner as such a route introduces unnecessary delays.

Self referral or presentation to the Eye Casualty/Clinic should be encouraged, especially in patients who have second eye involvement.

7.4.6 Resources

The contemporary management of RVO requires collaboration between the ophthalmology multidisciplinary team and physicians. [96] The multidisciplinary ophthalmic team is similar to that required for the management of wet age-related macular degeneration (wAMD). (http://www.rcophth.ac.uk/docs/publications/AMD_GUIDELINES_FINAL_VERSION_Feb_09.pdf ***/***). Intravitreal injection facilities will exist and be shared with AMD services.

It is expected that all patients with RVO will require refraction LogMAR visual acuities, FFA and OCT at the commencement of treatment. Subsequent follow up will require OCTs, and FFA thereafter only when indicated.

7.4.7 Low Vision and Living with RVO

It is known that the sudden onset of visual loss whether unilateral or bilateral results in significant distress. CRVO is reported to be associated with a decreased vision-related quality of life as measured by the VFQ-25.[22,23]

Patients with reduced BCVA secondary to RVO or other causes are offered the opportunity of accessing low vision support and advice at an early stage. Advice and use of task lighting and magnifiers reduce the early impact of sight loss and the risk of falls. It is important 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 considering referring an individual to low vision and rehabilitation services.

It is easier to introduce the patient to low vision services at an earlier than latter stage of the disease. An individual can learn how to use their remaining vision more effectively, retaining independence and confidence.

8 TABLES

8.1 Table 1: Predominant associations for retinal vein occlusions

Patient group	Hypertension	Hyperlipidaemia	Diabetes Mellitus	No obvious cause
Young patients less than 50 years old	25%	35%	3%	40%
Older patients over 50 years	64%	34%	4 – 15%	21%
Asian	64%	50%	29%	10.7%
West Indian	83%	33%	38%	8.3%
Recurrent cases	88%	47%	3%	6%
Odd ratio	1.8 – 2.5	----------	1.6 – 2.1	----------

8.2 Table 2: Initial Medical Investigations for Patients Presenting with Retinal Vein Occlusion

ALL PATIENTS
Full blood count and ESR or plasma viscosity Urea, electrolytes, creatinine Random blood glucose Random cholesterol and HDL cholesterol+ Plasma protein electrophoresis ECG+ Thyroid function + It is essential to record these investigations for the Framingham equation

MORE SPECIALISED TESTS ACCORDING TO CLINICAL INDICATION
Thrombophilia screen Anti-cardiolipin antibody, lupus anticoagulant C-reactive protein Serum ACE Auto-antibodies - rheumatoid factor / anti-nuclear / anti DNA / ANCA Chest X-ray Fasting homocystine level

8.3 Table 3: Guide to diagnosis and targets for cardiovascular risk factors

Blood pressure (mmHg)	Diagnosis of hypertension > 140/ and, or > 90 sustained Optimal blood pressure is < 140/85 Audit standard is < 150/<90
Cholesterol (mmol/l)	Primary prevention - (CHD risk > 15% or total CVD risk > 20% 10 year risk)* +, statin usually required Secondary prevention target is <4.8 mmol/l, use of statin required
Diabetes mellitus	Diagnosis = fasting glucose > 7.0 mmol/l (multiple sampling) Glycosylated haemoglobin target is < 7% Optimal blood pressure is <130/80 Audit standard is <140/<80

Aspirin	Indicated if CHD risk > 15% 10 year* and (or CVD risk > 20%)+, in hypertensive patients, providing satisfactory blood pressure control and no contra-indication (peptic ulcer, allergy, history of haemorrhage e.g. recent haemorrhagic stroke, or in the initial stages of a severe haemorrhagic retinal vein occlusion)

Coronary Heart Disease (CHD) and Total CardiovascularDisease (CVD) risk calculated using the Framingham Equation, either using chart, discs or computerised programs (See Joint British Guidelines and British Hypertension Society guidelines).

Variables required for the calculation include random cholesterol, HDL cholesterol, systolic blood pressure levels, and age, sex, the presence of diabetes mellitus, smoking, and the presence of left ventricular hypertrophy on ECG.

+ British Hypertension Society guidelines 2004

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