



The ROYAL COLLEGE of
OPHTHALMOLOGISTS

Clinical Guidelines

Retinal Vein Occlusion (RVO) Guidelines

July 2015

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Summary

RVO Guidelines Expert Working Party Members

Chair:

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Miss Sobha Sivaprasad, Moorfields Eye Hospital and Kings College Hospital, London

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Declarations of Interest

The Chair has received research and educational grants from Novartis, Bayer, Allergan, and has worked on consultancy for Bayer, Allergan and Novartis.

Miss Sobha Sivaprasad has received an honorarium for advisory board meetings and speaker fees from Allergan, Novartis, Bayer and Roche. Been awarded institutional research grants by Novartis, Bayer, Allergan. Received support from industry towards publication for the AURA study and RELIGHT, and research grants from Research Grants: Novartis, Bayer, Allergan.

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 is has been involved with Pharma-sponsored Clinical Trials: Allergan, Bausch and Lomb, Novartis, Pfizer 2009 – 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 Tom Williamson has worked with research groups for Axsys Systems, and received funding for reports and publication work from Bayer. He is a member of an advisory committee for Bausch and Lomb and is a Director/Employee of the Consultant Eye Surgeons Partnership London and the London Claremont Clinic.

Mr James Talks has attended Advisory Boards for Bayer, Novartis and Allergan. He has participated in Pharma-sponsored Clinical Trials for Bayer and Novartis. He has also received educational travel grants from Bayer.

Dr Katherine Talks has been a member of an Advisory Board for Bayer which was not related to any aspect of these guidelines.

Consultation process

The guideline development group invited comments on this guideline from all UK consultant ophthalmologists and The Royal College of Ophthalmologists Lay Advisory Group prior to publication.

Search Strategy

Medline was used by individual authors of each section with relevant search terms scanning the database for duration up to 30th June 2014. The previous edition of the RCOphth guidelines and NICE single technology appraisals were used as reference sources. The format of the guidelines was changed to reflect the RCOphth Diabetic Retinopathy Guideline.

Review Date: September 2017

Preface

Since the publication of the previous edition of the Royal College of Ophthalmologists Retinal Vein Occlusion Guidelines (2010), a number of clinical studies have expanded the understanding of the condition and its management. Similarly, technological advances in retinal imaging including high definition Optical Coherence Tomography (OCT) and wide field retinal angiography have helped broaden clinical knowledge and facilitate treatment decisions. Novel therapies, rapidly becoming standard treatments, have revolutionised the management of RVO patients in clinical practice. The new guidelines aim to reflect all these changes and provide up to date guidance for busy clinicians. They will be updated on-line as necessary so as to keep abreast of significant further developments in the field.

The aim of the guidelines is to provide evidence-based, clinical guidance for the appropriate management of different aspects of RVO. The foundations of the guidelines are based on evidence taken from the literature and published trials of therapies as well as consensus opinion of a representative expert panel convened by the Royal College of Ophthalmologists with an interest in this condition. The scope of the guidelines is limited to current diagnostic tools, management and service set-up and delivery to facilitate delivery of optimal clinical care pathways and management for patients with RVO. The guidelines are prepared primarily for ophthalmologists; however they are relevant to other healthcare professionals, service providers and commissioning organisations as well as patient groups. The guidelines do not cover the rare, complex, complicated or unusual cases. It is recommended that readers refer to other relevant sources of information such as summaries of product characteristics (SPCs) for pharmaceutical products as well as the National Institute of Health and Care Excellence (NICE) and General Medical Council (GMC) guidance.

The new guidelines incorporate established and applicable information and guidance from the previous version with revision. Other chapters have been extensively revised and some new chapters are added. As stated in the previous version, the guidelines are advisory and are not intended as a set of rigid rules, since individual patients require tailored treatment for their particular circumstances. However, it is hoped that, if used appropriately, the guidelines will lead to a uniformly high standard of management of patients with RVO.

EVIDENCE is graded on three levels:

Level 1: Evidence based on results of randomised controlled trials (RCTs) power calculations or other recognised means to determine statistical validity of the conclusion.

Level 2: Evidence based on results of case studies, case series or other non-randomised prospective or retrospective analysis of patient data.

Level 3: Evidence based on expert opinion, consensus opinion or current recognised standard of care criteria where no formal case series analysis was available.

RECOMMENDATIONS for practice are based on treatment protocols and measures, which were recognised to improve patient care and/or quality of life based on:

Level A: where strength of evidence was universally agreed

Level B: where the probability of benefit to the patient outweighed the risks

Level C: where it was recognised that there was difference of opinion as to the likely benefit to the patient and decision to treat would be made after discussion with the patient

Section 1: Terminology and Disease Definition

Retinal vein occlusion (RVO) is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein. The most common aetiological factor is compression by adjacent atherosclerotic retinal arteries. Other possible causes are external compression or disease of the vein wall e.g. vasculitis.

Central retinal vein occlusion (CRVO) results from thrombosis of the central retinal vein when it passes through the lamina cribrosa.^{1,2} It 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 all four quadrants of the retina. In less severe forms the disc oedema may be absent. A previous CRVO may show evidence of optic disc and retinal collaterals, a telangiectatic capillary bed and persistent venous dilation and tortuosity, perivenous sheathing, arteriolar narrowing, and macular abnormalities (chronic macular oedema and retinal pigment epithelial changes).

Branch retinal vein occlusion (BRVO) is caused by venous thrombosis at an arteriovenous crossing where an artery and vein share a common vascular sheath.^{3,4} It has similar features to CRVO except that they are confined to that portion of the fundus drained by the affected vein.

Hemi-retinal vein occlusion (HRVO) affects either the superior or inferior retinal hemisphere, and the retinal haemorrhages are nearly equal in two altitudinal quadrants (the nasal and temporal aspects) of the involved hemisphere.

The two main complications of RVO are macular oedema and retinal ischaemia leading to iris and retinal neovascularisation.

Macular Oedema (MO): Thrombosis of the retinal veins causes an increase in retinal capillary pressure resulting in increased capillary permeability and leakage of fluid and blood into the retina. Co-existent retinal ischaemia (see below) may exacerbate this process by the production of vascular endothelial growth factor (VEGF) which in turn promotes retinal capillary permeability and leakage into the extracellular space resulting in further development of MO. MO is the most common cause of visual impairment in RVO, followed by foveal ischaemia.

Retinal ischaemia and iris and retinal neovascularisation: Varying degrees of retinal ischaemia due to non-perfusion of retinal capillaries may occur and principally depends on the degree of retinal vein thrombosis. These changes result in increased production of VEGF and other cytokines, which promote new vessel formation principally but not exclusively involving the iris and angle in CRVO and the retina in BRVO. These complications can lead to neovascular glaucoma, vitreous haemorrhage and tractional retinal detachment with severe visual impairment.

Ischaemic versus non-ischaemic RVO: Both CRVO and BRVO can be broadly classified into ischaemic and non-ischaemic types based on the area of capillary non-perfusion, and this distinction is useful for clinical management. The Central Retinal Vein Occlusion study (CVOS) defined ischaemic CRVO as fluorescein angiographic evidence of more than 10 disc areas of capillary non-perfusion on seven-field fundus fluorescein angiography.^{5,6} However, this definition may require revision to be appropriate for the more recently adopted wide-angle imaging. It is important that a clear distinction is made between foveal ischaemia and an ischaemic RVO (i.e. global retinal ischaemia).

Ischaemic CRVO is associated with one or more of the following characteristics:-

1. Poor visual acuity (44% of eyes with vision of <6/60 develop rubeosis [CVOS])^{5,6}
2. Relative afferent pupillary defect
3. Presence of multiple dark deep intra-retinal haemorrhages
4. Presence of multiple cotton wool spots
5. Degree of retinal vein dilatation and tortuosity
6. Fluorescein angiography showing greater than 10 disc areas of retinal capillary non-perfusion on 7-field fluorescein angiography (CVOS)^{5,6}
7. Electrodiagnostic tests (ERG): reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time on the electroretinogram^{7,8,9,10,11}

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 eyes with initially non-ischaemic CRVO may convert to ischaemic subtype.^{11,12,13,14} This is usually heralded by further rapid visual deterioration and requires additional assessment.

The prevalence and incidence of ischaemic BRVO is not fully defined. Ischaemia involving the macula causes visual impairment. However, ischaemia may occur in peripheral areas of the retina and result in retinal neovascularisation and vitreous haemorrhage. Neovascular glaucoma is rare in ischaemic BRVO.

Section 2: Natural History of Retinal Vein Occlusions

Central Retinal Vein Occlusion

Although some patients with CRVO can experience an improvement in MO and visual acuity, visual acuity generally decreases over time. A systematic review on the natural history of untreated CRVO reported that only a small proportion of patients showed spontaneous improvement in visual acuity and their final visual outcome at 3 – 40 months was not typically greater than 73 ETDRS letters (Snellen equivalent ~6/12). Only 20% of patients who

present with an initial visual acuity of 35 – 65 ETDRS letters (Snellen equivalent 6/60 to 6/18) are likely to improve spontaneously.

Non-ischæmic CRVO may resolve completely without any complications. Follow-up of such cases for at least two years is usually recommended but the development of disc collaterals and the resolution of macular oedema for at least 6 months should allow the discharge of the patient from clinical supervision. However, 30% may convert to an ischæmic CRVO over three years due to an increase in area of non-perfusion. More than 90% of patients with ischæmic CRVO have a final visual acuity of 6/60 or worse.^{5,6}

Branch Retinal Vein Occlusion

Based on the Branch Retinal Vein Occlusion study (BVOS),¹⁵ the prognosis of BRVO is better than CRVO with approximately 50 – 60% of untreated BRVO cases retaining a visual acuity \geq 6/12 after one year.

Therefore when a patient presents 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.

However, many patients may not present immediately and only 18 – 41% of eyes with MO due to BRVO at presentation show spontaneous improvement and, on average, visual acuity does not improve above 6/12 in this cohort. Approximately 20% of untreated MO due to BRVO experience significant deterioration of visual acuity over time.¹⁵

Bilateral involvement

The majority of RVO cases present as a unilateral condition. However, 5 – 6% present with evidence of bilateral BRVO and 10% of the BRVO patients will have fellow eye involvement over time. Similarly, approximately 10% of CRVO patients present with bilateral involvement at baseline and 5% may have fellow eye involvement over a one year period.¹⁶

Section 3: Epidemiology of Retinal Vein Occlusion

Retinal vein occlusions are a common cause of visual loss in the United Kingdom, and are the second commonest cause of reduced vision due to retinal vascular disease after diabetic retinopathy, with BRVO occurring 2 – 6 times as frequently as CRVO.¹⁵ There is no prevalence or incidence data from England or Wales. US data reported in 2008 indicate a 15 year incidence of 500 new cases of CRVO per 100,000 population and 1800 BRVO cases per 100,000 population.¹⁷

The incidence and prevalence of both these conditions increases with age. Australian data suggests that the prevalence of RVO is 0.7% for those younger than 60 years, 1.2% for those 60 – 69 years, 2.1% for those 70 – 79 years and it increases to 4.6% in people aged 80 years or above. No gender or racial differences in prevalence of both these conditions have been reported.

Most patients are unilaterally affected by this condition. Under 10% of CRVO are bilateral at presentation (range 0.4% to 43%). The fellow eye involvement over a one year period is

approximately 5%. Similarly, only 5% – 6% of patients at baseline have BRVO in both eyes at diagnosis with 10% showing bilateral involvement over time.

Visual impairment is more frequent with CRVO than BRVO. Macular oedema (MO) is the leading cause of visual impairment. It is estimated that approximately 11,600 people with BRVO and 5,700 people with CRVO suffer from visual impairment due to MO each year in England and Wales based on an annual incidence of BRVO of 0.12% and CRVO of 0.03% in people aged 45 years or older and 85% of BRVO and 75% of CRVO developing MO within two months of diagnosis and 50% of BRVO and 100% of CRVO experiencing visual impairment due to MO (NICE 2011).

Section 4: Aetiology and risk factors of Retinal Vein Occlusions

Retinal vein occlusion is due to thrombosis of retinal veins (central, hemi or branch).^{1,2,18} Atherosclerosis of the adjacent central retinal artery possibly compresses the central retinal vein at the lamina cribrosa leading to consequent thrombosis in the venous lumen. Rarely, retrobulbar external compression from thyroid eye disease, orbital tumour, or retrobulbar haemorrhage may be a cause. Whether primary thrombosis plays a role in this condition remains questionable. The clinical appearance is largely related to retinal ischaemia and the effects of elevated concentrations of VEGF in the vitreous and retina. Animals injected with VEGF will develop retinal hemorrhages and the use of anti-VEGF causes retinal hemorrhages to resolve. Branch retinal vein occlusions may relate to the point of arterial venous crossing in the retina.

Associations with retinal vein occlusions

The following conditions have variably been reported as associations:

- Hypertension^{17,19,20,21,22,23,26}
- Diabetes^{17,19,20,21,23,24}
- Hyperlipidaemia²⁵
- Hyperhomocysteinaemia
- Blood coagulation disorders: high plasma viscosity such as due to leukaemia, myeloma, Waldenstrom's macroglobulinaemia, myelofibrosis, changes in protein C pathway, Factor V Leiden.
- Systemic inflammatory disorders (Behçets disease, polyarteritis nodosa, sarcoidosis, Wegener's Granulomatosis and Goodpasture's Syndrome)
- Glaucoma
- Shorter axial length
- Retrobulbar external compression

The most common associations of 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.

The Eye disease case control study¹⁹ compared 258 patients diagnosed with CRVO between 1986 – 1990 in five centres, with 1142 age-matched controls. The controls were recruited a year after the diagnosis of CRVO, from the same eye clinics. This study found an association with increased systemic hypertension, diabetes and glaucoma. These associations were

higher with ischaemic CRVO. 65% had hypertension (167/257) compared to 44% of controls (506/1139) odds ratio 2.5 (1.8 – 3.4). Only 2% were started on anti-hypertensive medication at the time of diagnosis. CRVO was less common with moderate alcohol intake. The incidence of diabetes was 16% (43/258) compared to 9% in controls (102/1142); odds ratio two (1.3 – 2.9).

In a study looking at the association of mortality risk with CRVO, 439 patients diagnosed with CRVO in Denmark, between 1976 and 2010, were compared to 2195 age and sex matched controls from the Danish national patient registry alive at the date of diagnosis of CRVO.²¹ Co-morbidity was recorded for 10 years pre-diagnosis and over follow up for five years. CRVO was rare in the general population. Hypertension was found in 68% compared to 55% of controls, odds ratio 2.03(1.48 – 2.78), based on assessing hospital discharge records and drug prescriptions. Diabetes incidence was 16% vs 8.7%, OR 2.08 (1.41 – 3.08). However, it is possible that there may have been a selection bias in this study, as the CRVO cases were recruited in the hospital whilst the controls were from the general population.

In the Geneva Study (2010) which evaluated 1267 retinal vein occlusions (CRVO/BRVO) and their response to Ozurdex, hypertension was found in 64% of patients and diabetes in 12%.²⁷ Their average age was 65. This is in keeping with the rates found in the aforementioned studies.

The incidence of hypertension is common in the population. Indeed the incidence of hypertension in persons over 65 years of age in the UK (NICE CG127, 2011)²⁸ and in the USA is currently approximately 65%. The United States (US) National Health and Nutrition Examination survey of 2009 – 2010 showed that the age-specific and age-adjusted prevalence of hypertension among adults aged 18 and over was 6% in age group 18 – 39 years, 30.4% in 40 – 59 years, and 66.7% in people aged 60 years or above.²⁹

The guidelines on diagnosing and managing hypertension are summarised in the NICE CG127 for hypertension: ‘Clinical management of primary hypertension in adults’ which was published in August 2011.

Diagnostic criteria are:

Stage 1: Clinic BP 140/90 or higher and ambulatory blood pressure monitoring (ABPM) day time average, or average home blood pressure monitoring (HBPM) is 135/85 or higher.

Stage 2: Clinic 160/100mmHg or higher and subsequent ABPM or HBPM average blood pressure is 150/95

Severe hypertension: Clinic systolic BP is 180mmHg or higher or diastolic BP is 110 or higher.

The current incidence of diabetes in the population seems to be as common as in the reported cases of vein occlusions. The UK 2013 statistics has reported an overall prevalence of diabetes of 6% from data collected in 2012/13, and the highest prevalence of 26.05% and 26.46% in England and Wales, and Scotland respectively in the 60 – 69 years age group.³⁰ In the United States, the national diabetes statistics in 2014 estimated diabetes was present in 25.9% in people aged over 65 years.³¹ 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 7.5% (NICE TA315, 2014). (<https://www.nice.org.uk/guidance/TA315>: Canagliflozin in combination therapy for treating type 2 diabetes. Accessed 19 Sep 2014).

Section 5: The relation of RVO to systematic vein occlusions and the role of testing for venous occlusions risk factors

The main risk factors for systemic venous thromboembolism (VTE) are: age, immobilisation, surgery, cancer, pregnancy, oestrogen containing oral contraceptives and HRT. There is no good evidence that these are a significant risk for RVO. Conditions that cause systemic inflammation or hyperviscosity increase the risk of VTE and can rarely be associated with a retinal vein occlusion.

An individual may have an increased risk of VTE due to an inherited or acquired thrombophilia. The British Committee for Standards in Haematology (BCSH) Clinical Guidelines for testing for heritable thrombophilia (2010)³² and the Unusual Site VTE BCSH guidelines (2012)³³ concluded that such testing was not appropriate for retinal vein occlusions. Meta-analyses have not identified a statistically significant relationship with RVO and heritable thrombophilia, but suggested that Factor V Leiden, F5G1691A (OR 1.5) and factor II gene, F2G20210A (OR 1.6) mutations might be weak risk factors.³⁴ A more recent analysis confirmed an odds ratio of 1.5 for F5G1691A indicating a much weaker association with RVO than with lower limb DVT.³⁵ Acquired thrombophilia includes anti-phospholipid syndrome (APS), myeloproliferative disorders and paroxysmal nocturnal haemoglobinuria (PNH). APS is an acquired autoimmune disorder associated with thrombosis (arterial, venous or microvascular) and/ or defined pregnancy morbidity. Although a number of other possible clinical associations have been reported RVO is not recognised as a clinical event in the most recent consensus statement on classification criteria.³⁶ Guidelines on the diagnosis and management of APS in the UK have been recently updated.³⁷ These guidelines detail the laboratory testing criteria required for the diagnosis of APS which require persistence of test abnormalities on repeat testing >12 weeks apart. Antibodies may be detected as a lupus anticoagulant (LA) using coagulation based assays (e.g. DRVVT) or solid phase ELISA tests for IgG anti-phospholipid antibodies. For the latter the specificity, isotype and titre of the antibodies are important with only IgG antibodies considered to be relevant for thrombosis risk. Sample collection and preparation can affect the detection of LA. The diagnosis of APS therefore depends on a thorough assessment of the clinical history, consideration of alternative causes of thrombosis or pregnancy morbidity and review of the laboratory data in the light of knowledge of the limitations of the assays.

Anti-phospholipid antibodies (aPL) are a common incidental finding e.g. in the Leiden thrombophilia study, a population-based case control study of VTE, LA was present in 0.9% of unaffected controls (compared to 3.1% of cases), and anti-β2GPI in 3.4% of controls (compared to 7.5% of patients).³⁸ In a larger study, 178 asymptomatic carriers of aPL were followed up for 36 months and no episode of thrombosis was detected.³⁹ A diagnosis of APS can only be made in the context of recognised clinical features and persistent laboratory test abnormalities and influences the therapeutic management decisions on duration of anticoagulation and use of anti-platelet agents to reduce the risk of recurrent clinical events. As there is no consensus that treating RVO with anticoagulation is beneficial, the testing for aPL is not recommended for a RVO occurring in isolation of other recognised APS clinical associations.

Hyperhomocysteinemia is independently associated with an increased risk of thrombosis. However, elevation of plasma homocysteine is found in 5 – 7% of normal people, and pharmacological strategies to lower plasma homocysteine have so far failed to reduce vascular events.⁴⁰

Section 6: Cardiovascular morbidity and mortality

Not surprisingly given the association with hypertension and diabetes some studies have found a higher incidence of cardiovascular and cerebrovascular morbidity and mortality in RVO patients compared to controls. However this has not been found in all studies.

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)^{41, 42, 43, 44}

Cardiovascular disease under age 70 was noted in one study⁴³ but not in another report⁵

- Peripheral arterial disease²¹

Peripheral venous disease (13/439 3% pre diagnosis of CRVO).²¹

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.

Is RVO a predictor for the future development of stroke?

Tsaloumas and associates reported that RVO did not increase the rate of stroke development in a hospital-based study on 549 RVO patients after a mean follow-up period of 9.08 years.⁴² These findings were confirmed in a retrospective population based study in Taiwan on 350 RVO versus 2100 controls.⁴³ However, Cugati et al found that men with RVO are associated with a non-significant 2.3-fold higher risk of cerebrovascular mortality for all ages in a pooled cohort of two-population based studies.⁴⁴ Similarly, a population-based study utilizing pooled data from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study reported that carotid artery plaques are more common in patients with RVO⁴⁵; however, this association was not noted in another population-based study.⁴⁶ In the study by Bertelsen et al (2014) the incidence of stroke was higher both before and after the diagnosis of CRVO.²¹

Is RVO associated with increased mortality?

Reports on this subject are conflicting too. Bertelsen et al (2014) found a higher overall increased mortality compared to controls for CRVO (5.9 deaths/100 person years compared to 4.3 deaths/100 person years (HR, 1.45;95% CI,1.19 – 1.76).²¹ However, when the data was adjusted for overall occurrence of cardiovascular disorders including hypertension, peripheral vascular disease, ischaemic heart disease, myocardial infarction, congestive cardiac failure, cerebrovascular disease and diabetes, the mortality rate was comparable to that in the control population (HR 1.19;95% CI,0.96 – 1.46).²¹

Using the same methodology, this finding of no specific increase in mortality was also found for BRVO.⁴⁷ Participants with BRVO at baseline did not have an increased 8-year risk of mortality due to ischaemic heart disease in the Beaver Dam study.⁴⁷ A population based study reported that RVO did not predict acute myocardial infarction.⁴⁷ Similarly, other reports show that RVO is not associated with cerebrovascular mortality.^{20,49} However, Cugati et al (2007) found that men with RVO were associated with a non-significant 2.3-fold higher risk of cerebrovascular mortality for all ages in a pooled cohort of two-population based studies.⁴⁴ In another population-based study (Beijing Eye Study), RVO was significantly associated with an increased overall mortality rate in subjects aged below 69 years.⁵⁰ Based

on the current evidence, careful cardiovascular assessment and treatment of cardiovascular risk factors by the patient's physician are advocated in young male patients with RVO.⁵¹

Section 7: Distinct clinical entities of retinal vein occlusion

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.¹² The risk of disc neovascularisation appears greater for hemispheric vein occlusion than either ischaemic CRVO or BRVO.⁵² The management of hemispheric vein occlusion is similar to that described for branch retinal vein occlusion.

RVO in 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.⁵³ The causation of RVO in the younger person is still unclear in most cases. A role for dehydration in such cases has been suggested but remains unproven.⁵⁴

Section 8: Medical investigations in retinal vein occlusions

In general, the aims of investigations in a medical condition are to potentially treat causative factors that might improve the condition, prevent progression or prevent recurrence in the same eye or in the other eye, and to reduce the risk to overall health. Apart from the rarely associated hyperviscosity conditions, there is little evidence that the natural history of a RVO will be influenced or a further RVO prevented, and 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

Testing the BP, serum glucose, FBC and ESR will detect associations with retinal vein occlusions that require urgent action such as severe hypertension, uncontrolled diabetes or rarely blood conditions such as leukaemia. A raised ESR may represent an inflammatory condition or a blood disorder such as myeloma.

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. For example, hypertension and diabetes are common and NICE guidance for assessment and management

should be followed such as ambulatory BP measurements, which are not easily performed from an eye clinic; testing the lipid profile may require a fasting test.

The history, ocular examination and initial test results may direct further investigations. For example, raised plasma viscosity or raised white cells could point to Waldenstrom's macroglobulinaemia and so questions about symptoms such as night sweats, a physical examination for lymphadenopathy and immunoglobulin electrophoresis may be indicated.

Bilateral presentation or any sign of a vascular disturbance in the other eye, such as a few dot haemorrhages should increase suspicion of an underlying systemic condition.

The British Society of Haematology does not recommend routine thrombophilia testing for retinal vein occlusions.^{32,33} Testing for acquired thrombophilia in an isolated retinal vein occlusion is also not recommended. (See section 5).

It is recommended that oestrogen-containing hormone replacement therapy and oral contraceptives not be commenced in those women with a history of retinal vein occlusion. However, the continued use in a patient who develops RVO does not appear to be associated with a higher rate of recurrence. 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.

Section 9: Ophthalmological management of CRVO

Macular oedema

Laser photocoagulation

Macular oedema following CRVO results from leakage of perifoveal capillaries into the macular area and is typically associated with visual loss. There was no proven treatment for this condition until five years ago. The CVOS study failed to indicate benefit from grid treatment, although a trend in favour of treatment was observed in younger patients.⁵⁵ 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.

Intravitreal steroids

The rationale for the use of intravitreal triamcinolone acetonide (IVTA) to treat MO is that corticosteroids reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF.^{56,57} Evidence from the SCORE study indicates that it may produce anatomical and functional improvement of MO related to CRVO but the effects are short-lived.⁵⁸ Repeated IVTA may not necessarily improve vision.⁵⁸ This treatment is rarely offered to patients today. It is important to appreciate further that the preparation of triamcinolone used for intravitreal injections in the SCORE Study is unpreserved (TRIVARIS, Allergan), and different from the preparation freely available in the UK (Kenalog, Squibb), which is recommended for intra-articular injection.

The rationale for the use of intravitreal dexamethasone to treat MO is similar to that of IVTA, although dexamethasone has been shown to be a more potent corticosteroid than IVTA. However, intravitreal dexamethasone, in its free form, has a short half-life, which limits its clinical usefulness.⁵⁹ A pre-filled applicator for single-use, sustained release with a biodegradable implant containing 0.7mg of dexamethasone (Ozurdex, Allergan) was analysed in the GENEVA study programme.²⁷ In this study, Ozurdex and an alternative dose

of dexamethasone implant (0.35mg) were compared to sham injection, in patients with CRVO and BRVO in two parallel multicentre studies, the results and analyses of which were published together as the GENEVA study. Re-treatment was possible six months after the first injection under pre-specified re-treatment criteria. 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. Subgroup analysis also revealed that sham-treated eyes in the BRVO subgroup were more likely to improve spontaneously than sham-treated CRVO eyes, corroborating previous natural history data from the CVOS and BVOS studies. In terms of safety, raised IOP peaked at month two (3.2% of patients had an IOP >35 mmHg), but declined significantly by month three and was close to 0% by month six, with 19% of patients requiring an IOP-lowering agent at month six and 0.7% of patients requiring any IOP-lowering surgical procedures. Similarly, rates of cataract progression were low with 7% progression at month six, compared to 4% in the sham group.²⁷

The results further indicate that eyes treated earlier had a better chance of visual acuity gain, and that those treated later (i.e. controls that were subsequently treated) never achieved the final visual acuity gains of those treated promptly.

Based on the GENEVA study programme²⁷, 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 MO following CRVO. NICE TA 229 has recommended the use of Ozurdex in the treatment of MO secondary to CRVO.

Anti-VEGF Therapies

Anti-VEGF agents are now a popular choice for treatment of MO due to CRVO based on the fact that VEGF-A is a key cytokine that mediates vascular leakage and causes MO in RVO. Intraocular VEGF levels are significantly high in CRVO compared to controls.

1. Ranibizumab

The pan-VEGF-A blocker, ranibizumab (LUCENTIS, Novartis) is EMA approved and recommended by NICE (NICE TA238, May 2013) for the treatment of visual impairment due to MO secondary to RVO.

Ranibizumab is a humanized recombinant monoclonal antibody fragment that selectively binds to human VEGF-A, and prevents it from binding to its receptors. The licensed dose of ranibizumab is 0.5mg/0.05ml given as a single intravitreal injection. The interval between two injections is at least 4 weeks. The pivotal Phase III randomized controlled trial that evaluated ranibizumab (0.3mg and 0.5mg) in MO due to CRVO was the CRUISE study.⁶⁰ Eligible patients with MO due to CRVO of less than 12 months duration with BCVA of 20/40 to 20/320 and central macular thickness of $>250\mu\text{m}$ on Stratus OCT were randomized 1:1:1 to receive monthly injections of 0.3mg, 0.5mg or sham injections for a six month period followed by a further six-month observation period in which all patients in the study (including sham group) were monitored monthly and received ranibizumab PRN if they met pre-specified re-treatment criteria. Functional and anatomical retreatment criteria included Snellen equivalent BCVA $\leq 20/40$ or mean central subfield thickness of $\geq 250\mu\text{m}$ in the study eye. At baseline, patient demographics and ocular characteristics of study participants were

similar across the three randomly allocated treatment groups. The primary efficacy end-point of the CRUISE study was mean change from baseline BCVA (ETDRS letters) at 6 months. The mean gain in BCVA in the 0.5mg ranibizumab group (n=130) was 14.9 letters. 95% CI for mean was 12.6 to 17.2. The difference in mean with sham arm was 14.1. 47.7% gained ≥ 15 ETDRS letters at six months. The secondary efficacy end-point included mean change in BCVA from baseline to 12 months, categorical visual acuity outcomes, anatomical changes evaluated by OCT and patient reported-outcomes. Approximately 85% of the participants completed the 12 months study. The mean number of injections in the first six months in the ranibizumab (0.5mg) was 5.6 (SD 1.2) and 3.3 (SD 2.1) in the six months observation period. The sham arm received a mean of 3.7 (SD 2.2) in the observation period.⁶⁰ The mean change from baseline BCVA at 12 months was 13.9 letters (95% CI for mean 11.5 – 16.4) and 50.8% gained ≥ 15 letters from baseline. 12.3% had a visual acuity of less than Snellen 20/200 at month 12.

Patients who completed the 12 month CRUISE trial entered an open-label, single arm, multicentre follow-up study called the HORIZON extension study in which they could continue to receive 0.5mg ranibizumab on a PRN basis.⁶¹ The primary outcome was mean change from HORIZON baseline BCVA score at 24 months. The long-term safety and efficacy was evaluated in this open-label study. Sixty percent (60%) of CRUISE patients (n=181) completed month 12 of the HORIZON study. A total of 151 patients with CRVO received ranibizumab therapy in the HORIZON study and the mean (range) number of injections was 3.9 (range 0 – 12). The HORIZON Study showed that the mean letters gained at 12 months of HORIZON from CRUISE baseline was +12 letters in the initial ranibizumab 0.5mg arm and 7.6 letters in the initial CRUISE sham arm.⁶¹ The mean change in BCVA score from HORIZON baseline to 12 months was -4.1 ETDRS letters in the ranibizumab (0.5mg) group. A key finding from the HORIZON was that long-term use of ranibizumab is well-tolerated. Reduced frequency of injections in the second year of treatment was associated with worse visual and anatomical outcomes. There are clear differences in outcomes for BRVO and CRVO patients. CRVO patients required frequent follow-up and continued ranibizumab therapy to control oedema.⁶¹

The RETAIN Study included patients with CRVO and BRVO in a prospective follow-up of a subset of patients from two phase three trials of ranibizumab in RVO.⁶² The mean follow-up was 49.7 months for CRVO patients, where 14 of 32 patients (44%) had edema resolution, with 71% receiving their last injection within two years of treatment initiation. However, in unresolved patients, a mean number of 5.9 injections of ranibizumab were given in year 4. In eyes with resolved disease had greater improvement in BCVA compared to baseline (25.2 vs. 4.3 letters; $p=0.002$).⁶²

2. Aflibercept

The pan-VEGF-A, VEGF-B and placental growth factor (PlGF) blocker, aflibercept, continues to be evaluated in clinical trials which thus far have shown promise, resulting in NICE issuing TA305 in February 2014 with regards to the use of aflibercept in CRVO. COPERNICUS was a phase three, prospective, randomized, double-masked trial (n=187) comparing monthly intravitreal injection of aflibercept 2mg (n=115) with sham (n=74) for the treatment of MO secondary to CRVO.⁶³ Patients included were treatment naïve adults with MO secondary to CRVO with CRT on OCT of ≥ 250 μm and ETDRS BCVA of 20/40 to 20/320. The primary efficacy endpoint was the proportion of eyes with a gain of ≥ 15 ETDRS letters in BCVA from baseline to week 24. Between weeks 24 and 52, masking was maintained and all patients were dosed PRN according to pre-determined retreatment criteria. Patients received a sham injection if retreatment was not indicated.

Key secondary efficacy endpoints (all assessed at week 24) were change from baseline in BCVA scores and change from baseline in central retinal thickness (CRT) as well as the proportion of patients progressing to neovascularization. Treatment was then continued on a PRN basis in all patients between weeks 52 and 100.⁶³

At 52 weeks, the initial aflibercept treatment group gained a mean of 16.2 ETDRS letters vs sham-treated eyes (including sham and sham/crossover to aflibercept patients) which gained 3.8 letters ($P < 0.001$).⁶³ BCVA improved steadily in the aflibercept group beginning at week four and continued until week 24, with visual acuity decreasing in the sham group. At week 100, patients in the aflibercept treatment group showed a mean change from baseline BCVA of 13.0 ETDRS letters, compared to sham-treated eyes, which gained 1.5 letters ($P < 0.001$). In addition 49.1% of aflibercept treated participants had gained ≥ 15 ETDRS letters in BCVA at 100 weeks. This study also showed that unless treatment is instigated early, there is likely to be a degree of irrecoverable visual loss.⁶³

The aflibercept group demonstrated a rapid reduction in CRT by week 24 and this was maintained to week 52. However, by week 52, participants initially on sham treatment who crossed over to aflibercept treatment achieved a similar decrease in central retinal thickness to those who started on aflibercept. This similarity in anatomical response between the two groups was maintained to 100 weeks (CRT $-413.0 \mu\text{m}$ for aflibercept initially/aflibercept PRN later vs $-381.8 \mu\text{m}$ for sham initially/aflibercept PRN later). In summary, therefore, although the anatomical response in the sham/aflibercept PRN patients largely caught up with that of the aflibercept/aflibercept PRN group, the BCVA did not. This may suggest that persistence of structural change can lead to irreversible functional loss.

Progression to ocular neovascularization during the first 52 weeks was eliminated in the aflibercept group (0% vs. 6.8% in the sham treatment group $P = 0.006$). All neovascularization seen in the sham group occurred in the anterior segment.

Between weeks 24 and 52 weeks, the mean numbers of injections given were 3.9 (SE = 0.3) and 2.7 (SE = 0.2) in the sham/aflibercept PRN and aflibercept/aflibercept PRN groups, respectively, with the median time to first PRN injection being 29 days for the initial sham/aflibercept group and 68 days for the aflibercept/aflibercept group.

Most patients in the aflibercept /aflibercept PRN group needed 2 injections between 24 and 52 weeks versus five in the sham/aflibercept PRN group. Only 24.5% of those in the aflibercept/aflibercept group required more than four injections in the second six months of the study compared to 50% in the sham/aflibercept group. Between week 24 and 100, the aflibercept/aflibercept group required a mean of 6 injections versus 7.1 injections in the sham/aflibercept group. This suggests that once disease control was obtained over several months of loading, less frequent injections were needed subsequently.⁶³

GALILEO^{64,65} was a phase 3, randomised, double-masked trial comparing intravitreal aflibercept with sham for MO secondary to CRVO. The study included treatment-naive patients ($n = 177$) aged ≥ 18 years with MO secondary to CRVO with CRT $\geq 250 \mu\text{m}$ and ETDRS BCVA of 20/40 to 20/320.⁵⁸ Patients were randomized 3:2 to receive either aflibercept 2 mg or a sham injection every four weeks for 24 weeks (and then treatment was continued, masked but PRN, until week 76). There was no crossover in this study. The primary efficacy endpoint was the proportion of patients who gained ≥ 15 letters in BCVA at week 24

compared with baseline. Secondary endpoints included the change from baseline to week 24 in BCVA and CRT.⁶⁴

Patients receiving aflibercept had a significantly greater mean change in BCVA than the sham-treated patients at week 24 (18.0 vs 3.3 letters, respectively; $P < 0.0001$).⁶⁴ The difference reduced slightly at week 52 (16.9 vs 3.8 letters, $p < 0.0001$), and was smaller still by week 76 (13.7 vs 6.2 $p < 0.0001$).⁶⁵ There was a loss of ETDRS letters by four between weeks 24 to 76. At week 76, 57.3% of aflibercept treated patients had gained ≥ 15 ETDRS letters in BCVA. The difference between the groups in mean changes in CRT at week 24 was 279.3 μm . This difference reduced to 211.1 μm at week 52 (mainly due to decrease in CRT of the sham group) and further to 83 μm at week 76 (the gap narrowing due to change in both groups). Thus by week 76 the anatomical change between the initial sham and the initial aflibercept group was similar.^{64,65}

3. Bevacizumab

Currently, increasing short-term data support the fact that multiple intravitreal bevacizumab injections reduce MO due to CRVO.^{66,67} The most common treatment regimen is two to three injections over the first five to six 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.

A Cochrane meta-analysis on anti-VEGF agents for the treatment of MO secondary to CRVO included high-quality data from 937 participants in six RCTs, who were either treated with intravitreal anti-VEGF (aflibercept, bevacizumab, ranibizumab or pegaptanib sodium) or sham injection.⁶⁸ It found that participants receiving anti-VEGF therapy were 2.71 (95% confidence interval for risk ratio 2.10 to 3.49) times more likely to gain at least 15 letters of visual acuity at six months compared to participants treated with sham. High-quality evidence from five trials suggested anti-VEGF treatment was associated with an 80% lower risk of losing at least 15 letters of visual acuity at six months compared to sham injection (RR 0.20; 95% CI 0.12 to 0.34). Moderate-quality evidence from three trials (481 participants) revealed that the mean reduction from baseline to six months in central retinal thickness was 267.4 microns (95% CI 211.4 microns to 323.4 microns) greater in participants treated with anti-VEGF than in participants treated with sham. In addition, high-quality evidence from six trials suggested that anti-VEGF treatment was associated with an 82% lower risk of developing iris neovascularization at six months compared to sham injection (RR 0.18; 95% CI 0.09 to 0.36).

Translation of current clinical trials on anti-VEGF therapy in CRVO into clinical practice

1. Duration of CRVO: The CRUISE study included participants with CRVO diagnosed in the previous 12 months whilst COPERNICUS and GALILEO included CRVO of less than nine months duration.^{60,63,64} It is unlikely for more long standing CRVO cases to present to medical retina clinics at present due to an established referral system for this condition since the availability of Ozurdex for CRVO in 2009. Nevertheless, the effect of these agents in chronic MO of more than 12 months duration remains unclear. However, treatment with anti-VEGF may be initiated in these patients if the treating retinal specialist expects an improvement or stabilization of VA based on his/her judgment. The change in visual acuity after three loading injections should help decide if further anti-VEGF treatment is worthwhile.

2. Duration of MO and VA outcome: Most participants in the CRUISE trial (71.2%) had a duration of MO of less than three months and approximately 55% of participants in the aflibercept trials had less than two months duration. Sub-group analysis of all the anti-VEGF trials to date indicates that the visual outcome is best in participants with a shorter duration of MO. In the aflibercept trials, the proportion of participants who gained at least 15 letters at week 24 was higher in those with CRVO of less than two months duration. It is therefore essential that patients are referred and treated promptly.

3. Early referral and prompt treatment: The studies also show that 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. This may be due to reasons such as the presence of a mild CRVO with minimal MO as the oedema in these eyes may show spontaneous recovery. However, there were modest visual acuity gains in sham arm participants who were initiated on anti-VEGF after six or 12 months and, therefore, such patients may still benefit from anti-VEGF therapy. Response to the loading phase may help determine whether further treatment is useful in this group of patients with delayed presentation.

4. Presenting VA: The lower limit of BCVA at entry of CRUISE, GALILEO and COPERNICUS was 24 letters (Snellen 6/96). Therefore, the dosing regimen, number of injections required and the visual outcome in patients presenting with less than 24 letters remain unclear. Anecdotal clinical experience, however, indicates that eyes with Snellen VA<6/96 do well with treatment as long as there is no gross afferent pupillary defect.

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.

5. Poor VA at presentation and VA outcome: Approximately 20% of the patients in the CRUISE, GALILEO and COPERNICUS trials had a visual acuity of Snellen 6/60 to 6/96. A greater gain of visual acuity is expected in this group due to the floor effect as shown in the aflibercept trials. However, the final visual acuity of patients in this category and the impact of the final visual acuity on the patient's quality of vision remain unclear. 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.

6. Definition of ischaemic CRVO: Ischaemic CRVO is currently defined as 10DA or more of non-perfusion on seven-field fundus fluorescein angiography, but this may not be an accurate definition as novel wide-field imaging techniques have improved accuracy of detection of extent of ischaemia. The CRUISE study excluded patients with a relative afferent pupillary defect indicative of significant retinal ischaemia while this was not an exclusion criterion in aflibercept trials. This may explain why COPERNICUS (15.5%) and GALILEO (14%) included a higher proportion of patients with posterior non-perfusion compared to CRUISE (1.5%). However, these definitions should not be rigidly applied in clinical practice today and patients should not be excluded from treatment based on them. However, careful consideration should be given to further therapy in 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.

7. Monitoring intervals: The visual acuity outcomes at 52 weeks in CRUISE, GALILEO and COPERNICUS trials were based on patients being monitored monthly for up to 52 weeks. There is no data at present to show similar outcomes if the monitoring intervals are increased in the first year. Although treatment should be individualized, it is recommended that these patients are monitored monthly if a PRN dosing regimen is planned for optimal visual outcomes. In the second year, visual acuity gains obtained with monthly monitoring in year one are unlikely to be sustained if quarterly monitoring is undertaken as shown in the HORIZON and GALILEO trials. Eight weekly monitoring in the COPERNICUS trial also showed a mean decline in four letters from that achieved in year one. This data indicates that there is a subgroup of patients who require monthly monitoring to achieve and maintain maximal visual benefit.

8. Ocular neovascularisation: the incidence of ocular neovascularisation after anti-VEGF treatment is low. In the COPERNICUS trial, approximately 32% of eyes were categorized as non-perfused or perfusion status was indeterminable at baseline. In the GALILEO trial, 14% of eyes were non-perfused or perfusion was indeterminable at baseline. Iris neovascularisation was an exclusion criteria for both GALILEO and COPERNICUS. In these studies, 2.9% (n=3) of aflibercept treated eyes developed ocular neovascularisation by 24 weeks and 5% developed it by 52 weeks. All these eyes had CRVO of less than two months' duration and included both perfused and non-perfused CRVO at baseline. Only one patient required PRP in GALILEO by 24 weeks. The time to development of ocular neovascularisation was 240 days from baseline. This suggests that anti-VEGF may delay this complication and, as such, these patients should be monitored for ocular neovascularisation and conversion of non-ischemic cases to ischaemic CRVO for longer periods.

9. Previous treatment: No previous treatment with anti-VEGF, steroids, macular laser or panretinal photocoagulation was allowed in the study eye in the GALILEO trial. The COPERNICUS trial also excluded any previous anti-VEGF treatment but allowed intraocular or periocular steroids up to three months prior to randomization. The CRUISE trial excluded previous anti-VEGF therapy in the study or fellow eyes within three months of randomization. 12.3% were treated with previous anti-VEGF therapy and 6.2% were treated with tramcinolone. It is likely that there will be a significant number of patients in Medical Retina Clinics who have already been commenced on Ozurdex or one of the anti-VEGF agents. Currently, there is no robust data on outcomes of switching steroid to an anti-VEGF agent or switching between anti-VEGF agents or combining steroids with anti-VEGF agents for MO due to CRVO. However, patients may be switched from one agent to another if the treating physician expects a better visual or anatomical outcome with another agent and after an informed decision has been made by the patient. This also applies to a trial of combination of a steroid preparation with an anti-VEGF agent if deemed to be beneficial to the patient.

10. Anatomical outcomes: The maximum reduction of central macular thickness is at four weeks after the first injection whether the treatment is started immediately or after a delay as shown in the sham groups in the anti-VEGF trials. In both immediate and delayed treatment groups, the OCT CST thickness remains at a plateau after the initial reduction by one month for all three anti-VEGF trials during the monthly injection phase up to 24 weeks. Despite a slight increase in thickness at the start of PRN dosing with monthly monitoring, this plateau effect remains. However, the mean retinal thickness increases with increased monitoring intervals. As anatomical changes normally precede visual acuity changes, this suggests that any increase in macular thickness due to MO during follow-up visits warrants aggressive treatment and more frequent monitoring visits to sustain maximal visual benefit.

11. Injection frequency: All anti-VEGF trials were designed for monthly injections in the first six months. Therefore, the effect of less frequent injections from baseline is unclear. However, sham group participants in whom anti-VEGF therapy was deferred by six to twelve months and who were then initiated on a PRN dosing regimen showed a mean gain of less than five letters. The PRN regimen and the chronicity of oedema may have contributed to this small visual acuity gain in these participants. Therefore, it is recommended that monthly injections are initiated until maximum visual acuity gain is achieved and the visual acuity is stabilized before any other treatment regimen is considered. Although the risk of endophthalmitis is low with intravitreal therapy (1:1000), repeated injection increases the 'per patient' risk and this should be explained to patients who require multiple injections.

12. PRN dosing: Only 7.3% of patients in the aflibercept arm of the COPERNICUS trial did not require further injections from week 24 to week 52. Another 50% required three to five injections in this period. The mean time to first injection in the PRN phase was 68 days in the aflibercept arm whilst the sham arm required the first PRN dose at 29 days suggesting that eight-weekly dosing may be sufficient after six months of monthly injections of aflibercept but is insufficient if a PRN dosing follows a PRN induction phase (as shown in the sham arm). In the CRUISE Study, the mean number of injections from month six to twelve was 3.3. As such, all anti-VEGF trials to date show persistent or recurring MO continue through to 52 weeks and 1:2 patients will require a further three to five injections up to week 52 to sustain the visual benefit obtained at 24 weeks. In the RETAIN Study, 44% of eyes with ranibizumab-treated CRVO had oedema resolution and good outcomes at four years, but most (56%) still required frequent injections in order to maintain good outcomes. As such, if a PRN regimen is contemplated, these patients should be monitored monthly. Otherwise a treat and extend regimen may allow for more individualized regimen. An eight weekly fixed dosing from 24 – 52 weeks may also ensure that at least 3 further injections are given after 24 weeks. However, 40% of patients required more than three injections after 24 weeks in the COPERNICUS study. Such eight weekly fixed regimen may result in under-dosing in some patients.

13. Relation of functional and anatomical outcomes: There is an argument that MO in CRVO is an inner retinal response and so may be resistant to intermittent increases in outflow obstruction as the visual acuity gain was sustained despite a mean increase in macular thickness when fixed monthly dosing was followed by PRN dosing with monthly monitoring up to 52 weeks in the anti-VEGF trials. However, one should note that the visual acuity gains were only maintained due to timely PRN dosing as a result of monthly monitoring. It is unlikely that a visual acuity benefit would be maintained if a prolonged monitoring interval and a PRN dosing regimen was advocated in the first year of treatment given that in the second year, reduced efficacy of the drugs were reported in both HORIZON and COPERNICUS patients when monitoring was extended to at least every quarter.

14: Re-treatment criteria: Thresholds for retreatment were relatively low in both the ranibizumab and aflibercept trials. In the latter, eyes were re-treated if they had a >50µm increase in CRT compared to the lowest previous measurement, new or persistent cystic retinal changes or subretinal fluid, persistent diffuse oedema >250µm in the central subfield or loss of ≥ 5 letters from the best prior measurement in conjunction with any increase in CRT or an increase of ≥ 5 letters in BCVA from the most recent visit suggesting that the patient may not have reached maximum response. In the CRUISE study, re-treatment was given if BCVA was ≤20/40 or centre subfield thickness was ≥250 µm. In order to achieve similar results, it is recommended that one should treat in a similar way, i.e. with a low

threshold for reinjection to ensure that the macula is dry and visual acuity remains within five letters of best achieved visual acuity.

15. Long-term treatment of CRVO: The RETAIN study has provided up to 48 months' data on 32 patients of the 392 patients with CRVO induced MO initially enrolled in the CRUISE study. On a PRN dosing regimen with a review at least every three months and a mean of two injections, 53.1% gained BCVA of 15 letters or more, and 43.8% of patients had a final BCVA of 20/40 or better at 48 months. Fourteen of these patients had unresolved oedema and had poorer visual outcome despite being on treatment compared to 13 patients who had complete resolution of fluid for at least six months.

Ischaemic central retinal vein occlusion

Patients with ischaemic CRVO are at risk of neovascular glaucoma for which laser photocoagulation is beneficial. This risk of iris neovascularisation is higher if the area of retinal ischaemia (retinal non-perfusion as determined by FFA) is >10 disc diameters CVOS).^{5,6}

Management of ischaemic central retinal vein occlusion and anterior segment neovascularisation

Pan-retinal photocoagulation (PRP) remains the mainstay of treatment when iris new vessels (NVI) or angle new vessels (NVA) are visible. Ischaemic CRVO should ideally be monitored monthly for new vessels of the iris and/ or the angle.⁶ However, as this is not logistically possible in most centres, two to three monthly reviews may be sufficient, unless there are particular risk factors. Pan-retinal photocoagulation is advocated at the earliest sign of iris or angle new vessels.

In circumstances when regular follow-up is impractical, prophylactic treatment may be appropriate.

Inhibitors of vascular endothelial growth factor (anti-VEGF agents) such as ranibizumab, aflibercept and bevacizumab have anti-angiogenic properties and may be used as adjuvants to pan-retinal photocoagulation in patients with anterior segment neovascularisation secondary to ischaemic CRVO.⁶⁹ At present, recommendations for the use of anti-VEGFs as an adjunct to photocoagulation cannot be made based on available evidence. (The effects of these drugs in pregnancy and breast-feeding are unknown).

Management of 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 with panretinal photocoagulation for anterior segment neovascularisation. Panretinal photocoagulation may be useful in preventing vitreous haemorrhage.

Pan-retinal Photocoagulation Technique

Pan-retinal photocoagulation for CRVO with NVI or NVA requires a significant number of laser shots delivered adequately to cover the ischaemic retina to ensure regression of NVI and /or NVA over time. Either single spot or multi-spot lasers may be used. Treatment is usually placed in the periphery avoiding areas of retinal haemorrhage. Some cases require further treatment if the iris neovascularisation fails to regress.⁶

Management of established neovascular glaucoma

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 or cyclo-ablative procedures. In addition, regression of NVI and NVA seem to offer a long term chance of maintaining ocular comfort.

Intravitreal and intracameral anti-VEGF agents have been shown to cause regression of iris new vessels and decrease angle obstruction. Comparative case series indicate that iris new vessels regress faster after intravitreal bevacizumab with PRP than with PRP alone. The reports also suggest that bevacizumab may reduce the need for surgical interventions and may also serve as a useful adjunct to filtering surgery.^{70,71}

Recommendations for Further Follow-up

In eyes that have significant ischaemia (> 10DA non-perfusion), follow-up after six months should be every three months for one year. In non-ischaemic eyes initial follow up every three months for six months is advised. Subsequent follow-up for all patients will depend upon treatment given and complications within the earlier period, but will not normally be required after two years in uncomplicated cases. The development of disc collaterals +/- resolution of the CRVO indicates a good outcome, and should lead to discharge from clinical supervision. However, data available on the treatment of MO with anti-VEGF agents indicates that MO may recur for several years and therefore follow-up beyond current recommendations may be required in a proportion of patients to ensure long term maintenance of stabilized visual acuity gains.

Experimental treatments

McAllister and colleagues evaluated the effectiveness of a laser-induced chorioretinal venous anastomosis as a treatment for non-ischemic CRVO and observed that visual acuity improved significantly in eyes in which successful anastomosis were created.⁷² However, chorioretinal anastomosis remains an experimental treatment. There are significant complications associated with the procedure eg choroidal neovascularisation, retinal and subretinal fibrosis or traction⁷³, and vitreous haemorrhage.⁷⁴

Trials of other treatments such as radial optic neurotomy with pars plana vitrectomy, and thrombolytic therapies are under way.^{75,76} These treatments, however, are only experimental at present and are, therefore, not recommended except as part of clinical trials.

Section 10: Ophthalmological management of BRVO

The diagnosis of BRVO is clinical, as described above. 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, as well as peripheral ischaemia. Macular oedema and neovascularisation of the retina or disc are the two major complications that may require therapy. Retinal neovascularisation occurs in 36% of eyes with >5 DD and 62% with >4DD area of non-perfusion.^{15,77}

Treatment of macular oedema

1. Observation

A systematic review of the natural history of BRVO reported that visual acuity is moderately poor at baseline (Snellen <6/12). Although visual improvement is more prevalent in BRVO than CRVO, few studies reported improvement beyond 6/12.¹⁶ The Branch Vein Occlusion Study (BVOS) was a multicentre, prospective, randomized trial designed to study the natural history and effect of laser treatment in this condition. This study demonstrated that, after three years of follow-up and based on available data on 43 participants, 28 (63%) of laser-treated eyes had improved ≥ 2 lines of vision, compared with 13 (37%) out of 35 untreated eyes that remained in the study for 36 months.⁷⁸

2. Laser photocoagulation

In the BVOS study, the average improvement in VA in the laser arm after three years of follow-up was 1.3 lines. The BVOS also reported that 40% of treated eyes (n=43) had worse than 20/40 visual acuity at three years, and 12% of treated eyes had 20/200 or worse visual acuity at three years highlighting the need for better treatment options. Today, the 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. Furthermore, laser therapy is typically further delayed three to six months after the onset of BRVO to allow for spontaneous improvement to occur (30%) and for macular haemorrhage to lessen to permit appropriate treatment.

This may further compromise visual potential in eyes with persistent MO.⁷⁸ If laser therapy is planned, fluorescein angiography should ideally 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. It will also help to avoid laser treatment to collateral vessels. 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 the treatment. Laser photocoagulation using a 50 to 100um spots size for MO requires mild photocoagulation spots only, i.e. faint grey discoloration of the retina only. The power setting required will vary from patient to patient and should be adjusted accordingly. 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 and any surrounding areas of capillary closure. Collaterals should be avoided.

3. Intravitreal steroids

Intravitreal triamcinolone acetonide (IVTA): The long-term safety and efficacy of IVTA (using preservative-free triamcinolone) was evaluated in the Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study (SCORE) that showed that this treatment is not beneficial for this condition.⁷⁹

The GENEVA study that evaluated safety and efficacy of an intravitreal implant of dexamethasone (Ozurdex; Allergan Inc., Irvine, California, USA) in participants with MO secondary to retinal vein occlusion showed that the outcome of this drug in MO due to BRVO was better than in the control participants. In the GENEVA study programme²⁷,

Ozurdex (0.7mg) and an alternative dose of dexamethasone in an implant (0.35mg) was compared to a sham injection in patients with CRVO and BRVO in two 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 ETDRS BCVA. 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 (29%). 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 similarly managed CRVO eyes. Anatomically, improvements in MO were seen with OCT. In terms of safety, raised IOP peaked at month two (3.2% of patients had an IOP >35 mmHg), but declined significantly by month three. Nineteen percent of patients required an IOP lowering agent at month six and 0.7% of patients required IOP lowering surgical procedures. Cataract incidence and progression is a significant complication of Ozurdex therapy.²⁷

Based on the GENEVA study programme, Ozurdex received FDA and EU approval for the 0.7 mg preparation, and is licensed in the UK for the treatment of adult patients with MO following either BRVO or CRVO.⁵¹

4. Intravitreal anti_VEGF therapy

(i) The pan-VEGF blocker, **ranibizumab (Lucentis, Novartis)** given in two doses (0.3mg and 0.5mg) every month for 6 months, was compared with sham, in the BRAVO study.⁸⁰ At six 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 versus 29% in the sham treated group. However, from months three to five, 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 $\leq 20/40$ or mean central subfield thickness ≥ 250 μm , and compared with the visit three months before the current visit, the 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 six months, all patients were enrolled into an open-label extension for an additional six months and the overall 12 months' results suggest that the visual gain established in the first six months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.7 injections in the first 6 months, vs. 2.7 injections in the second PRN six month phase).⁷⁶

Ranibizumab 0.5mg (Lucentis) for MO secondary to BRVO was subsequently endorsed via a NICE TA283 in May 2013. The TA stated that ranibizumab should be considered if laser has failed or has been deemed an unsuitable treatment.

Further to BRAVO⁸⁰ the open label extension of the HORIZON trial looked at 304 previous BRAVO patients with MO secondary to BRVO to assess the long term safety and efficacy of ranibizumab treatment. Patients entered the trial after one year in BRAVO and were enrolled for a further 12 months in HORIZON.⁶¹ Patients were seen at least every three months and given an intravitreal ranibizumab 0.5 mg if pre-specified retreatment criteria met.

Patients were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if visual acuity was less than or equal to 20/40 or center subfield thickness was ≥ 250 μm . Patients with BRVO were eligible for rescue grid laser therapy if BCVA was $\leq 20/40$ (6/12) caused by MO. The mean change from baseline BCVA at 12 months was 0.9 in the sham/0.5mg, -2.3 in the 0.3/0.5mg ranibizumab and -0.7 in the 0.5mg groups respectively. There were no new adverse events identified.⁸⁰ As such the long term administration of ranibizumab in a prn regimen was well tolerated and efficacious in patients with MO secondary to BRVO. The more recent RETAIN Study included 34 patients with BRVO in a prospective follow-up of a subset of patients from two phase three trials of ranibizumab in RVO.⁶² Over a mean follow-up of 49.0 months, 17 of 34 BRVO eyes (50%) had resolution of their oedema (defined as no intraretinal fluid for six months or more after the last injection). The last injection was given within two years of treatment initiation in 76%. The mean number of injections required in unresolved patients in year four was 3.2. In eyes where the oedema had resolved, a mean improvement in BCVA of 25.9 letters was achieved versus 17.1 letters ($p= 0.09$) in eyes with unresolved oedema. This shows that the long-term outcomes of BRVO eyes treated with ranibizumab was excellent, although about half of them required continuing treatment.⁶²

(ii) **Aflibercept (Eylea, Bayer)** is also recently licensed by the EMA for MO secondary to BRVO based on the VIBRANT Study.⁸¹ A total of 183 subjects with treatment naïve MO due to BRVO with sufficient clearing of macular haemorrhage to allow laser treatment at baseline and best corrected visual acuity of 24 – 73 ETDRS letters were randomized to four weekly aflibercept versus macular laser. At six months, 53% of subjects gained 15 letters after a mean of 5.7 injections compared to 27% in the laser arm treated with a mean of 1.7 sessions of macular laser. The mean gain in best-corrected visual acuity was 17 ETDRS letters versus 6.9 ETDRS in the laser arm. The functional outcomes mirrored the significantly more reduction in mean central retinal thickness in the aflibercept arm (-280.5 μm) compared to the laser arm (-128.8 μm).

(iii) Currently, increasing short-term data support the fact that multiple intravitreal bevacizumab injections reduce MO secondary to BRVO including those that had failed previous laser treatment. The most common treatment regimen is two to three injections over the first five to six months.^{82,83} 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.

Table 1 shows the summary of visual outcomes in the various randomized clinical trials evaluating therapies in macular oedema due to BRVO.

Table 1: Visual outcomes of macular oedema due to branch retinal vein occlusion in randomised clinical trials.

| STUDY | STUDY ARMS (n) | Baseline BCVA | Mean gain in BCVA | | | Proportion with ≥15 ETDRS letter gain | | |
|---------|---------------------------|---------------|-------------------|--------------|--------------|---------------------------------------|--------------|--------------|
| | | | In 6 months | In 12 months | In 36 months | at 6 months | at 12 months | at 36 months |
| BVOS | Observation (n=35) | | | | +0.23 line | | | |
| | Laser (n=43) | | | | +1.33 line | | | |
| SCORE | 1mg IVTA (n=121) | 58.2 | | 5.7 | 4.4 | | 25.6 | 25 |
| | 4mg IVTA (n=125) | 56.1 | | 4.2 | 8.0 | | 27.2 | 50 |
| | Laser (n=121) | 56.8 | | 4.0 | 12.9 | | 28.9 | 48 |
| GENEVA | 0.7mg Ozurdex (n=427) | 54.3 | | | | 41 | | |
| | Sham (n=426) | 53.9 | | | | 23 | | |
| BRAVO | 0.3mg ranibizumab (n=134) | 56.0 | 16.6 | 16.4 | | 51.2 | 56 | |
| | 0.5mg ranibizumab (n=131) | 53.0 | 18.3 | 18.3 | | 61.1 | 60 | |
| | Sham (n=132) | 54.7 | 7.3 | 12.1 | | 28.8 | 44 | |
| VIBRANT | 2 mg Aflibercept (n=85) | 58.6 | 17 | | | | 57 | |
| | Laser (n=83) | 57.7 | 6.9 | | | | 41 | |

Translation of clinical trials in BRVO into clinical practice:

1. The natural history of MO due to BRVO indicates that MO may resolve or reduce over time with an approximate mean gain of 7.3 ETDRS letters at six months (BRAVO sham arm). However, a delay of six months in initiating anti-VEGF therapy in this condition also results in an inferior visual outcome compared to prompt treatment at diagnosis. As BRVO is a predominantly unilateral disease, there is often a delay in the patient being aware of the visual impairment, timely diagnosis of the condition and referral for therapy. Therefore, prolonged delays of six months or more after the diagnosis is established should be avoided unless the patient wishes to delay treatment.

2. Macular laser has been the treatment of choice for this condition for the last 20 years. However, with the availability of anti-VEGF agents, the role of laser as first-line treatment should be restricted to patients unsuitable or unwilling to receive anti-VEGF therapy. This recommendation is supported by the BVOS study in which only 40% of patients had a final visual acuity of 6/12 at 36 months despite macular laser treatment.

3. Intravitreal triamcinolone is not licensed for intraocular use and the clinical trials on triamcinolone do not support its use in MO due to BRVO.

4. Anti-VEGF agents (ranibizumab and aflibercept) have shown significant visual gains in patients with MO due to BRVO. The BRAVO trial followed by the HORIZON and RETAIN showed that ranibizumab with rescue laser is superior to sham. As in CRVO, these clinical trials demonstrate the need for prompt initiation of treatment and the need for monthly injection until stable vision is attained. The BRAVO, HORIZON and RETAIN studies showed that if PRN treatment is commenced after maximal visual acuity gain, patients need to be monitored monthly initially followed by at least three monthly to sustain the visual benefit. The long-term outcomes in eyes with BRVO treated with ranibizumab are excellent with appropriate follow-up and treatment. The VIBRANT trial showed that four weekly aflibercept is superior to macular laser at six months. NICE has not yet evaluated aflibercept in the treatment of MO secondary to BRVO.

5. Ozurdex was the first intravitreal agent that was recommended by NICE (NICE TA229) for this indication based on the GENEVA study results. The agent is being used for this indication in the NHS. Real-life experience indicates that more frequent dosing (than six-monthly used in GENEVA) is required to produce optimal results. The impact of frequent dosing of Ozurdex is the higher rate of progression of cataract. There are no head-to-head comparisons of more frequent dosing of Ozurdex versus anti-VEGF agents in this condition reported yet. Ozurdex (700ug) is the only licensed intraocular steroid for this condition. As inflammation likely plays a role in MO due to RVO, Ozurdex is a useful treatment modality.

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.¹⁵ 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 three to four 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 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.

Experimental Treatments

An RCT comparing arteriovenous sheathotomy and IVTA showed similar benefits.⁸⁴ Based on these results and the known complications rate of vitreo-retinal procedures, this procedure is not recommended at present.⁸⁵

Section 11: Treatment Algorithm

Treatment algorithm for CRVO

A. Treatment of risk factors (to be managed by patient's physician).

B. Ophthalmic management

I. NON-ISCHAEMIC CRVO

Baseline

Visual acuity measurement, colour fundus photographs and fluorescein angiography, OCT, IOP, gonioscopy if ischaemic CRVO is suspected.

If no iris or angle NV and there is OCT evidence of MO:

(a) If visual acuity is 6/96 or better, commence on either intravitreal anti-VEGF therapy or Ozurdex implant

(b) If visual acuity is less than 6/96, the potential for significant improvement in visual acuity is minimal and the risk of ocular neovascularisation is high.

However, eyes with VA < 6/96 may be offered treatment as some of these eyes may respond. The patients should be watched for NVI/NVA

(c) If visual acuity is better than 6/12, it is reasonable to observe the patient for spontaneous resolution as per the judgment of the treating ophthalmologist.

Choice of agent

Ranibizumab and aflibercept are the two anti-VEGF agents recommended by NICE for MO due to CRVO. Ozurdex, a dexamethasone implant is also recommended by NICE for this condition. There is no visual acuity or central macular thickness restriction in the commencement of treatment with any of these agents.

Although any of these drugs may be used as first line for this condition, anti-VEGF is preferred in eyes with a previous history of glaucoma and younger patients who are phakic. Ozurdex may be a better choice in patients with recent cardiovascular events and in those who do not favour monthly injections.

Re-treatment

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

If ranibizumab is the first line of treatment, monthly intravitreal injections are continued until maximum visual acuity is achieved, which is defined as stable visual acuity for three consecutive monthly assessments while on ranibizumab therapy. If no improvement in visual acuity over the course of the first three injections is observed, cessation of treatment may be considered and is recommended after six injections. Patients who achieve visual acuity stability should be monitored monthly and treatment with ranibizumab is resumed when

monitoring indicates loss of visual acuity due to MO secondary to CRVO. Monthly injections should then be administered again until stable visual acuity is reached for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month.

If aflibercept is chosen as the first line treatment, it is given monthly until maximum visual acuity is achieved, which is defined as stable visual acuity for three consecutive monthly assessments while on aflibercept therapy. If no improvement in visual acuity over the course of the first three injections is observed, cessation of treatment may be considered and is recommended after six injections. Monthly treatment should continue until visual and anatomical outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered. The summary of product characteristics states that monitoring is recommended at the injection visits and that the monitoring schedule should be determined by the doctor responsible for the patient's care based on the response of the condition to treatment.

If Ozurdex is the first line of treatment, re-treatment may be required at four to six monthly intervals until visual stability is obtained. The occasional patient may require treatment at three 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) and formation or progression of cataract.

Stopping treatment

Stopping ranibizumab and aflibercept therapy should be considered if after three consecutive monthly treatments, visual acuity has not improved by at least five letters and CMT has not reduced from baseline. However, reduction in retinal oedema 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 six consecutive monthly treatments, visual acuity has not improved by at least five letters and CMT has not reduced from baseline. Ozurdex should be used with caution in eyes with raised IOP.

Switching agents

If an anti-VEGF agent is stopped due to lack of efficacy, there is 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 three months may be given to assess the efficacy of the switch.

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.

II. ISCHAEMIC CRVO

If iris or angle neovascularisation occurs and the anterior chamber angle is open

Urgent PRP is recommended and with review at two weeks initially and then less frequently as regression occurs. PRP plus intravitreal bevacizumab (off license) can be repeated if NVI/NVA persist.

If iris or angle NV 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, transcleral diode therapy and retinal cryotherapy can be used. An early specialist glaucoma opinion should be sought.

If an ischaemic CRVO is present without NVI/NVG and limited follow-up is likely and especially but not necessarily only if the FFA shows > 30 DA non-perfusion, prophylactic PRP should be considered. Macular oedema in eyes with ischaemic CRVO is treated in the same way as those with non-ischaemic CRVO. However, the guarded prognosis should be explained to the patient.

Treatment algorithm for BRVO

- A. Treatment of risk factors by patient's physician.
- B. Ophthalmic management of BRVO

I. NON-ISCHAEMIC BRVO

Baseline

1. If VA better than 6/12, it is reasonable to regularly observe progress for three months.
2. If VA is 6/12 or worse with macular oedema and haemorrhages are not masking fovea:
 - a) FFA is recommended to assess foveal integrity
 - b) If no macular ischaemia is identified, regularly observe for three months if macular oedema is mild and in opinion of clinician likely to spontaneously improve (30% chance)
 - c) If mild to moderate macular ischaemia is present consider treatment with ranibizumab or Ozurdex if spontaneous improvement is unlikely
 - d) If severe macular ischaemia is present — no treatment is recommended, and regularly observe for NV formation
3. If VA 6/12 or worse + macular oedema and haemorrhages are masking macula
 - a) Monthly ranibizumab or baseline Ozurdex for three months.
 - b) Perform FFA at 3 months to assess foveal integrity
 - c) If severe macular ischaemia is found to be present at three months, no treatment will likely be beneficial and further therapy should be carefully considered

At three months follow-up

1. Consider modified grid laser photocoagulation if persistent macular oedema, no or minimal macular ischaemia and other treatments unsuccessful or unavailable
2. If VA \geq 6/9 or no macular oedema detected, continue to observe if initially observed. If on anti-VEGF or Ozurdex therapy, continue as suggested in MO due to CRVO.

Further Follow-up

1. If under observation only, follow-up three monthly intervals for 18 months
2. In case of recurrence or new macular oedema, consider re-initiating intravitreal ranibizumab or Ozurdex therapy

II ISCHAEMIC BRVO

- a) Watch carefully for NV
- b) If NVE — consider sector laser photocoagulation applied to all ischaemic quadrants. Intravitreal bevacizumab (off-license) may also be given in combination with laser.
- c) Follow-up at three monthly intervals for up to 24 months.

Section 12: RVO Service Provision

Patients with RVO have previously been evaluated and followed up in eye clinics. Essentially, these clinic visits were aimed at identifying modifiable risk factors and managing sight threatening complications of retinal 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), aflibercept (Eylea) and the dexamethasone implant (Ozurdex) in stabilizing and improving visual acuity in retinal vein occlusion.

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 the United States, Europe, Asia, and Australia that there are about 520 new cases per million population of RVO.¹⁶ 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. BRVO occurs two to three times as commonly as CRVO.

Existing service provision and referral pathways

The management of an individual patient depends on the type of RVO and associated complications. Until recently, the mainstay of management of retinal vein occlusion has been macular laser photocoagulation for macular oedema in BRVO, and panretinal photocoagulation for iris or retinal neovascularization (CRVO and BRVO). Some cases of iris neovascularisation require cyclodiode laser or in extreme cases trans-scleral diode or retinal cryotherapy. With the introduction of intravitreal anti-VEGF treatments and the dexamethasone intravitreal delivery device, the management of RVO is undergoing a significant transformation and it will be a major challenge to deliver within the NHS framework.

Anticipated workload

Given the effectiveness of anti-VEGF therapies and intravitreal steroid injections in all types of RVO, the number of patients eligible for treatment and the treatment frequency has increased significantly. Patients receiving anti-VEGF therapy require four to six weekly visits whilst those receiving dexamethasone will not only require injection every four to six months, but also monitoring visits every six to ten weeks. These changes will represent a very significant increase in workload for Ophthalmologists. It will be impractical to ask patients to travel long distances repeatedly (e.g. to regional centres) for treatments at very frequent intervals. There is therefore an important need to provide such services in local hospital eye units wherever possible.

RVO Service Specifications

Early access

It is recommended that the 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. This recommendation is based on reports from the CVOS that reported that the final visual acuity is dependent on the visual acuity at presentation. More recently, the GENEVA Study²⁷ and anti-VEGF (ranibizumab and aflibercept) studies^{60,61,62,63,64,79} also suggested that visual recovery was better for eyes that were treated early after the onset of RVO.

Geographical equity of access to all regions within the UK

There needs to be immediate access to an ophthalmologist 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.

Minimum clinical services required for effective management

These include:

- Best corrected visual acuity assessments by optometrist or certified VA examiners
- Colour Fundus photographs and Fundus Fluorescein angiography (FFA) 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

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.

Resources

The contemporary management of RVO requires collaboration between the ophthalmology multidisciplinary team and physicians.⁸⁶ The multidisciplinary ophthalmic team is similar to that required for the management of wet age-related macular degeneration (wAMD) and diabetic macular oedema (DMO). It is expected that intravitreal injection facilities exist and will be shared with AMD and DMO services.

It is expected that all patients with RVO will require refracted LogMAR visual acuities, FFA and OCT at the commencement of treatment. Subsequent follow up will require regular LogMAR visual acuities, and OCTs, and FFAs only when indicated. Complications of intravitreal therapies in RVO are similar to those in other diseases eg neovascular AMD and will require appropriate resources to manage them. It is also important to explain to patients

that intravitreal therapies in RVO may be multiple and repeated over a number of years and require significant time and caregiver support.

Low Vision and Living with RVO

It is known that the sudden onset of visual loss whether unilateral or bilateral results in significant distress. BRVO and CRVO are reported to be associated with a decreased vision-related quality of life as measured by the VFQ-25.^{84,85} 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.^{87,88} 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.^{89,90}

Patients with reduced BCVA secondary to RVO should be 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 referring an individual to low vision and rehabilitation services.

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

Section 13: Research

A study on the epidemiology of RVO in a UK population would be helpful in determining the true disease burden in the population.

There are yet unreported studies comparing the efficacy of Ozurdex and anti-VEGFs in the treatment of MO secondary to RVO. The SCORE 2 study is comparing the visual outcomes of monthly bevacizumab and aflibercept as first line treatment for six months for MO due to CRVO and then the trial will continue to evaluate the role of Ozurdex as a second line option. Similarly, there is an on-going NHIR HTA-CEAT funded study evaluating the efficacy of the different available anti-VEGFs in MO secondary to CRVO (LEAVO trial).

The surgical treatments for RVO currently remain experimental. Innovative therapies in the treatment of ischaemic RVOs, where current therapies are ineffective, may allow visual preservation or restoration.

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