Retinal vascular involvement in uveitis and new treatment options

Dr Amy-lee Shirodkar

UCL

Ophthalmology MD(Res)

Declaration

I, Amy-lee Shirodkar confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I dedicate my research to my father who sadly passed away during the writing of this thesis and to the rest of my friends and family who have continually offered support and encouragement.

Secondly I offer thanks to Simon Taylor and my fellow colleagues in the department at Moorfields eye hospital for the advice and education they have provided me during my development through this process. I also am grateful for the work of Dr Thomson and his team at St Thomas' hospital collecting the data I required to complete chapter three and Hazel Lawrence and Sarah Mayhew for helping me acquire the medical notes for all the patients.

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And a final note to myself to remember that the time I have put into producing this thesis and the skills that I have gained are only the beginning of what I must continue to use and develop during the rest of my career.

Abstract

Retinal blood vessels become occluded due to inflammation and thromboembolic diseases, the complications of which can cause dramatic visual loss. The main aim of this thesis is to identify features of vascular occlusions in two groups of patients, one with co-existing ocular inflammation and the other with circulating anti-phospholipid antibodies (aPL) to better understand risk factors for their development.

Demographic and clinical variables were extracted from medical records belonging to patients from these separate sample groups at Moorfields Eye hospital. 34 patients were identified with a history of retinal vein occlusion (RVO) upon attending uveitis clinics between 2009-2011. The patients presented with a RVO at a younger age compared to the general population, with an overall prevalence of 1.83%. In the absence of active inflammation, cardiovascular disease (CVD) risk factors were present which were found to be associated with systemic steroid treatments. Highlighting the need to assess long term CVD risk in young uveitic patients on steroid treatments to prevent future RVO risk.

It is known that aPL promote thombus formation contributing to systemic and ocular complications. To understand this disease within an Ophthalmology setting, patients who had aPL testing performed during 2010 were followed. aPL testing was found to be potentially over investigated in low risk patients with other systemic risk factors and confirmatory re-testing was rarely performed. Important suggestions for investigation and re-testing of aPL are made.

Patients recruited into the initial Ozurdex for uveitis phase III clinical trial were followed to investigate the lasting effects of the implant beyond 6 months. Long term efficacy and safety of the Ozurdex steroid implant to treat uveitis macular oedema are detailed. In addition to a favourable side effect profile compared to intravitreal preparations, after implantation, tapering down of high dose systemic immunosuppression to maintenance levels were experienced over three years.

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List of abbreviations

AC - anterior chamber

ACE - Angiotensin converting enzyme

APS - anti-phospholipid syndrome

AMD - Age related macular degeneration

AZA - Azathioprine

BCVA - best corrected visual acuity

BMES - Blue mountain eye study

BMI - body mass index

BP - blood pressure

BRAO - Branch retinal artery occlusion

BRVO - Branch retinal vein occlusion

CDR - cup-to-disc ratio

CF - Counting fingers

CI - confidence interval

CMO - cystoid macular oedema

CRAO - Central retinal artery occlusion

CVD - cardiovascular disease

CRVO - central retinal vein occlusion

DEXA - Dual Energy X-ray Absorptiometry

DM - Diabetes mellitus

DMO - diabetic macular oedema

DNA - Deoxyribonucleic acid

DVT - deep vein thrombosis

ERM - epiretinal membrane

FA - fluorescein angiogram

FDA - Food and Drug Administration

HDL - high density lipoprotein

HM - Hand movements

Il - interleukin

IOP - Intraocular pressure

IVTA - intravitreal triamcinolone

IS - immunosuppressant

JIA - Juvenile idiopathic arthritis

LogMAR - logarithm of the minimum angle of resolution

MI - myocardial infarction

MMF - Mycophenolate mofetil

MXT - Methotrexate

NICE - National Institute for Health and Clinical Excellence

NPL - no perception of light

NVG - neovascular glaucoma

OCT - optical coherence tomographic

OFI - orbital floor injection

PE - pulmonary emboli

PL - Perception of light

PRP - panretinal photocoagulation

RAPD - relative afferent pupillary defect

RNA - Ribonucleic acid

RPE - Retinal pigment endothelium

RVO - retinal vein occlusion

SD - standard deviation

TNF - Tumour necrosis factor

VA - visual acuity

VEGF - Vascular endothelial growth factor

VH - vitreous haemorrhage

VKH - Vogt-Koyanagi-Harada syndrome

1. Introduction

Inflammation in humans is an involuntary bodily response with the aim of removing a stimulus and initiate healing. The process can be split into two, an exudative component involving vascular changes, oedema and blood stasis. The other involving leukocytes, granules and mediators, the cellular part. Antibodies bind to antigens, mechanical irritation or tissue trauma. In reaction to these stimuli, inflammatory mediators are synthesised and released into the blood, causing localised vasodilation, increased vascular permeability, extravasation of proteins and migration of leukocytes to the affected tissues, which in turn cause the patient to experience heat, pain, redness, swelling and loss of function of a particular tissue. This in turn stimulates, through positive feedback loops, the production of additional inflammatory cells known as cytokines. The hypothalamic–pituitary–adrenal axis as well as steroids limit and resolve this inflammatory process. Inflammation can be classified into: ulcerative, granulomatous, fibrinous, purulent or serous. Acute inflammation involving granulocytes can takes place in a controlled manner, if localised and can be beneficial, however if chronic or excessive, inflammation can cause destruction of healthy tissue, a process that can occur within the eye. (1–3)

1.1 UVEITIS

Uveitis is a group of ocular inflammatory diseases which can affect patients of any age and can cause significant visual loss in one or both eyes. It is the fifth commonest cause of visual loss in developed countries and importantly is potentially treatable in many cases.(4) Inflammation flourishes within the uveal structures, in part or as a whole, including the iris, ciliary body and choroid as well as affecting the optic nerve, vitreous, retina and surrounding vasculature. The reported incidence of uveitis globally varies between 14 to 52.4/100,000 people and peaks during the 20 to 50 age groups. The overall global prevalence is approximately 0.73%.(3,4) The pathogenesis of uveitis is not well understood, endogenous cases could be due to autoimmune processes or infection, commonly herpes viruses, toxoplasma gondii, mycobacterium tuberculosis or treponema pallidum. Associations with systemic

diseases such as Sarcoidosis, Behçet's or HLA-B27 positive diseases have been identified in the past. However, the majority of new uveitis cases are idiopathic.(4)

1.1.1 Classification of uveitis

Uveitis can be classified in various ways:

1.1.1.1 Anatomical Classification

The Standardisation of Uveitis Nomenclature (SUN) criteria was introduced to help standardise clinical trial reporting. (5) The classification system is based on the anatomical location of inflammation noted on clinical examination of the eye. Inflammation occurring primarily in the anterior chamber is termed anterior uveitis; inflammation primarily in the vitreous is called intermediate uveitis; inflammation in the retina or choroid is also known as posterior uveitis and panuveitis is inflammation occurring throughout the eye.

1.1.1.2 Pathological Classification

Causes of uveitis can also be divided into granulomatous or non-granulomatous types. Granulomatous uveitis can be caused by an infection with toxoplasma gondii, mycobacterium tuberculosis, treponema pallidum or a virus which are generally treatable. Local reactivation of ocular Toxoplasmosis is the most commonest cause of posterior uveitis worldwide. (5) A granulomatous uveitis can also be associated with systemic inflammatory diseases such as Sarcoidosis, Behçet's disease, VKH, masquerade syndromes (Lymphoma, leukaemia or ocular metastasis) which should be considered in patients over 60 presenting with their first episode of uveitis, or in the presence of human leukocyte antigen eg HLA-B27. Acute anterior uveitis is associated with HLA-B27 in 60% of cases.

1.1.1.3 Classification by pattern of disease

Uveitis is also classified temporally according to the acute or chronic pattern of the disease process. Acute anterior uveitis is the most common type of acute disease and carries the best visual outcome. Anterior uveitis that persists longer than 3 months is classed as chronic. The other classes of uveitis tend to be chronic and can be associated with systemic disease. Chronic persistent disease can cause inflammatory

damage to ocular structures and are associated with visually impairing complications such as macular oedema, cataract and glaucoma. A poor visual prognosis is generally associated with Posterior or Panuveitis.

1.1.2 Prognosis and complications associated with uveitis

Loss of vision in patients with uveitis can occur due to many reasons including: macular oedema, glaucoma, cataract and retinal ischaemia. Macular oedema can occur at any time during the course of uveitis and often responds to treatment with corticosteroids or immunosuppressive agents.(6) In the long term however, macular oedema may become resistant to treatment and management frequently involves a difficult balance of efficacy versus safety. Together, cataract and macular oedema are responsible for visual loss in 64.5% of uveitis patients, which can be preventable and/or treated successfully when managed early. The time to resolution of uveitis varies, some patients experience complete resolution but others develop a visually impairing chronic disease pattern that results in chronic damage to important ocular structures such as at the macula. Visual prognosis in patients with uveitis is poor (6/60 or worse) in patients with posterior and panuveitis. (4)

1.1.3 Local and systemic treatments for uveitis

The control of inflammation in uveitis can be very complex and require many changes in therapy until the correct diagnosis and regime is found individually for each patient. The correct treatment of uveitis is important to treat sight threatening inflammation and minimise complications from the inflammation to preserve vision and prevent ocular and non-ocular morbidity. Essentially current uveitis management plans should aim to: suppress immune reactions, eradicate any infectious causes and reverse causes of visual loss. For example, the treatment of anterior uveitis should control pain, photophobia, posterior synechiae and macular oedema. Likewise, retinitis, chorioretinitis, macular oedema, optic disc oedema and retinal vasculitis should be controlled to prevent visual loss due to posterior segment inflammation.

Corticosteroids are steroid hormones that are produced in the adrenal gland cortex of humans and are useful for treating non-infectious cases of uveitis and macular

oedema. They are involved in the normal physiology for stress, immune responses and regulate inflammation, carbohydrate metabolism, protein catabolism and electrolyte levels. One form of corticosteroids are known as glucocorticoids, which are powerful immunosuppressive agents that act in a complex manner through multiple signalling pathways reducing wound scarring and inflammation. They provoke immune cell apoptosis, differentiation, inhibition of cytokine circulation and migration. In the eye, steroids reduce the immune response and repress inflammation by suppressing the production of inflammatory mediators: interleukin-6, prostaglandins and VEGF, whilst reducing fibrous proliferation. In addition, these steroids augment endothelial and RPE cell adhesion by stabilising RPE tight junctions. As a result steroids reduce blood-retinal barrier breakdown, vascular permeability, neovascularisation and scarring.(7)

The basic structure of corticosteroids are adapted at various sites to produce different biological properties and effects. A hydroxyl group on C17 in the α-position is present in corticosteroids with anti-inflammatory properties. Prednisolone has an extended half life due to an added second double bond between C1 and C2. Dexamethasone and Triamcinolone have a fluorine atom at C9 which creates a more potent anti-inflammatory effect.(1,8)

Commonly used steroid treatments in patients with uveitis include Prednisolone, Dexamethasone and Triamcinolone. They have an average onset rate of approximately 24 to 48 hours. Different mechanisms of drug delivery for corticosteroids are also available and include oral, intravenous, topical, intravitreal implants and injections. Among these, Dexamethasone is one of the most potent, with an anti-inflammatory activity that is six-fold greater than that of Triamcinolone.(1,7,9) Delivering the correct therapeutic level of steroid to the eye is difficult when simultaneously trying to minimise systemic exposure and associated side effects. Topical steroids are used to treat anterior located inflammation in uveitis but are inadequate for treating posterior segment diseases due to their pharmacokinetic properties. Therefore, difficulty arises when treating posterior segment inflammation as drug delivery into this area of the eye is complex owing to the presence of the blood-retina barrier.

Unfortunately steroids are associated with many side effects that can involve multiple organ systems such as those shown in Table 1-1. Side effects can be greater in patients using a prolonged steroid course at high doses. Some of the side effects such as in mesenchymal tissues cause skin atrophy, muscle weakness and osteoporosis, which appear to be due to the catabolic actions of steroids. Insulin resistance and diabetes can also be caused by steroids through disruption of metabolic gluconeogenesis the liver. Subconjunctival, orbital floor and intravitreal routes produce effective but short lived concentrations of steroid to the eye and are still associated with significant side effects. (9-10)

Adrenal gland	Adrenal atrophy, Cushing's syndrome
Cardiovascular system	Dyslipidemia, hypertension, thrombosis, vasculitis
Central nervous system	Changes to behaviour, cognition, memory, and mood cerebral atrophy
Gastrointestinal tract	Gastrointestinal bleeding, pancreatitis, peptic ulcer
Immune system	Immunosuppression, activation of latent viruses
Skin	Atrophy, delayed wound healing, erythema, hypertrichosis, perioral dermatitis, petechiae, acne, striae, telangiectasia
Musculoskeletal system	Bone necrosis, muscle atrophy, osteoporosis, retardation of longitudinal bone growth
Eyes	Cataracts, glaucoma
Kidney	Increased sodium retention and potassium excretion
Reproductive system	Delayed puberty, fetal growth retardation, hypogonadism

Table 1-1: Systemic side effects of steroids(2)

Steroid induced ocular hypertension has been reported for over 40 years ago.(10) All routes of steroid delivery have an associated increased risk of elevating IOP. This is thought to be due to increased aqueous outflow resistance and upregulation of glucocorticoid receptors on the trabecular meshwork. Patients with steroid induced ocular hypertension are detected on clinical examination as patients have very few symptoms. IOP rises depend on the steroid dose administered. Responses are seen usually after 3 to 6 weeks after topical steroid use, but can be variable. The normal

population can be divided into 3 groups according to their response to topical corticosteroids shown in table. Increases with systemic corticosteroids average approximately 60% of those produced by topical steroids. Steroid induced IOP can be seen as 1.4 mm Hg increases in mean IOP for each 10 mg increase in the average daily dose of oral Prednisolone but is also variable.(10)

Risk factors associated with higher IOP rises include patients with primary open-angle glaucoma and a positive family history; older ages; and patients with type 1 diabetes or rheumatoid arthritis, high myopia, and angle recession glaucoma. The steroid-induced intraocular pressure increase is usually short-lived and reversible by discontinuation of steroids if the drug has not been used for more than 1 year. The definitive treatment for steroid induced ocular hypertension requires the discontinuation of steroid therapy. IOP usually returns to normal within 2 to 4 weeks once the steroid has been withdrawn, but normalisation of IOP may take longer in patients with a history of chronic steroid use. Discontinuation of a steroid treatment may not always be an easy decision to make. If the steroid treatment needs to be continued, a lower dose, concentration, or strength of steroid could be considered to reduce the risk of glaucomatous damage as a result of uncontrolled IOP rises. In cases with repository steroid injection and high intraocular pressure, removal of the residual sub-conjunctival or intraocular steroid may or may not4 help. With systemic steroids, steroid-sparing agents, such as systemic non-steroidal anti-inflammatory agents, are a potential substitute. However, it may not be possible to discontinue the steroid and the elevated intraocular pressure should be managed medically or surgically. Most patients who develop steroid induced glaucoma can be controlled with topical anti-glaucoma therapy. In those who are unresponsive to medical therapy, laser trabeculoplasty or surgical interventions such as trabeculectomy may be required.

In eyes at risk of steroid induced ocular hypertension, Rimexolone, or Loteprednol are topical steroids associated with a lower risk of inducing IOP changes. The management of IOP elevation after IVTA therapy is made difficult by the inability to remove the inciting agent, the significant magnitude of IOP elevation in many cases, the long duration of IOP elevation after even a single injection, and the failure of

conservative management to lower IOP to a safe range in a significant minority of cases.

1.1.3.1Local steroid treatments for uveitis

Topical, periorbital and intravitreal routes of steroid administration are used for the management of uveitis and will be discussed in detail in chapter four.

1.1.3.2Systemic corticosteroids

Oral steroids are commonly used to treat classes of intermediate and posterior uveitis typically involving bilateral cases or those associated with systemic diseases. Oral steroids are rapidly absorbed from the small intestine, with plasma levels peaking after approximately 1 to 2 hours. Systemically administered Dexamethasone is able to penetrate cells within the choroid, retina and sclera better than topical routes. (2)

Adult dosing of oral corticosteroids varies according to: the severity of the uveitis, previous individual response to treatment and in association with systemic disease. To control uveitis, adult starting doses are: 1–2 mg prednisolone per kilogram per day. When choosing to use oral steroids their side effects should not outweigh their benefits in patients with uveitis. Patient education of side effects is important as well as monitoring of blood pressure, blood sugar and weight changes. DEXA imaging scans are needed to monitor and diagnose osteopenia or osteoporosis which is a recognised side effect of steroid use. In patients with chronic disease, initial treatment with high dose oral prednisone, followed by a tapering down regime and long term low maintenance does of corticosteroid therapy may be necessary to control the inflammation. (3)

1.1.3.3Intravenous corticosteroid

Intravenous methylprednisolone is reserved for the rapid control of the inflammation in severe sight-threatening cases of uveitis for example in Behçet's disease, VKH and uveitis associated with multiple sclerosis. Intravenous methylprednisolone 1g over 1 hour for 3 days is followed by oral prednisolone 1 mg/kg/day. Hospitalisation of the patient is necessary, not only for the treatment itself, but also to monitor for

potential side effects including: seizures, anaphylactic reactions and rarely sudden death. (24)

1.1.3.4Immunosuppressive drugs

Second line agents such as Cellcept and Ciclosporin for example, may be added to the treatment regime when steroids are not effective at controlling the unrelenting intraocular inflammation or are used when vision is severely compromised. When systemic corticosteroids are insufficient to control the inflammation or a corticosteroid-sparing agent is required to reduce corticosteroid side effects or long-term use of systemic corticosteroids, immunosuppressive drugs can play a role. Classes of Immunosuppressive drugs include: anti-metabolites (Azathioprine, Methotrexate and Mycophenolate Mofetil), T-cell inhibitors (Ciclosporin, Tacrolimus) and alkylating agents (Cyclophosphamide. and Chlorambucil). They can take several weeks to start working, so initial treatments would include oral corticosteroids as well. Once stable, corticosteroids are tapered to stop or are maintained at a lowered dose.(11)

1.1.3.5Azathioprine (AZA)

Oral AZA is administered orally at a dose of 1 to 3 mg per kg per day (adjusted based on response and side effects). It is a purine nucleoside analogue, its metabolites which influences DNA replication and RNA transcription. AZA decreases peripheral T and B lymphocytes and reduces mixed lymphocyte reactivity, interleukin-2 synthesis and IgM production. Randomized clinical trials data are limited. The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study(12) outcomes of a large number of ocular inflammation patients. AZA was administered to patients with ocular inflammatory diseases (2.4% of the total SITE cohort), 63% had uveitis. 62% of patients treated with AZA reached complete inactivity of inflammation for approximately 28 days. AZA required several months to achieve successful outcomes. 47% tapered associated systemic corticosteroids to ≤ 10 mg daily and stabilised inflammation for at least 1 year. AZA was most effective in managing intermediate uveitis (90% of inflammation were stabilised within 1 year). Common reasons for stopping AZA treatments for uveitis include: side effects, ineffectiveness or disease remission. Reversible bone marrow suppression

can occur with AZA in addition to: hepatoxicity, gastrointestinal upset (nausea and vomiting) and is a reason for stopping treatment. Thus regular monitoring of blood counts and liver function tests are needed. If levels are raised, the dose should be reduced or stopped accordingly. AZA is not used in conjunction with MXT or MMF. (13)

1.1.3.6Methotrexate (MXT)

MXT is a folic acid analogue and acts on DNA replication to reduce cell proliferation of leukocytes and other rapidly dividing cells. MXT has an anti-inflammatory effect, increasing the rate of T-cell apoptosis and alters cytokine production. MXT is administered once a week along with folate concurrently to reduce nausea. MXT is used in the management of rheumatoid arthritis, juvenile rheumatoid arthritis and systemic lupus erythematosus for example, it takes roughly 6 to 8 weeks to work. MXT has been reported to preserve or improve VA, as well as reduce corticosteroid use and reduce ocular inflammation. Of 384 patients from the SITE(12) study managed with MXT, 32.8%, 9.9%, 21.4%, had anterior uveitis, intermediate uveitis, posterior or panuveitis respectively. In these groups, complete suppression of inflammation was sustained for over 28 days but many months are required before therapeutic success is obtained. MXT allowed for corticosteroid-sparing within 6 months among 46.1%, 41.3%, 20.7%, of anterior uveitis, intermediate uveitis, posterior or panuveitis, respectively. MXT was generally well tolerated, within a year MXT was stopped in 42% of patients: 13% due to ineffectiveness, 16% due to side effects. Side effects were reversed when MXT was stopped or reduced. Side effects of MXT include: gastrointestinal upset, nausea, hepatoxicity (0.1% risk of cirrhosis),low blood counts and pneumonia it is contraindicated in pregnancy. Blood counts should be monitored every 1 to 2 months. MXT is not used together with MMF or AZA. (13)

1.1.3.7Mycophenolate mofetil (MMF)

MMF is effective for control of ocular inflammatory disease, when used in combination with other agents. MMF is used for non-infectious ocular inflammation. It is a selective inhibitor of inosine monophosphate dehydrogenase, an enzyme that interferes with guanosine nucleotide synthesis. MMF prevents T and B lymphocyte

proliferation, suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium and decreases recruitment of leukocytes to sites of inflammation. Caution should be shown with using MMF in patients with renal impairment or gastrointestinal disorders which might affect absorption. MMF is an effective corticosteroid-sparing agent which can act faster than Methotrexate and Azathioprine. (13)

236 (397 eyes) patients from the SITE study treated with MMF, 20.3%, 11.9%, and 39.8% had anterior uveitis, intermediate uveitis, and posterior uveitis or panuveitis respectively. Inflammation was controlled for 28 days in 73% of patients within 1 year of commencing treatment. Oral Prednisolone was reduced to 10 mg or less, while maintaining sustained control of inflammation, in 41% and 55% of patients in 6 months and 1 year, respectively. 12% discontinued MMF within the first year because of reversible side effects of therapy. Side effects include: gastrointestinal problems (nausea, vomiting, and diarrhoea), pain, myalgia, fatigue and headaches. Blood counts should be monitored regularly for leucopenia and liver function. MMF is not used in conjunction with MXT or AZA. (12,13)

1.1.3.8 Ciclosporin

Ciclosporin (A) is an 11-amino acid cyclic peptide, which inhibits transcription of T lymphocytes during cell division phases G0 and G1 blocking their replication and the ability of the body to produce lymphokines (IL-2) necessary for the proliferation and maturation of T cells, interferon-γ and the activation of macrophages. Ocular uses in oral preparations are typically used and available in 2 forms: oil-based gelatin capsules and a microemulsion, which has a greater consistent bioavailability. Of 373(681 eyes) patients in the SITE study treated with Ciclosporin, 33.4% by 6 months and 51.9% by 1 year gained sustained or complete control of inflammation for at least 28 days. Corticosteroid-sparing success was achieved by 22.1% by 6 months and 36.1% within 1 year. 10.7% stopped treatment due to toxicity within 1 year, which was three times more common to occur in patients over 55. Ciclosporin is administered in an equally divided dose based on response and side effects. Prolonged treatment with high doses of Ciclosporin can cause nephrotoxicity. Other side effects include: hypertension (blood pressure should be monitored at clinic

visits), rarely hepatotoxicity, gingival hyperplasia, myalgia, tremor, paresthesiae, hypomagnesemia and hirsutism. (14)

1.1.3.9Cyclophosphamide

Cyclophosphamide is cytotoxic to both resting and dividing lymphocytes. Cyclophosphamide suppresses both primary and established cellular and humoral immune responses and generally inhibits the immune system. It is a nitrogen alkylating agent with active metabolites which alkylate purines in DNA and RNA. Resulting cross-linking, aberrant base pairing, ring cleavage and depurination occurs preventing cells from replicating leading to increased cell death. Activated T lymphocytes decrease, helper T lymphocyte functions are suppressed and B lymphocytes decreases for months thereafter. (12,13)

Cyclophosphamide can be administered orally or intravenously. It can be used to manage ocular manifestations of systemic autoimmune diseases such as: Wegener granulomatosis, systemic lupus erythematosus, rheumatoid vasculitis, polyarteritis nodosa and Behçet's disease. Side effects of Cyclophosphamide include: fatigue, nausea, vomiting, alopecia and headache. Bone marrow suppression occurs and is more common in over 65s. Suppression is reversible and dose dependent. Blood counts should be monitored for neutropenia, which increases the risk of bacterial infections and lymphopenia, which increases the risk of opportunistic infections. Myelodysplasia can occur with long-term oral therapy. Cessation of treatment is indicated with bladder toxicity and is contraindicated in pregnancy, ovarian suppression, testicular atrophy, and azospermia. (12,13)

20.4% of patient with uveitis from the SITE study were treated with cyclophosphamide. 76% gained sustained control of inflammation within 12 months. Corticosteroid-sparing success was gained by 30.0% and 61.2% by 6 and 12 months, respectively. Disease remission at or before 2 years. Cyclophosphamide was discontinued by 33.5% of patients within 1 year because of side effects, usually of a reversible nature. titrate therapy properly and to minimize the risk of serious potential side effects, a systematic program of laboratory monitoring is required. (12,13)

1.1.3.10 Biologics

Another classes of drugs used for the treatment of uveitis are Biologics, they include antibodies and monoclonal antibodies and such as: TNF antagonists (including Etenercept and Infliximab), Monoclonal antibodies (Rituximab), Immunoglobulins (interferon alpha) and Kinase inhibitors.

TNFα is a cytokine produced by monocytes and macrophages. It is implicated in the pathogenesis of many chronic inflammatory diseases such as rheumatoid arthritis. It mediates the immune response by increasing the transport of white blood cells to sites of inflammation and through additional molecular mechanisms which initiate and amplify inflammation. Inhibition of its action by anti TNFs reduces the inflammatory response needed when treating autoimmune disease. They effect the function of myofibroblasts, osteoclasts, and production of interleukin-10 but not pro-inflammatory cytokines. Infliximab is a chimerical monoclonal antibody against TNF-α. systemic infliximab for the treatment of different types of ocular inflammation. TNF-α antagonists treatment of some chronic inflammatory diseases by It neutralizes soluble TNF-α or blocks TNF receptors from binding to their ligands promoting an anti-inflammatory microenvironment. The use of infliximab in ophthalmology is more commonly used for JIA and Behçet's associated uveitis and vasculitis and scleritis. It works quickly and toxicity depends on the individual medication and includes exacerbation of heart failure and multiple sclerosis for example. Infliximab is very costly and concerns remain with regard to the inhibition of TNF and the risk of malignancy development. Therefore their use is balanced against the potential risks and benefits in patients with uveitis. (14)

Interferon α-2B is being investigated to control ocular inflammation in Behçet’s disease. It is delivered subcutaneously and side effects include: headaches, malaise, thrombophlebitis, sterile meningitis, abnormal liver enzymes and occasionally stroke. (14)

Rituximab is a chimeric monoclonal antibody that works against proteins found on B Lymphocytes. It is used for treatment of Lymphoma, Leukaemia and Autoimmune

disorders such as Rheumatoid arthritis. Rituximab can reduce ocular inflammation in Wegner's Granulomatosis.

1.1.3.11 Morbiditiy and mortality with immunosuppressant medication

Nearly any ocular inflammatory disorder requiring chronic systemic corticosteroid treatment may require immunosuppressive drugs in an effort to reduce the dose of corticosteroids. The probability of using an immunosuppressive drug will vary depending on the severity of the underlying disease. However, the immunosuppressive agents most commonly used for treatment of ocular inflammation, have potential short term toxicities which can be overcome if recognized early. There are also long term risks of which raise important concerns as to whether some of these agents may increase the risk of cancer and mortality. (15)

Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs were investigated in a retrospective cohort study of 2340 of 7957 patients with ocular inflammation treated with immunosuppressive drugs. Immunosuppressive drugs tested included: MXT, AZA and MMF, cyclosporin, systemic corticosteroids. They found no significantly increased risks of death or of death from cancer after adjusting for confounding factors. Treatment with cyclophosphamide was not associated with significant increases in overall mortality, but there was a non-significant suggestion of increased cancer mortality. Long term data for TNF inhibitors and MMF require further investigation to report any increases of overall or cancer mortality. Thus risk benefit analysis should be evaluated prior to commencing any of these medications. (15)

2. Retinal Vein Occlusions in uveitis patients

2.1 INTRODUCTION

Retinal vein occlusions (RVO) are a common retinal vascular disorder second to diabetic retinopathy in incidence and prevalence. RVO are classified into either branch (BRVO), central (CRVO) or hemi (HRVO) retinal vein occlusions according to the site of obstruction within the retinal venous circulation and can present as monocular or rarely bilateral disease. RVO can occur at any age and when left untreated can result in ocular complications and significant visual loss.(16) The Blue Mountains Eye Study(17) found RVO was the fifth most frequent cause of unilateral blindness, after age-related macular degeneration, cataract, amblyopia, and trauma.

2.1.1.1Epidemiology

The incidence of BRVO is 3 to 10 times(16) greater than CRVO. Population studies estimate globally from pooled data, 16.4 million adults are affected by RVO (2.5 million by CRVO and 13.9 million by BRVO). (18) The age and sex standardised prevalence is 5.20 (per 1000) for any RVO and in populations aged over 30 years: 4.42 for BRVO and 0.80 for CRVO. (18) The prevalence of RVO is strongly associated with increasing age, ethnic differences but not gender.(17)(18)

2.1.1.2Pathogenesis

A combination of mechanisms contribute to the pathogenesis of thrombus formation in RVO including the presence of diseased endothelial vascular cells, abnormal blood constituents and/or increased blood viscosity reducing retinal blood volume and increasing stasis.(17)(19)(20) Impaired venous drainage cause capillaries to become permeable leaking red blood cells and plasma and a hypoxic retinal becomes ischaemia. This upregulates the release of cytokines VEGF and IL6 to stimulate angiogenesis, further increasing vascular permeability and breakdown of the blood

retinal barrier causing retinal and macular oedema. Eyes with increased blood and plasma viscosity have been shown to be more vulnerable to retinal ischaemia.(21) Those with narrowing of the veins primarily at arterio-venous crossing sites cause distal endothelial damage and thrombus formation, (22) and localised endothelial swelling of deep vascular layers.(23) Normally, blood flows through the vascular circulations of both the retina and choriocapillaris but immediately after an occlusion of a retinal vein, a process called reversed capillary blood flow, has been described.(24)(25) A rise in intravascular pressure causes the capillaries to dilate, leak and eventually close off leaving behind localised retinal oedema.(26) If an area is left non-perfused, the retina becomes hypoxic and ischaemic changes ensue.(27) Collateral vessels later develop to assist the flow of blood from areas of capillary non-perfusion and are associated with improved visual outcome in the long run. Occlusive retinal vasculitis, involving inflammation of small blood vessels can be idiopathic or associated with autoimmune or infective processes.

2.1.1.3 Presenting features of RVO

A summary of the characteristics of different RVO types are shown in Table 2-1. Whether a patient is likely to present with visual symptoms of RVO commonly depends on macular involvement, although significant peripheral visual loss can also occur. In an eye with a RVO, patients can experience sudden painless decrease in vision, which is worse in the morning(30). Baseline BCVA is generally reduced to 6/12 - <6/60 (16) worse with CRVO, with an associated visual field defect in BRVO eyes. (16) (31)

2.1.1.4 Examination findings of branch and central retinal vein occlusions

The diagnosis of RVO is essentially based on clinical examination findings including haemorrhages, cotton wool spots, vessel tortuosity, disc swelling. Ischaemic changes including a RAPD, new vessels (at the angle, iris, disc or elsewhere on the retina) and macular oedema may also be found. Signs of vasculitis may include vitritis, arteroilar attenuation, sheathing, cotton wool spots, microaneurysms or telengectatic vessels. (16)(31)(32)

Characteristic	Branch retinal vein occlusion	Central retinal vein occlusion
Frequency	1.8% 5years (28) 0.9% 15 years (19) 0.42 per 1000 (18)	0.5%15-year incidence (28) 0.80 per 1000 (18)
RVO	66% (16) 69.5%(17)	34%(16) 25% (17)
Presenting VA	67% present with good VA (16)	6/60 or less in 60%
Age at presentation	46% younger ages BRVO 17% >80(29)	13% < 45 years (29) 53% >80
Retinal signs	retinal signs found only in one area of the retina: scattered superficial and deep retinal haemorrhages retinal oedema optic disc hyperaemia/oedema occluded and sheathed retinal veins dilated and tortuous veins	extensive retinal signs are seen in all 4 quadrants including: scattered superficial and deep retinal haemorrhages retinal oedema optic disc hyperaemia/oedema occluded and sheathed retinal veins dilated and tortuous veins

Table 2-1: Characteristics of different retinal vein occlusion types

2.1.1.5Investigations - Ocular and systemic

Ocular risk factors for RVO such as raised IOP should also be excluded. A detailed history should be taken for patients presenting with RVO, including a thorough clinical assessment and laboratory investigations to check for the presence of risk factors such as hypertension, hypercholesterolemia and diabetes, associated with a higher risk of recurrent RVO. Thrombophilia is an associated RVO risk in 51.4 % of young patients. High serum alpha 2-globulin, resistance to activated protein C, factor XII deficiency, hyperhomocysteinemia, anticoagulant protein deficiency and anti-phospholipid antibodies are also associated with a higher risk of RVO in younger age groups see Table 2-2. Once risk factors are identified they should be well controlled to reduce further visual loss associated with RVO.(33)

Young patients <45 years	Patients over 50 years
Resistance to activated protein C	Hypertension
Anti-phospholipid antibodies	Elevated serum IgA levels
Anticoagulant proteins deficiency	
Factor XII deficiency	

Table 2-2: Different risk factors for retinal vein occlusions according to age(33)(34)

2.1.1.6Investigations - Imaging

Colour fundus photographs, fluorescein angiogram (FA) and optical coherence tomographic (OCT) images are all modalities used to document and evaluate the severity of RVO and associated complications including macular oedema and capillary non-perfusion. The Early Treatment for Diabetic Retinopathy Study and the SCORE Study provide grading systems for classification of FFA and OCT findings associated with RVO and macular oedema. (35)(36)

2.1.1.7Fluorescein angiogram (FA)

FA involves the intravenous injection of fluorescein sodium into a patient's upper limb vein, then a rapid sequence of fundus photographs using a special camera image the dye passing through the retinal vessels. The purpose of which would show leakage from the vessels and areas of non-perfusion and ischaemia. FA can be difficult to interpret in RVO involving masking by intra-retinal blood which may be falsely interpreted as areas of capillary non-perfusion. Signs of RVO on FA would include delayed arterio-venous transit time which may affect a particular branch, hyperfluroescence along vascular arcades, extension of the foveal avascular zone. Macular oedema can be notes by the presence of late macular staining. Capillary non-perfusion is defined as the absence of retinal arterioles and/or capillaries seen as a darker appearance of the choroid. capillary non-perfusion and fluorescein leakage are measured by comparing late and early phase images. Leaking capillaries are shown on FA when performed 3 months after RVO. The fovea is a depression in the retina where highest visual acuity is maintained and blood vessels are absent. This foveal avascular zone enlarges with RVO and is associated with impaired vision. Macular oedema is seen as areas of cystoid changes during late phase images. Large diffuse areas of retinal thickening may also be seen.(37)

2.1.1.8Optical coherence tomographic (OCT)

Optical coherence tomography (OCT) is a non-invasive, safe, reliable, high-resolution, imaging technique to quantify anatomical changes. This technique involves infrared light, reflectance, interference showing patterns of retinal structures and measures retinal thickness. OCT can be used to monitor and diagnosing structural defects such as intraretinal cystoid spaces, subretinal fluid, and vitreoretinal interface abnormalities when slit lamp examination and FA are inadequate. OCT is able to provide additional information regarding the pathophysiology of RVO such as frequency of occurrence of subretinal fluid and subretinal haemorrhage. According to protocols from the ETDRS and SCORE guidelines cystoid spaces can be identified as round, well-defined spaces within the neurosensory retina. The cyst cavity is dark or minimally reflective. Similarly subretinal fluid appears as a dome-shaped dark space between the posterior boundary of the neurosensory retina and an intact RPE/Bruch junction. Abnormalities on OCT images of RVO eyes can be due to large superficial and deep retinal haemorrhages that cause shadowing. Moreover, the quality of the OCT images should be evaluated for artefacts that could affect retinal thickness measurements. (35)

2.1.2 Branch retinal vein occlusion – BRVO

The second most common retinal vascular disease after diabetic retinopathy is BRVO. Previous population based studies have reported prevalence rates of BRVO ranging from 0.3% to 1.1%, 4.42 per 1000 in pooled analysis. (16)(38) Venous thrombosis occurs at arteriovenous crossing sites, a sign of arterial disease. Thickening and atherosclerosis of a retinal artery causes compression of adjacent vein which share a common adventitial sheath. Hypoxia ensues as a result of localised endothelial damage, increased flow and thrombus formation.

2.1.2.1 Risk factors for BRVO

Over half (51%)(29) of BRVO cases occur in patients over 65 years, (incidence is 0.7% <60s compared to 4.6% >80 years(17)). Risk factors for BRVO include older age, coexisting cardiovascular diseases and signs of chronic hypertensive damage to the retina (focal retinal arteriolar narrowing and arteriovenous nicking), see photograph 2-1. The strongest risk factor associated with an increased risk of BRVO is hypertension. Hypertension is associated with 50% - 63% of BRVO cases.(39) Poor control of hypertension is associated with recurrence of RVO in either the same or fellow eye. Hayreh et al(31) found that patients with BRVO had a significantly higher prevalence of hypertension, peripheral vascular disease, venous disease, peptic ulcer, and other gastrointestinal disease than in patients with CRVO. Type two diabetes is also a common risk factor for BRVO, 17.9 % vs 7.9% when compared to controls.(33) Diabetic patients present with RVO at an earlier age (compared to controls) in association with hypertension and hyperlipidaemia.(40) BRVO is not associated with the presence of diabetic vascular disease and retinal neovascularisation is not more likely to occur.(41)

2.1.2.2 Classification of BRVO

The location of the branch involved in a RVO should be documented and classified into two main groups, major (first order) or macular (second order). The prognostic value of the two classes differs. If an occlusion is isolated to a macular branch, macular oedema is frequently a complication affecting the vision achieved, whereas VH and NVG is less common. In addition, major branch occlusions may be

asymptomatic in patients when involving nasal or peripheral vessels as vision is less likely to be affected.(16)

Cardiac risk factors	**Blood abnormalities**	**Ocular risk factors**	**Inflammatory risks**
hypertension	high serum alpha 2-globulin	Raised IOP	Arteriosclerosis
cigarette smoking	resistance to activated protein C (APCR)	shorter axial length < 22.89 mm.	Sarcoidosis
diabetes	factor XII deficiency	Hypermetropia (63.68%-70.7%) of BRVO eyes	Behcets disease
increased BMI at 20 years of age	Hyperhomocysteinemia Factor V Leiden		Polyarteritis nodosa
History of CVD or IHD	Anticoagulant protein deficiency		Wegners granulomatosis
	Antiphospholipid antibodies		

Table 2-3: Ocular and systemic risk factors for branch retinal vein occlusion(16)

2.1.2.3Branch of retinal vein involved in BRVO

Published studies have found that branch vein occlusions frequently occur in temporal retinal vein branches in 77.7% to 99%(42)(43) of eyes and are more common than occlusions that occur in nasal branches due to the higher numbers of arterio-venous (artery over vein) crossing sites.(44) Therefore the risk of BRVO in an eye is also related to the number of arterial overcrossings present in a vulnerable eye compared to fellow or control eyes. With superio-temporal occlusions more likely to be symptomatic than nasal occlusions

2.1.2.4Clinical features of BRVO

Symptomatic BRVO cases present with poor VA at baseline, mean presenting BCVA is approximately 0.75 logMAR units or worse. Depending on which retinal vein branch is occluded, arcuate, central, or paracentral scotomas together with a visual field defect causing a segmental reduction in peripheral vision. Commonly inferior and nasal BRVO are an incidental finding. In BRVO clinical signs are present in only one quadrant of the retina depending on which venous branch is

affected including: retinal oedema, superficial and deep retinal haemorrhages, occluded and sheathed retinal veins, dilated and tortuous veins, see photograph 2-1.(16)

2.1.2.5Prognosis and complications of BRVO

Prognostic factors associated with retinal vein occlusion are shown in Table 2-4. Vision in an untreated BRVO eye generally improves with time, but only 50% retain a vision of 6/12 or better, whilst 25% will have vision of <6/60. It has been shown that occlusions involving the superotemporal vein are associated with a better visual prognosis compared to inferior vein occlusions. (16)

Good visual prognostic factors	**Poor prognostic factors**
Ages 41-60	Ages <40 or > 60
superior and inferotemporal BRVO	ischaemic maculopathy
No pre-retinal neovascularisation	pre-retinal neovascularisation
No vitreous haemorrhage	vitreous haemorrhage
	subfoveal serous retinal detachment

Table 2-4: Prognostic factors associated with retinal vein occlusion(16)(45)

2.1.3 Central retinal vein occlusion - CRVO

CRVO are a major contributor of sight-threatening retinal vascular diseases. Prevalence rates of CRVO range from 0.1% to 0.5% in older populations and it is rare in young adults under 40 years of age (10–15%). (32) Occlusion of the central retinal vein can occur at or proximal to the lamina cribrosa where the central retinal vein exits the eye. The central retinal vein travels along with the central retinal artery in one sheath to the lamina cribrosa through which the retinal vein narrows making the vessel vulnerable to occlusion if compressed by an atherosclerotic artery for example see photograph 2-2. (39)(46) HRVO occurs with occlusion of one branch if there is an anatomical bifurcation of the central retinal vein through the lamina cribrosa which in turn causes signs visible on one half of the retina.

2.1.3.1 Risk factors for CRVO

Atherosclerosis of the central retinal artery causes compression of the adjacent vein. Resulting venous stasis, endothelial damage and increased blood viscosity contribute to thrombus formation causing occlusion of the central retinal vein. Systemic risk factors associated with cardiovascular disease contribute to altering the above factors including hypertension, arteriosclerosis and diabetes. Hayreh et al(29) showed that patients with ischemic CRVO have a significantly greater prevalence of arterial hypertension and diabetes compared to patients with non-ischemic CRVO.

2.1.3.2 Classification and clinical features of CRVO

CRVO are divided into either ischaemic or non-ischaemic types which is important as their natural history differs. Retinal ischaemia results after areas are left without blood flow after occlusion of the central retinal vein which in turn increases the pressure and non-perfusion of the capillary system. An ischaemic retina is generally defined by 10 disc areas of capillary non-perfusion on fluorescein angiography. VA at presentation is very poor (Snellen VA of 6/60 or worse) in approximately 90% of ischaemic eyes and is usually associated with a relative afferent pupillary defect. Haemorrhages and cotton wool spots are seen in both CRVO types but are more extensive with the presence of ischaemia. (31)(32) Signs of an old RVO include

collaterals and the disc, macular oedema, RPE changes, venous dilatation, tortuosity, sheathing and arteriolar narrowing.

2.1.3.3 Prognosis and Complications of CRVO

In general the visual prognosis of an eye with a CRVO depends on the BCVA at presentation. The Central Vein Occlusion Study (CVOS) (47) gave prognostic signs for VA over three years. If a patient presents with a good VA, visual prognosis is favourable. Patients presenting with a visual acuity of 6/12 or better could retain good vision in the long run, but generally an improvement of more than 6/9 is rarely seen. However 80% of patients who present with a VA of 6/60 or worse are less likely to see any visual improvement over time when left untreated. (31)(32) A non-ischaemic CRVO at presentation can convert to the ischaemic type with a reported conversion rate of 3.3% (range 0% to 27%) from non-ischemic to ischemic CRVO 4 months after RVO and 34% by 3 years. (47)

2.1.4 Complications and causes of visual loss with CRVO

Complications of a RVO can compromise the visual prognosis of the affected eye through the development of retinal ischaemia, macular oedema, vitreous haemorrhage, neovascularisation and neovascular glaucoma as a result of hypoxic damage. Long term monitoring of eyes is required because complications can arise at or after presentation. (16)(31)(32)

2.1.4.1 Macular oedema

Macular oedema is essentially due to the breakdown of the blood retinal barrier, leaky capillaries and VEGF production. Fluid collects around photoreceptors in intercellular spaces in the outer plexiform layer. Following starling's law, osmosis and hydrostatic pressure processes, hypoxia causes dilation of arterioles reducing resistance and increased pressure in capillaries and venules pushing water out. Dilated vessels are therefore a sign of high hydrostatic pressure. Macular oedema can be observed on examination of both RVO types at presentation but is more commonly seen in eyes with a CRVO. Macular oedema can develop in an eye with a BRVO within one year if not present initially.(16) The impact of visual loss due to

macular oedema for patients is often significant. Increased levels of VEGF and IL-6 appear to be involved in the pathogenesis of macular oedema at areas of non-perfusion.(48) Published data detailing the percentage of eyes that develop macular oedema due to RVO varies depending on the study you read and can fall anywhere between 5-15% and 60% in some eyes. Macular oedema has been shown to resolve in approximately 18 to 41% of eyes within 4 and 7 and a half months without treatment but can take longer in eyes with a CRVO. (16)(31)(32)

2.1.4.2Neovascularisation

Angiogenesis is the formation of new blood vessels from pre-existing ones. Factors stimulate receptors of endothelial cells (VEGFR) causing proteases (tyrosine kinase) that degrade the basement membrane of endothelial causing cells to escape and proliferate in the surrounding matrix space migrating using integrins connecting blood vessels. Neovascularisation or the formation of new blood vessels are more likely to develop in over half of eyes with greater than 4 disc diameters of retinal non-perfusion. (16)(31)(32) Ischemia triggers the release of factors (VEGF, PDGF, TGF-B, integrins, PAI-1 and FGF) that both inhibit and promote the ocular angiogenesis pathway of new vessel growth. Elevated levels of VEGF released from retinal cells. New vessels can develop on the iris (NVI), angle (NVA), optic disc (NVD) or elsewhere on the retina (NVE) from 0 to 20% over 8 to 9 months in ischaemic CRVO eyes.(49) The incidence of neovascularisation in eyes initially presenting as non-ischaemic CRVO ranges from 0 to 33% over 12 to 15 months in association with the late development of ischaemia which supports the need for long term follow up of eyes even with the absence of ischaemia on presentation. These new blood vessels are fragile and can cause visually impairing vitreous haemorrhage when injured.(26) The development of vitreous haemorrhage has been reported to occur in 41% and 10% of BRVO and CRVO eyes respectively within 9 months of presentation.(16)(32)

Peripheral anterior synechiae and progressive angle closure cause neovascular glaucoma (NVG) due to obstruction of the trabecular meshwork by a proliferation of fibrovascular tissue, including vessels over the trabecular meshwork associated with retinal ischemia. This causes intraocular pressure to rise, which is often difficult to

control, increasing the risk of visual loss for the patients. The cumulative incidences for NVI or NVG at 12 and 36 months were 6.1% and 8.5%, respectively in the SCORE-CRVO trial and 1.3% and 2.4% in the SCORE-BRVO trial.(50)(51) The CRVO Study(52) found that 10% of eyes with non-ischemic CRVO and 6% of eyes with ischemic CRVO had neovascularisation of the angle without iris new vessels.

2.1.4.3Fellow eye involvement

RVO can present as unilateral or bilateral disease. Bilateral RVO is rare, affecting 4.5 to 6.5% of BRVO eyes and between 0.4 and 4.3% for CRVO eyes. Patients with BRVO have a 10% chance of fellow eye involvement and 1.4% for CRVO eyes over 3 years. 5% of CRVO cases developed a further RVO over a 1 year period.(16)(32)

2.1.4.4Morbidity and mortality

RVO may be the first presenting feature of a systemic disease associated with significant morbidity and mortality. Investigations for associations such as cardiovascular disease risk factors on presentation of RVO. A higher cardiovascular mortality rate has been shown in patients aged under 70 presenting with RVO from pooled data from the BMES and BDES. 15.7% and 4.1% mortality due to cardiovascular and cerebrovascular disease over 12 years. Long term studies following RVO patients are needed to evaluate the possibility that RVO is associated with a higher long term risk of vascular mortality. (53)

2.1.5 Current management options and guidelines for BRVO

The management of RVO is aimed at preventing and treating complications that cause loss of vision and identifying and controlling risk factors.

2.1.5.1Referral for medical investigation and treatment of associated risk factors

The Royal College of Ophthalmologists suggests appropriate tests for cardiovascular disease risk factors along with a medical referral should be made within 2 months of diagnosis including the recommendation of lipid and glucose level control, blood pressure monitoring and weight reduction. The Framingham algorithm (1991) can

accurately determine cardiovascular risk to aid initiation of treatment for high risk patients appropriate to prevent disease recurrence and other potential sites of organ damage.(33) However updated NICE guidelines (2010) to say calculations based on the Framingham equation may overestimate risk in UK populations and recommends the use of QRISK or ASSIGN methods which are more applicable to our patients. ASSIGN was developed using a Scottish cohort and QRISK using data from UK general practice databases to evaluate 10 year risk. They include measures of social deprivation and family history in addition to age, ratio of serum total to HDL cholesterol, systolic BP, BMI, smoking status, and use of one or more BP treatments.(54)(55) When such cardiovascular risk factors are within a normal range, screening for coagulation disorders is warranted, especially in young patients, and patients presenting with bilateral disease who have a of previous or family history of thrombosis. (56)

2.1.6 Current management options and guidelines for RVO

Various treatments have been studied to manage the complications associated with BRVO as only 50% of eyes with BRVO will retain a VA of 6/12 or better without treatment. The management varies in the presence of macular oedema, neovascularisation and ischaemia. Even with the initiation of a treatment for either RVO type visual prognosis is guarded if the initial VA is poor. (16)

The Royal College of Ophthalmologists published guidelines for the management of RVO in September 2010.(57) A summary of their recommendations and supporting evidence are described below.

2.1.6.1 Management of Branch retinal vein occlusion

Macular grid and sectoral panretinal photocoagulation (PRP)

Early treatment benefits of retinal laser were first reported prior to 1974.(58) Laser works through the theory of destroying healthy retina coagulating photoreceptors and RPE leaving inner retina intact. Oxygen consumption and therefore demand of the retina is then reduced. The outer retina gets the majority of its supply from the choriocapillaris. Destroying the outer retina allows the inner retinal oxygen supply to increase. Increasing vascular diameters reducing oxygen tension. Increased oxygen

levels cause vasoconstriction and reduced flow. Laser causes vessels to constrict. (59) The Branch retinal vein occlusion study looked at grid laser treatment for macular oedema versus observation. Laser to treat macular oedema is beneficial for eyes with moderate visual loss (no worse than 6/60) when initiated early.

Grid photocoagulation should be used to manage macular oedema after three to six months after presentation and after the majority of haemorrhages have disappeared. Multiple treatments may be required (59) The Branch Retinal Vein Occlusion study(60) showed that VA can improve by up to 1.33 lines by 3 years, compared to only 0.23 lines in untreated eyes with grid laser. However the effects of grid laser are associated with a guarded visual prognosis if a patient presents with a VA of worse than 6/60, macular ischaemia or if the treatment is delayed for more than 12 months.

- burns of 50-100 micrometers in diameter with exposure of 0.05 to 0.1 seconds were applied in a grid pattern to the macula - with burns no closer to the fovea than the edge of the foveal avascular zone and extending no further than the arcades. Repeat treatments were performed as necessary.

Sectoral argon photocoagulation applied to the area of capillary closure is used to manage neovascularisation in the presence of retinal ischaemia.

- eyes without neovascularisation, treated eyes developed significantly less neovascularisation ($P<0.009$) than non-treated eyes over the course of follow-up (mean follow-up 3.7 years)
- eyes with neovascularisation, treated eyes developed significantly less vitreous haemorrhage ($P=0.005$)
- sectoral PRP was performed in the region of distribution of the affected vein. 100 to 400 laser burns were applied with spot size 200 to 500 microns in diameter and exposure 0.1 to 0.2 seconds, avoiding the fovea and optic disc (60)(61)
- Collaterals should be avoided and so should the foveal avascular zone
- 1200-1500 burns 0.5mm can reduce oxygen consumption by 20%.

The results of the BVOS trial established macular grid laser as the Gold-Standard treatment for macular oedema due to branch retinal vein occlusions and sectoral

scatter PRP as the Gold-Standard treatment for prevention of neovascularisation and vitreous haemorrhage in branch vein occlusions. Recent evidence suggests that newer treatment modalities may be more efficacious than laser in this condition.

Steroids

Triamcinolone is a potent steroid to improve vision, however effects of one injection are short lived and are associated with complications including cataract and ocular hypertension. (51) The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Study(51) showed that repeated doses of IVTA can reduce macular oedema and improve visual outcome far better than observation but does not provide a better alternative to standard care grid laser and associated with more adverse events. Small case series have shown a significant improvement of VA with the combined treatment of IVTA followed by laser photocoagulation in patients with macular oedema secondary to BRVO.(62) OFI can also be used to treat macular oedema due to RVO, however the effects are short lived.

Ozurdex intravitreal dexamethasone implant for BRVO NICE have approved the use of the Ozurdex intravitreal implant for the management of macular oedema due to BRVO. Results from the Geneva study group showed 30% of eyes can achieve a >15 letter improvement at day 60 and improvement in BCVA at day 180 is better than in un-treated eyes. Eyes with shorter durations of macular oedema fair better. (63)

Anti-VEGF Agents

Patients with RVO have higher vitreous vascular endothelial growth factor (VEGF) levels than patients with unaffected eyes. Currently anti-VEGF treatments are not licenced in the UK for the treatment of CRVO.

Intravitreal Ranibizumab - Lucentis

Lucentis is a fast, effective, well-tolerated and safe treatment for macular oedema secondary to RVO approved in the US to treat macular oedema due to RVO. (64) It is an antibody derived Fab fragment of Avastin, that stays in the vitreous for 29 days. The Ranibizumab for the treatment of macular oedema following Branch Retinal

Vein Occlusion (BRAVO) showed Lucentis provided 3 lines improvement (≥15 ETDRS letters) in 61%, 55% and 29% were seen in 0.5 mg, 0.3 mg and control groups respectively. A rapid resolution of macular oedema (90% reduction in CRT) with low rates of associated adverse events were also found. At 12 months, improvements in VA were maintained in the initial Lucentis treatment groups. Macular oedema tended to recur between injections after 3 to 9 months. Risks include ocular (retinal tears, detachments and endophthalmitis) and systemic events (CVA, MI). Macular oedema recurs after 3-9 months. (65)

Intravitreal Bevacizumab - Avastin is a VEGF inhibitor that rapidly accumulates on VEGF receptors on vessel walls and within photoreceptors at the fovea.(1) Macular oedema responds quickly to Avastin leading to near normal macula anatomy after 7 days. Multiple injections are needed for significant short and long-term improvement of vision associated with a low risk of serious adverse side effects. (66)(67) Macular oedema recurs in 65.2% patients within approximately 13.3 weeks. 33.3% resolve after another injection. Avastin should be started within 12 months after RVO. Rebound of macular oedema may be effectively avoided by waiting at least 8 weeks after the onset of RVO. Poor visual outcome is seen in eyes with longstanding BRVO. (68) Repeated Avastin injections are a possible treatment for eyes that do not respond to laser treatment, but is still currently unlicensed. Short term results are similar those obtained for grid laser, and offer only a small improvement when compared to grid laser photocoagulation.

2.1.6.2 Management of Central retinal vein occlusion

The Royal College separates the management of ischaemic and non-ischaemic CRVO into different management plans.

Laser photocoagulation - macular grid and panretinal photocoagulation (PRP)

Treatment with laser photocoagulation was based on the results of the CVOS randomized clinical trial. (47)(69)(53) Macular grid photocoagulation was effective in reducing evidence of macular oedema but did not improve visual acuity. Prophylactic PRP for non-ischemic CRVO did not prevent the development of iris neovascularization in eyes with 10 or more disc areas of retinal capillary non-

perfusion confirmed by FA but can reduces the patients peripheral visual field as a complication. Therefore it was demonstrated that it is safe to wait for the development of early iris neovascularization before applying PRP.

Steroids

Macular oedema can be managed with IVTA, although RCT suggesting this tested a form of IVTA that is not available in the UK (TRIVARIS). IVTA can increase VA, including reading vision but its effects are less so in ischaemic eyes. The SCORE Study(50) showed that IVTA is far better compared to observation for treating vision loss associated with macular oedema secondary to RVO, but is no different to grid laser. The effects of 1 dose of IVTA last less than 1 year and are associated with complications. cataract formation, rises in IOP which can be controlled by topical medication. The Ozurdex intravitreal dexamethasone implant is approved for use to treat macular oedema due to CRVO. 29% of eyes achieve a >15 letter gain in VA by day 60. (63)

Anti-VEGF Agents

Currently anti-VEGF treatments are not licensed in the UK for the treatment of CRVO. Lucentis is approved in America, monthly Lucentis injections significantly increased BCVA and reduced macular oedema, compared with sham. Repeated injections were necessary to maintain improved VA. (54)

2.1.6.3RVO treatment options discussion

Differences in treatments used in current clinical practice and population types include in studies used to obtain support for the above treatments exist.

- Early trials with laser treatments for BRVO waited three months before treatment in perfused eyes with less than 6/12 vision once the haemorrhage had all cleared.
- SCORE trial investigating IVTA used a different non-dispersive preparation of the steroid to the type used in current clinical practice in the UK where the exact dose of the steroid administered into the eye is known.

- Duration of macular oedema included in trials differ that ultimately effects the visual prognosis with treatment. For example 40% of the SCORE population had CMO <3 months compared to 17% of the Geneva Ozurdex population.

Results with Avastin appear promising but is not yet licenced for the treatment of RVO. Results of Efficacy and Safety head to head trials of Ranibizumab Versus Dexamethasone Intravitreal Implant in Patients With CRVO (COMRADE-C) and BRVO (COMRADE-B) as well as the efficacy of large combination treatment trials are awaited.

In summary, where laser photocoagulation was the only beneficial treatment for macular oedema due to BRVO, newer treatments including the Ozurdex steroid implant and the various anti-VEGF agents have shown similar results. Where these new agents have come to afore is for the treatment of macular oedema secondary to CRVO where no treatment was proven to be of benefit in the past.

2.2 AIMS AND PURPOSE

Despite significant improvements in the treatments available for uveitis, visual loss still occurs in up to 35–40% of these patients.(4) As part of the vision loss in uveitis programme, retinal vein occlusion was identified as a cause of visual loss in this population. The frequency of retinal vein occlusion among patients with uveitis is not known, patients with a history of uveitis tend to be excluded from studies of RVO.

Oral steroids and second line immunosuppressive agents such as Cellcept and cyclosporin are used to manage inflammation associated with non-infectious uveitis affecting the posterior segments of the eye. However they are associated with undesirable side effects on blood pressure, insulin resistance, lipid profile, body weight, fat distribution and proteins involved in blood coagulation that significantly increase a patient's risk of CVD.(7)

The purpose of the study is to determine the relationship between exposure to steroid treatments and other immunosuppressive agents, cardiovascular disease risk factors and RVO events in patients with uveitis.

This study aims to:

1. outline demographic and ocular examination features of RVO in uveitis patients
2. identify whether cardiovascular disease risk factors such as hypertension and hyperlipidaemia are associated with an increased risk of RVO in uveitis patients
3. to find an association between oral steroid and IS exposure within subgroups that differ in the status of inflammation on presentation of RVO to identify whether the steroid and immunosuppressant agents used to manage uveitis contribute to increasing a patient's cardiovascular disease risk profile
4. outline visual outcome in these patients and complications including neovascularisation, vitreous haemorrhage and recurrence of disease.

2.3 METHODOLOGY

2.3.1 Study Population

Study participants were selected from those attending Moorfields Eye Hospital, a tertiary referral centre as part of the vision loss in uveitis programme (ethical approval LIGS1023 (Visual loss in uveitis)). Patients aged over 18 attending Professor Lightman's Uveitis clinic at Moorfields Eye hospital with a history of RVO were eligible for inclusion into the study. Patients were identified from a database of patients attending the uveitis clinic plus any new attendees during the study period from June 2008 to 2010.

2.3.2 Data collection and definitions

A retrospective review of consecutive medical records of patients who were diagnosed with a retinal vein occlusion was carried out. Demographic and clinical data from medical records were recorded on a proforma. Data included: age at onset of RVO, gender, eye(s) involved, presence and type of uveitis at RVO presentation, episodes of uveitis prior to, at and after RVO presentation, drug history including any steroid or immunosuppressant use at the time of diagnosis. Pre-defined co-morbidities of particular interest included vascular risk factors such as smoking, hypertension, diabetes and hyperlipidaemia.

Examination details recorded include: best corrected visual acuity prior to, at and after presentation of RVO (at 1,3,6,12,18 months and last recorded visit), associated ocular findings, date and location of RVO, location and severity of inflammation, duration of inflammation, prior and future episodes of uveitis activity, contributors visual loss. IOP was documented at presentation with specific reference to raised levels at baseline and changes over 1,3,6,12,18 months and last recorded visit. In addition, the presence of complications and surgical interventions were recorded including: macular oedema, neovascularisation, neovascular glaucoma and retinal detachment.

2.3.3 Definitions and classifications used in this study

The following are defined/classified below: central, branch and hemispheric retinal vein occlusion, hypertension, diabetes, cardiovascular disease, uveitis, Sarcoidosis, Behçet's disease, raised IOP, visual acuity, macular oedema.

Age

Current age was defined as the age at presentation of RVO.

Drug History

Medications were considered to be used if the patients were taking medication on a regular basis at the time of each ocular diagnosis. These determinations were based on historical chart notes at the time of diagnosis and not by later patient recall.

Steroid medications

All oral and intra/periocular steroid injections were included, all other methods of administration such as inhaled, topical routes were excluded. Dates of administration and doses were recorded.

Hypertension

A history of hypertension was defined from the patient history if they were being followed up by a GP for high blood pressure and/or currently receiving antihypertensive medication. Hypertension at presentation was defined as a mean systolic blood pressure of 140mmHg or higher and/or a mean diastolic blood pressure of 90 mm Hg or higher and/or current use of antihypertensive medication at the time of RVO presentation.

Cardiovascular disease

CVD was defined as a history of angina pectoris, myocardial infarction, or stroke.

Diabetes mellitus

DM was defined as a history of previous diagnosis controlled by diet, oral hypoglycaemic medication or insulin.

Smoking status

Status was considered as ever or never. Statistical calculations were only performed on the total number of patients with documented smoking histories.

Uveitis

Uveitis was classified according to the Standardization of Uveitis Nomenclature criteria(5). If inflammatory cells were found in the anterior chamber, vitreous or retina/choroid the diagnosis of anterior, intermediate or posterior uveitis was made and/or a previous diagnosis was documented in the notes or in referral letters from other ophthalmology units. Panuveitis was defined by inflammatory cells present throughout the eye (anterior chamber, vitreous and the retina or choroid). Inflammation was classed as acute if sudden onset and of a limited duration, recurrent if repeated episodes occurred in between episodes of inactivity without treatment ≥3 months in duration or chronic if persistent with relapse in <3 months. Uveitis remission was defined as inactive disease for ≥3 months after discontinuing all treatments for eye disease.

Sarcoidosis

Clinical features of Sarcoid uveitis include: mutton-fat keratic precipitates, iris nodules, peripheral anterior or posterior synechiae, vitreous cellular infiltrates, opacities, haze, posterior vitreous detachment, multiple, yellowish, elevated choroidal lesions, snowballs (white opacities) in the anterior inferior vitreous and vasculitis. Diagnosis of Sarcoidosis was confirmed if serum ACE levels were raised, along with the presence of hilar lymphadenopathy, pulmonary granulomas or a ground glass parenchymal appearance on chest xray if performed.

Behçet's disease

The classic fundus findings seen during ocular involvement in Behçet’s disease include: retinal vasculitis (both arteries and veins), venous engorgement, retinal haemorrhages, exudates, white focal retinal infiltrates and retinal oedema. Optic disc oedema and vitreous infiltrates are present in acute stages secondary to inflammation as are. sheathing of retinal vessels, chorioretinal scars and retinal and optic nerve atrophy may be present with repeated inflammation.

Central retinal vein occlusion

Central retinal vein occlusion was characterised by widespread scattered superficial or deep retinal haemorrhages with or without optic disc hyperaemia or oedema, retinal oedema, venous dilatation, or occluded and sheathed retinal veins. Further

sub-classification into non-ischaemic or ischaemic types were made based on the combined data from VA, slit lamp examination and FA.

Branch retinal vein occlusion

Branch retinal vein occlusion was characterised by retinal haemorrhages occurring within the retinal sector corresponding to the blood supply sector of the occluded venule. The affected branch (superotemporal, inferotemporal, superonasal or inferonasal) was documented.

Hemispheric retinal vein occlusion

Hemispheric retinal vein occlusion was classified when either the superior or inferior branch of the central vein was occluded creating fundal signs in the corresponding upper or lower half of the retina. Pathogenetically, central retinal vein occlusion and hemi-central retinal vein occlusion are identical in nature and were combined into a single group.

Visual acuity (VA)

Assessment of VA was measured using a Snellen chart viewed at six metres in the clinic. The Snellen chart is designed to measure visual acuity in angular units in which the numerator is the testing distance (in feet or meters), and the denominator is the distance at which a letter subtends the standard visual angle of 5 minutes of arc. The reciprocal of the Snellen fraction represents the minimum angle of resolution (MAR). The negative base 10 logarithm of the reciprocal Snellen fraction is the logarithm of the minimum angle of resolution (logMAR), which converts the geometric Snellen progression into a linear function. Baseline visual acuity was defined as the best corrected VA (BCVA) when vision is documented after correcting for refractive errors using a pinhole.

VA was documented and converted to logMAR see Table 2-5.(70) When Snellen VA was documented as incomplete lines, the nearest complete line was used. LogMAR values of 2.00, 3.00, and 4.00 were substituted for VA levels reported as “count fingers,” “hand movements,” and “no light perception,” respectively. A change of at least 3 Snellen lines, equivalent to a LogMAR 0.30, was considered a significant change. For evaluation purposes, patients were classified into three categories based on changes in VA after RVO: normal (6/12 or better), visual

impairment (6/12 or worse but better than 6/60) or severe visual loss (worse than 6/60)) in the effected eye.

LogMAR	Snellen Equivalent 6 Metres
-0.3	3
-0.2	3.8
-0.1	4.8
0	6
0.1	7.5
0.18	9
0.2	9.6
0.3	12
0.4	5
0.48	18
0.5	18.9
0.54	21
0.6	24
0.7	30
0.76	34.2
0.8	37.5
0.88	45
0.9	48
1	60
2	600
3	6000
LogMAR = logarithm of the minimum angle of resolution	

Table 2-5: LogMAR and snellen visual acuity conversion table

Raised Intra ocular pressure

Raised IOP was diagnosed when greater than 21mmHg on Goldmann applanation tonometry. Glaucoma was defined if previously known and/or the patient was using topical or oral intraocular pressure lowering medication. Ocular hypertension was diagnosed in participants with no characteristic glaucomatous optic disc changes present with an intraocular pressure greater than 21 mmHg in the effected eye. Rubeotic, secondary or angle closure glaucoma were also documented.

Macular oedema

Macular oedema is the accumulation of extracellular fluid in the outer plexiform layer of the retina. Visual acuity depends on the macular function. Poor visual acuity in RVO primarily is the result of macular oedema. Evaluation of the macular oedema could be made on clinical examination and confirmed by further imaging (FA and/or OCT) where appropriate.

2.3.4 Statistical analysis used in this study

Demographic and clinical variables were charted using a standardized data collection paper. Data were entered into a computer database and analyzed using SPSS and Excel. A chi-square test was used for all categorical variables and t tests were used for continuous variables. Fisher exact test was used when the sample number was less than five. Complication parameters were summarised and calculated including patients with BCVA improvements. Differences in risk factors, type of RVO and complications were investigated for all patients with the chi-square test. A P value <0.05 was considered statistically significant when comparing variables.

2.4 RESULTS

Between June 2008 and June 2010 a total of 2023 patients with uveitis were examined at Professor Lightman's uveitis clinic at Moorfields Eye Hospital. A history of RVO was documented in 37 patient's notes or a new event during the study period, giving a prevalence of 1.83% for RVO in our study population. A total of 29 patients were included in this study. Demographic and baseline characteristics for these patients are shown in Table 2-6 at each RVO event. 8 patients were excluded from any further analysis in this study either because presenting baseline characteristics at the time of RVO were not available from their medical notes or because the notes were not located.

Characteristics	**All RVO (n=34)**	**BRVO (n=25)**	**CRVO (n=9)**
Mean age at presentation (years)	54.44	54	55
% Right eyes	50%	52%	44%
% Male patients	53%	52%	56%

Table 2-6: Baseline gender and age characteristics for all retinal vein occlusions (RVO) types and events. BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion

2.4.1 Demographic details of patients with a history of RVO

2.4.1.1Age at presentation

The average age at presentation of RVO in our uveitis population was mean 54.44 years, median 58 years, (SD±15.03) (95% CI of the mean 49.20 - 59.69 years) and ranged from 25 to 79 years, see Table 2-6. No patients in our study population were aged over 80 years. Distribution of ages for all RVO events are shown in Figure 2-1, and according to RVO type in Figure 2-2 and Figure 2-3. No significant association between presenting age and RVO type were found (t test p=0.92).

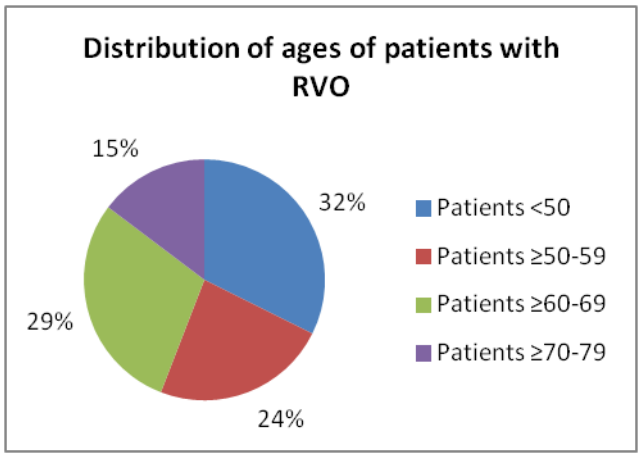


Figure 2-1: Distribution of ages of patients with retinal vein occlusion (RVO)

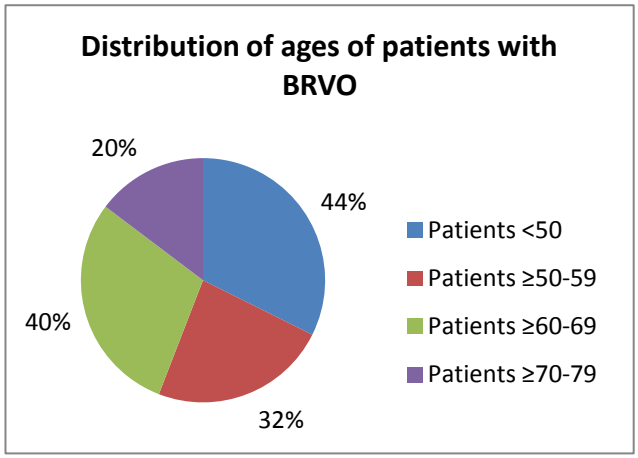


Figure 2-2: Distribution of ages of patients with branch retinal vein occlusion (BRVO)

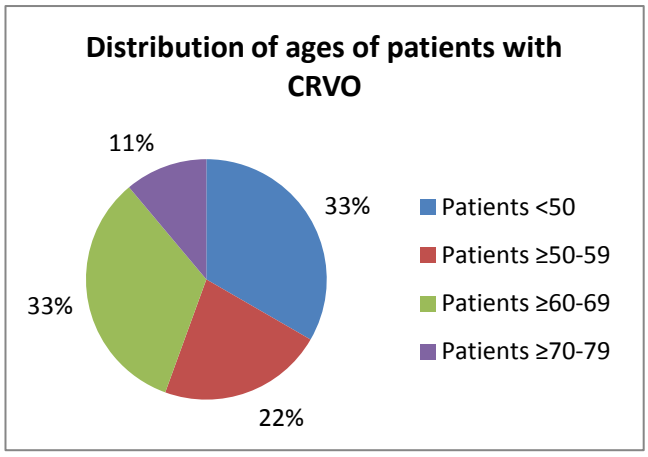


Figure 2-3: Distribution of ages of patients with central retinal vein occlusion (CRVO)

2.4.1.2 Gender and RVO

Of 34 RVO events 53% occurred in male patients, see Table 2-6. There were no significant associations between gender and RVO type (x^2 p=0.85).

2.4.2 Ocular examination findings on presentation of RVO

Of 34 RVO events, a history of BRVO was the most frequent presenting RVO type see Figure 2-4. There were no significant associations between RVO type and eye affected (x^2 p=0.35). From our sample population 2(6.9%) patients had a history of bilateral RVO and 10.34% with recurrent disease. All analysis from hereon have been calculated by RVO event including these bilateral and recurrent events (total number of RVO events =34) unless specified otherwise.

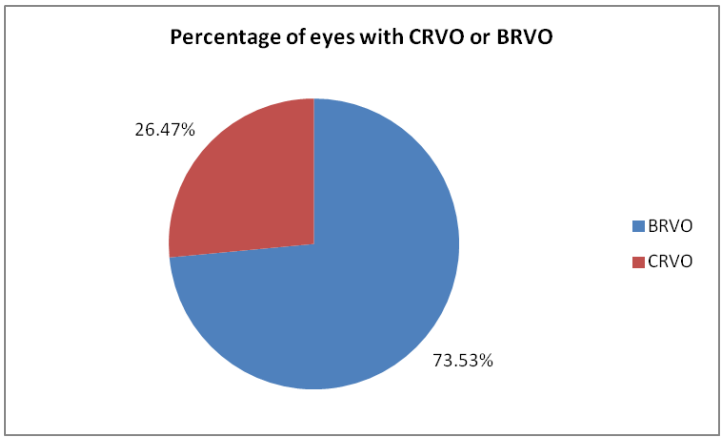


Figure 2-4: Percentage of eyes with CRVO = central retinal vein occlusion and BRVO = branch retinal vein occlusion

2.4.2.1 Visual acuity at presentation

76% of patients were symptomatic of one or more of the following: reduced vision, floaters, blurred vision or pain, on presentation of RVO. Mean presenting visual acuity was poor, 0.78 and 0.80 LogMAR for BRVO and CRVO eyes respectively, see Table 2-7. However no statistical significance between mean presenting LogMAR VA were found between RVO type (unpaired t test p=0.99).

LogMAR BCVA	BRVO (n=20)	CRVO(n=8)
Mean	0.78	0.80
Median	0.3	0.5
SD	0.98	0.83
SEM	0.22	0.30
95% CI	0.32-1.24	0.10-1.50

Table 2-7: Unilateral retinal vein occlusion by type and presenting LogMAR best corrected visual acuity (BCVA) BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion

2.4.2.2 Quadrant involved in BRVO

Frequency of quadrant involvement in BRVO are shown in Figure 2-5. Superotemporal BRVO counted for a total of 38% of all RVO events in our study population. Patients with bilateral BRVO had involvement of different retinal vein branches in either eye. One patient had a superonasal BRVO in one eye and an inferonasal BRVO in the other, whilst the other patient had an inferotemporal BRVO in one eye and superotemporal BRVO in the other. Involvement of nasal branches were commonly an incidental finding on routine follow up appointments.

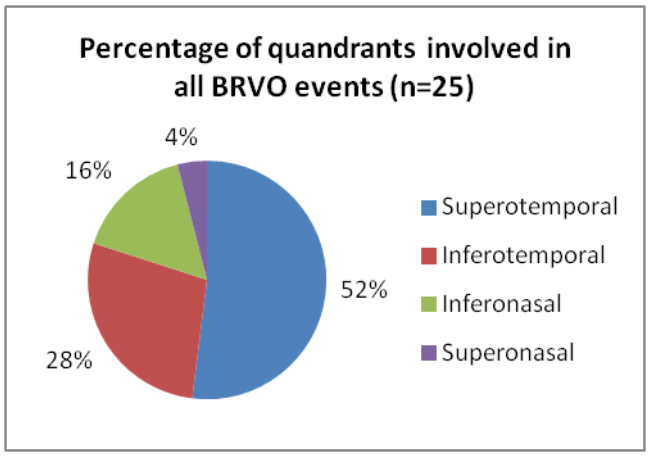


Figure 2-5: Distribution of quadrants involved in branch retinal vein occlusions (BRVO)

2.4.2.3 Other associated examination findings

Other ocular examination findings documented on presentation of RVO are summarised in order of frequency in Table 2-8.

Ocular findings	Number of eyes
No inflammation	13
AC Cells	10
Vitritis	11
Macular oedema	8
Vasculitis	4
Cotton wool spots	4
Vascular sheathing	1
Exudates	1
Neovascularisation	1
Retinitis	1
Retinal Oedema	1
Choroidal lesions	1

Table 2-8: Ocular findings at presentation of RVO in uveitis patients

2.4.2.4 Uveitis history

The percentage of patients with RVO by uveitis classification are shown in Table 2-9. A history of posterior or panuveitis was the most common uveitis type associated with RVO in our population in Table 2-9. 18(52.94%) eyes had signs of active intraocular inflammation on presentation of RVO of which 78% had a history of pan or posterior uveitis.

Uveitis type	All RVO	BRVO	CRVO
Anterior uveitis	6%	4%	11%
Intermediate uveitis	21%	29%	0%
Pan/posterior uveitis	55%	50%	67%

Table 2-9: Distribution of uveitis type and retinal vein occlusion type. BRVO=branch retinal vein occlusion, CRVO=central retinal vein occlusion

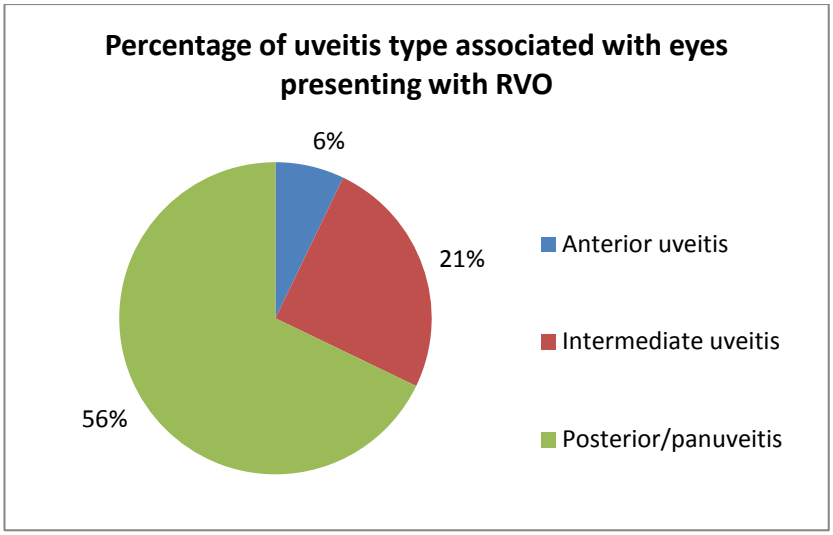


Figure 2-6: Percentage of retinal vein occlusion (RVO) events by uveitis type

Systemic inflammatory conditions including Sarcoidosis or Behçet's disease were associated with 13(38.24%) RVO events, see Table 2-10, with not quite a significant difference between presenting RVO type (x^2 p=0.07). Patients with Behçet's disease were younger, mean 42.17 years (SD11.84) compared to the rest of the sample population with RVO, mean 56.96 years (SD 14.58) (unpaired t test p=0.03). 57% and 83% of Sarcoid and Behçet's patients respectively had active intraocular inflammation, with no significant difference between RVO type (x^2 p=0.56).

	Sarcoidosis	**Behçet's disease**
Total number of eyes with a history of RVO	7	6
Mean age of patients at presentation of RVO (years)	54.86 (SD21.26)	42.17 (SD 11.84)
Number of BRVO:CRVO events	7:0	3:3

Table 2-10: Characteristics of retinal vein occlusions associated with Sarcoidosis or Behçet's disease

2.4.3 Presence of risk factors for retinal vein occlusion

Known risk factors for RVO include ocular hypertension, systemic inflammatory diseases such as Sarcoidosis and Behçet's disease and cardiovascular disease risk factors including hypertension, hyperlipidaemia and diabetes). A matrix of results are shown in Table 2-11. Raised intraocular pressure was present in 5(14.7%) eyes at

presentation of RVO of which 2 patients had a history of glaucoma or uncontrolled ocular hypertension.

	Raised IOP	Active inflammation	Presence of 1 CVD risk factor	Hypertension	Hyperlipidaemia	Diabetes	History of steroid/IS use
Age <50	1(20%)	8(47%)	3(23%)	1(11%)	3(27%)	1(25%)	8(44%)
Raised IOP	5(14.7 % of all eyes)	2(12%)	4(31%)	3(33%)	3(27%)	0(0%)	3(17%)
Active inflammation	[redacted]	17(50% of all eyes)	4(31%)	1(11%)	4(26%)	2(50%)	10(56%)
Presence of 1 CVD risk factor	[redacted]	[redacted]	13(38% of all eyes)	9(100%)	11(100%)	4(100%)	11(61%)
Hypertension	[redacted]	[redacted]	[redacted]	9(26.5% of all eyes)	7(64%)	2(50%)	8(44%)
Hyperlipidaemia	[redacted]	[redacted]	[redacted]	[redacted]	11(32% of all eyes)	2(50%)	8(44%)
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4(11.8% of all eyes)	2(11%)
History of steroid/IS use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18(53% of all eyes)

Table 2-11: Systemic and ocular risk factors on presentation of RVO. IOP=intraocular pressure, CVD = cardiovascular disease

Table 2-12 shows the significance of associations between cardiovascular disease risk factors and RVO type.

Risk Factors	**All RVO events (n=34)**	**BRVO (n=25)**	**CRVO (n=9)**	**Significance of risk factor between RVO type (Fishers exact test/x^2)**
Smoking	9(26%)	9(36%)	0	P=0.07
Hypertension	13(38%)	9(36%)	4(44%)	P=0.70
Hyperlipidaemia	9(26%)	7(28%)	2(22%)	P=1.00
Diabetes	2(6%)	2(8%)	0	P=1.00

Table 2-12: Frequency of cardiovascular disease risk factors for both retinal vein occlusion types, BRVO=branch retinal vein occlusion, CRVO = central retinal vein occlusion

Mean age of patients presenting with RVO in the presence of a cardiovascular disease risk factor are significantly greater (mean 60.95 years SD 10.25) than patients without (mean 44.93 years SD 14.20) (unpaired t test p=0.0013). A history of hypertension was a common presenting feature present in older patients compared to patients presenting with RVO without a history of hypertension, see Table 2-13. 7(20.59%) patients had raised blood pressure documented on presentation and 57% of these patients were already taking anti-hypertensive treatment.

Cardiovascular risk factor	**Mean age if risk factor present (SD)**	**Mean age if risk factor absent**	**Significance between groups (unpaired t test)**
Smoking	60.89(4.65)	52.00(16.86)	P=0.13
Hypertension	63.69(8.83)	48.38(15.30)	P=0.0025
Hyperlipidaemia	61.44(14.07)	51.80(14.89)	P=0.10
Diabetes	51.00(4.24)	54.56(15.53)	P=0.75

Table 2-13: Cardiovascular risk factor by age(years) for all retinal vein occlusion events

Analysis between eyes presenting with and without inflammation and RVO are shown in Table 2-14. These results also show that the presence of a CVD risk factor is more frequently found in a patient with no intraocular inflammation on presentation of RVO, of which hypertension is very nearly a significant association in this uveitis population.

Characteristics	**No-inflammation (n=17)**	**Inflammation (n=17)**	**Fischer's/x^2**
Mean age (years) Median Range 95%CI	58.24 60 25-79 54.12-65.35	50.47 55 26-78 42.40-58.54	Unpaired T test P=0.14
Gender %male	12(71%)	6(35%)	P=0.084
BRVO: CRVO	12:5	13:4	P=1.000
Sarcoidosis or Behçet's	5(29%)	8(47%)	P=0.481
1 CVD risk factor	9(53%)	4(29%)	P=0.296
Hypertension	8(48%)	1(12%)	P=0.057
Hyperlipidaemia	7(41%)	4(24%)	P=0.465
Diabetes	2(12%)	2(12%)	P=1.000
Previous or current steroid use	8(47%)	10(59%)	P=0.732

Table 2-14: Characteristics of eyes presenting with or without active intraocular inflammation and RVO

2.4.4 Oral steroids/immunosuppressive agents and cardiovascular disease risk factors

Prior to presenting with a RVO, 24(70.59%) patients had a past drug history documented in their medical notes. 16(66.67%) had a history of oral steroid use. Mean presenting age of patients on steroid treatment was 52.60 years (SD 15.83) compared to patients with RVO not on steroid treatments at presentation of RVO, mean 55.08 years (SD 15.07) (unpaired t test p=0.28). Oral steroid use was not associated with active inflammation on presentation of RVO when compared to non-steroid use RVO events from our study population (x^2 p=0.43).

14(41.17%) of RVO events were associated with at least one cardiovascular disease risk factor. Steroid of IS use was associated with 61% of patients with at least one CVD risk factor.

	Steroid /IS use N=18	**Non-steroid/ IS use N=16**
1 CVD risk factor	61%	38%
Hypertension	44%	25%
Hyperlipidaemia	44%	25%
Diabetes	11%	0%
Sarcoid or Behçet's disease	39%	31%

Table 2-15: History of steroid or immunosuppressant use and risk factors at RVO presentation

Table 2-16 shows a sub-group analysis of 17 patients without inflammation on presentation of RVO. A previous history of steroid/IS use was associated with a higher percentage of patients with at least 1 CVD risk factor compared to patients with no prior steroid/IS use (Fischer's p=0.0406).

Characteristics	Steroid/IS n=8	No steroid/IS n=9	Statistical significance (Fischer's/x^2)
Mean age (years) Median Range 95%CI	60.38 64 31-79 47.29-73.46	56.33 58 25-69 46.60-66.07	Unpaired t test P=0.565
Gender %male	5(63%)	7(78%)	P=0.620
BRVO: CRVO	6:2	6:3	P=1.000
Sarcoidosis or Behçet's	4(50%)	1(11%)	P=0.131
1 CVD risk factor	6(75%)	3(33%)	P=1.000
Hypertension	5(63%)	2(22%)	P=0.153
Hyperlipidaemia	5(63%)	2(22%)	P=0.153
Diabetes	2(25%)	0(0%)	P=0.206

Table 2-16: Sub-group analysis of patients with no inflammation on presentation of retinal vein occlusion and steroid/IS use

2.4.5 Visual outcome and complications of RVO in this uveitis population

Prognosis after RVO was measured by known complications associated with RVO including, visual loss, disease recurrence, ischaemia, macular oedema, vitreous haemorrhage and neovascularisation over a mean 39.47 months of follow up, range 0 to 128.7 months.

2.4.5.1 Visual loss and visual impairment

Changes in BCVA over time for both unilateral RVO types are shown in Figure 2-7. After one year of follow up, 50% of all eyes (n=18) saw an improvement in BCVA from baseline. Over half of all patients with BRVO improved vision in the effected eye after one year.

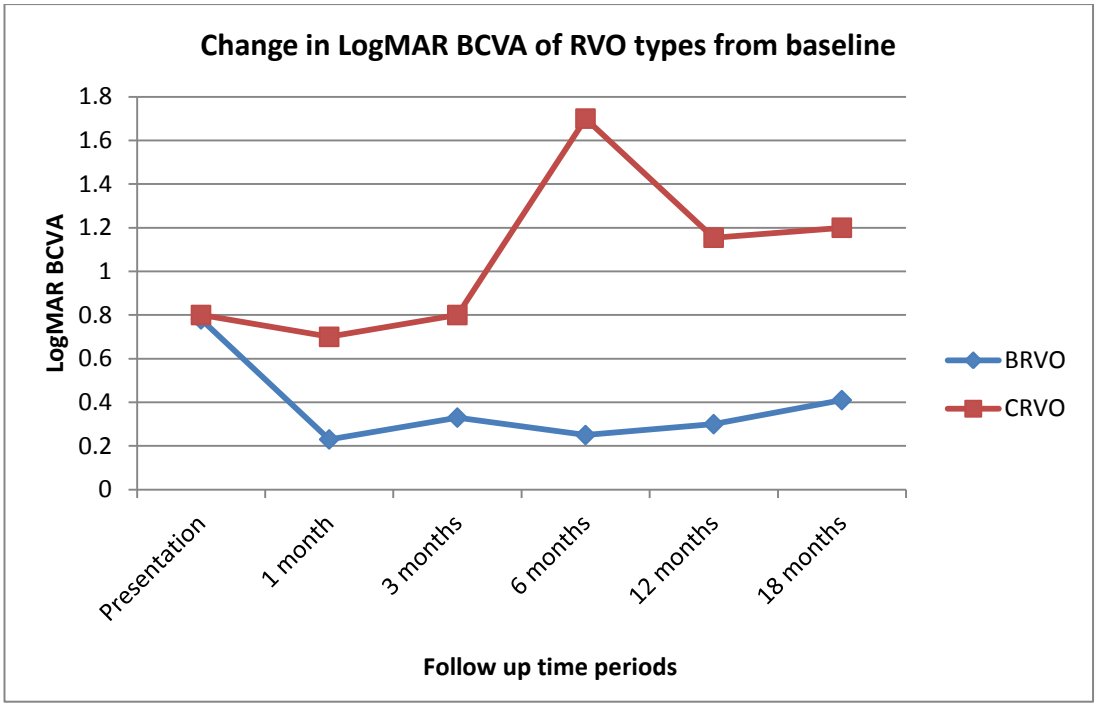


Figure 2-7: Changes in LogMAR best corrected visual acuity (BCVA) of retinal vein occlusion types from presentation and 1,3,6,12 and 18 months follow up. BRVO=branch retinal vein occlusion, CRVO = central retinal vein occlusion.

2.4.5.2Ischaemic RVO

3 patients presented with ischaemic CRVO, all in left eyes, see Table 2-17. 2 patients had a history of systemic inflammatory disease, one in combination with anti-phospholipid syndrome, and another with two cardiovascular disease risk factors. No patients converted from non-ischaemic to ischaemic CRVO over mean 32.55 months of follow up (range 8.9 months to 88.9 months).

CRVO type	Mean Age	Male:female ratio	Mean presenting LogMAR BCVA	Mean LogMAR BCVA at 1 year
Ischaemic (n=3)	45	1:2	1.73	2.00
Non-ischaemic (n=6)	57.8	1:3	0.29	0.84

Table 2-17: Characteristics of ischaemic and non-ischaemic central retinal vein occlusion (CRVO) events BCVA = best corrected visual acuity

2.4.5.3 Development of macular oedema

Macular oedema was present in 36% eyes at presentation, with no significant difference between RVO type (x^2 p=0.20). Age of patients with macular oedema at presentation was not statistically significant, mean 50.89 years (SD15.74) when compared to subjects without macular oedema, mean 55.60 years (SD14.99) (unpaired t test p=0.43). Macular oedema resolved in 4 eyes by 1 month, persisted in 5 eyes, and two eyes developed oedema at 1 month after presenting with RVO. 7(29.17%) eyes that did not develop macular oedema during follow up belonged to patients that were on steroid or immunosuppressant treatments. Time for macular oedema to resolve in untreated eyes ranged from a month to 1 year and 1 to 4 months in CRVO and BRVO eyes respectively. Late development of macular oedema occurred in 14% of eyes which resolved after approximately 1 month to 3 years later. CRVO eyes that later developed macular oedema during follow up, resolved after 2 and 7 months with no interventions.

	at presentation RVO	Developed later
Macular oedema	5(20%) BRVO	14% BRVO within 1 month to 1 year
	3(38%) CRVO eyes at presentation	2(25%) CRVO, one at 3 and the other at 6 months
Vitreous haemorrhage	2 CRVO	1 after 3 months
Neovascularisation	1 CRVO	1 CRVO after a month
Collaterals	2(25%) CRVO	1(13%) CRVO after 6 months
		2(10%) BRVO
Ischaemic CRVO	3	0

Table 2-18: Complications associated with retinal vein occlusion in uveitis patients

2.4.5.4Development of vitreous haemorrhage

2 eyes with CRVO developed vitreous haemorrhage, one was in an eye with recurrent RVO. The other belonged to a female patient under 50, with Lupus and APS, presenting with macular oedema and active ocular inflammation, whilst on steroid treatment. VH in this case persisted for 4 years resulting in HM vision. No BRVO eyes developed vitreous haemorrhage.

2.4.5.5 Development of neovascular outcomes

Development of new vessels at the disc or elsewhere on the retina were found in 2(6.25%) eyes with CRVO. No eyes developed neovascular glaucoma during mean 35.37 months follow up, range 8.9 to 88.9 months. Neovascularisation and neovascular glaucoma did not occur in any eye with BRVO.

2.4.5.6 Disease recurrence and fellow eye involvement

Of our uveitis patients with RVO, 3(10%) patients had a second RVO episode in the fellow eye within an average of 31 months follow up. One patient presented with a left BRVO then subsequently a right BRVO 4 years later. Another patient presented with a left CRVO then a right CRVO 2 years later and another with a right BRVO then left CRVO and BRVO within 2 years.

2.4.5.7Treatments used to improve vision after RVO

An OFI was administered to one patient 6 months after RVO, with no adjunct steroid treatment after presenting with 6/6 vision which deteriorated with continuing inflammation. One patient required IVTA 6 months after RVO after presenting with 1/60 vision and macular oedema, their final VA was improved to 3/60. Another patient was administered an IVTA at presentation of RVO with BCVA of CF which improved to 6/36 by 1 month and 6/18 by the last visit.

2.5 DISCUSSION

This study reports the characteristics of RVO in uveitis patients and highlights the risk of cardiovascular disease risk factors in patients treated with steroids and immunosuppressive agents in the absence of inflammation.

2.5.1.1Similarities of demographic and examination findings

Similarities were found between this cohort of patients with those included in general population studies. In this population, BRVO occurred 2.78 times more frequently than CRVO. In general population studies BRVO prevalence is much higher than CRVO by 3 to 10 times (50, 72). The prevalence of RVO in our population was 1.83%, which is similar to 1.89% in the BMES but a lot higher than many of the other larger studies shown in Table 2-19.

Population study	All RVO	BRVO (n)(%)	CRVO(n)(%)
ARIC	23 of 12,604	19(0.1)	4(0.03)
Beaver Dam	37 of 4792	29(0.6)	8(0.2)
Beijing Eye Study	35 of 4439	31(0.7)	5(0.1)
Blue Mountains Eye study	67 of 3542	50(1.4)	17(0.4)
Cardiovascular health study	8 of 2824	7(0.2)	1(0.03)
EUREYE	39 of 4753	30(0.6)	9(0.2)
Los Angeles Latino Eye Study	58 of 6013	51(0.8)	7(0.1)
Rotterdam Eye Study	39 of 6418	34(0.5)	6(0.1)
Shihpai Eye Study	22 if 1058	19(1.8)	3(0.3)
Singapore Malay Eye Study	22 of 3265	18(0.6)	5(0.2)

Table 2-19: Prevalence of retinal vein occlusion types from population studies. BRVO=branch retinal vein occlusion, CRVO = central retinal vein occlusion, ARIC= The Atherosclerosis Risk in Communities.(17,28,71–75)

Age and gender

In the general population average presenting age at RVO lies between 65 and 68 years. (109, 172), see Table 2-20. 53% of patients presenting with CRVO present over 80 years and only 2%-9% are aged under 50. Patients with BRVO have been

shown to present younger (less than 70) compared to those with CRVO (46% vs 13%). (51)(52)(173)(104) The average age at presentation of RVO in our uveitis population was younger than the general population, mean 54 years. 32% of our uveitis population presented with RVO aged under 50. No patients presented with RVO over the age of 80. This is significant as older age (over 70) is associated with different risk factors for RVO such as hypertension and visual prognosis.(106)

Age group (years)	SMES	BES	BDES	BMES	MESA	ARIC
Mean prevalence	0.7 (0.4 to 1.0)	1.3	0.8	1.6	1.1	
40 to 49	0.1(0.0 to 0.4)	0.3	0.3		0.3	< 60
50 to 59	0.5 (0.1 to 1.0)	1.3	0.4	0.7	1.1	0.1
60 to 69	1.2 (0.4 to 1.9)	2.1	1.2	1.2	1.5	0.3
≥70	1.0 (0.2 to 1.7)	2.8	1.9	2.1	1.3	0.6
p for trend	0.01		<0.0001			<0.001

Table 2-20: Age prevalence of retinal vein occlusion from population studies. (SMES=Singapore Malay Eye Study, BES=Beijing Eye Study, BDES=Beaver Dam Eye Study, BMES=Blue Mountains Eye Study, MESA=Multi-Ethnic Study of Atherosclerosis, ARIC=The Atherosclerosis Risk in Communities & Cardiovascular Health studies)(17,19,28,71,74)

VA at presentation compared to general population studies

Poor presenting visual acuity of our uveitis patients were associated with prior poor VA, male patients, CRVO, presence of ischaemia, macular oedema, amblyopia, vitreous haemorrhage, ERM and cataract. Presenting VA was poor in eyes with BRVO in older patients (over 50 years) and conversely worse in younger patients (under 50) in eyes with CRVO. Other factors are shown in Table 2-21. Eyes with chronic damage due to irreversible complications of uveitis prior to presenting with RVO would have a guarded prognosis. 60% of patients from the BMES had a VA of 6/60 or less with CRVO, and 14% with BRVO.(17)

Age and macular oedema	All RVO	BRVO	CRVO
Age <50 years	0.57(n=11)	0.33(n=8)	1.32(n=3)
Age >50 years	0.72(n=16)	0.80(n=11)	0.54(n=5)
Macular oedema	1.43(n=8)	1.44(n=4)	1.42(n=4)
No-macular oedema	0.34(n=19)	0.38(n=14)	0.17(n=4)

Table 2-21: The effect of macular oedema, steroids and age on presenting LogMAR best corrected visual acuity

2.5.1.2Steroids/IS agents and cardiovascular disease risk factors

Oral steroids and second line immunosuppressive (IS) agents used to manage uveitis can influence such risk factors including blood pressure, insulin resistance and lipid profile to significantly increase a patient's risk of CVD.(7) In the general population these factors are also known to contribute to a high risk for RVO due to atherosclerotic vessel damage.(39,46,71) Results from this study showed that patients presenting without inflammation and RVO with a previous history of oral steroid/IS use were associated with at least 1 CVD risk factor compared to patients with no prior steroid/IS use. Similarities can be drawn with other conditions where steroid treatments display pro-atherogenic effects increasing CVD disease risk factors in patients with SLE(76), ankylosing spondylitis, rheumatoid and psoriatic arthritis.(7)(77)(78)

This study highlights the need for uveitis patients that require oral steroid/IS agents be assessed as high risk for CVD compared to the normal population which would aim to prevent their future risk of RVO. Current methods of assessing patient's CVD risk for the general population may not accurately predict CVD risk for these patients due to their relatively younger age, which would be used if a patient suffers from a RVO. Therefore it is proposed that uveitis patients that require oral steroids be assess for CVD risk factors early and managed aggressively to prevent CVD events including RVO and its complications.

2.5.1.3Prognosis - visual outcome and complications

The difference between mean BCVA at 1 year by RVO type was found to be statistically significant (unpaired t test p=0.047). Worse visual outcome was

associated with CRVO eyes compared with BRVO eyes, 1.15 and 0.30 LogMAR units respectively. CRVO patients generally see a decline in VA over time, 50% of uveitis patients with CRVO get worse see Table 2-22 attributable to ischaemic damage to the retina. There were no significant findings with the presence of inflammation or steroid use at one year see Table 2-23.

	All RVO (n=18)(%)	**BRVO (n=12)(%)**	**CRVO (n=6)(%)**
Improve	9(50)	7(58.3)	2(33.3)
Stable	4(22.2)	3(25)	1(16.7)
Worse	5(27.8)	2(16.7)	3(50)

Table 2-22: Changes in visual acuity in eyes with retinal vein occlusion (RVO) from baseline to 1 year. BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion

Macular oedema might be another reason for the poor visual outcome in our population. If left untreated or undertreated, macular oedema may result in permanent photoreceptor damage of the macula and loss of central vision. (181) Macular oedema was present in 36% of eyes, with similar levels found for patients with intermediate, posterior and panuveitis. Macular oedema was associated with active inflammation in 17% of eyes. The development of macular oedema secondary to RVO in patients with uveitis, without active inflammation in 10% of cases could be due to RVO and not secondary to uveitis, macular oedema has been reported to occur in 20% to 44% of patients with intermediate uveitis and is a major cause of visual loss.(178-179) A lack of significant association could be as a result of the retrospective and size limitations of this study.

The majority of patients on steroids at the time of RVO presented with a poor VA compared to patients not on steroid treatment (mean logMAR 0.7 Vs 0.63). CRVO patients on steroids had worse than 3 lines difference in presenting BCVA compared to patients not on steroids.

Risk factor	LogMAR BCVA	SD	Unpaired t test comparison of means
Intermediate uveitis	0.83	1.02	
Pan/posterior uveitis	0.83	1.18	
Idiopathic uveitis	0.54	1.16	
Age <50 years	0.44	1.02	P=0.67
Age >50 years	0.63	0.98	
Active inflammation	0.74	1.12	P=0.46
No-inflammation	0.42	0.78	
Systemic inflammatory disease	0.16	0.38	P=0.12
No systemic inflammatory disease	0.84	1.13	
Steroids	0.83	1.27	P=0.35
No steroids	0.43	0.71	
Hypertension history	0.40	0.75	P=0.50
No Hypertension history	0.70	1.09	

Table 2-23: Ocular and systemic risk factors for retinal vein occlusion and best corrected visual acuity (BCVA) at 1 year of follow up where available

In uveitis patients it appears overall, only 58% of eyes see an improvement in VA over time. Prior damage due to uveitis and its complications including macular oedema and retina ischaemia could not be properly studied here because previous data was not present in all patients prior to presenting with RVO. Thus the influence on the visual prognosis and severity of ocular injury may not be solely attributed to RVO alone. Also the contribution of other ocular risk factors such age related macular degeneration and cataract would favour a poor VA. Populations which excluded uveitis patients, they report macular oedema develops in around 5-15% of patients. Macular oedema 18-40% is at presentation resolve, 18% resolve in 4.5 months, 41% by 7.5 months.23% of BRVO patients have macular oedema which is usually observed, and takes roughly 1-4 months to resolve.

The strengths and limitations of this study

Retrospective studies are useful in investigating diseases of low incidence, however the availability and integrity of medical records can be a concern of this method.

Owing to this study design there was no control over how the original data was collected and therefore dependent on what the Ophthalmologist decided to document at the time of consultation, which could be biased to include or not include certain pieces of information that would later be relevant for this study.

Again, the reliability and validity of medical record review for steroid and IS exposure are dependent upon completeness and accuracy of data documentation within the medical records by the consulting Ophthalmologist. Attempts were made to reduce this recall bias by scrutinising supporting documentation in medical records, drug prescriptions, GP summary forms and assumed all patients were compliant with their medication. Ultimately, these retrospective data cannot be used to determine causality between steroids/IS agents and CVD in uveitis. Longer term studies of this or similar populations would be warranted to document cardiovascular disease mortality and morbidity in this group of patients with a longer duration of steroid use in a patient's life time beyond this study period as well as observing future ocular complications associated with RVO.

2.6 SUMMARY OF RESULTS

This study emphasises RVO as a cause of unilateral visual loss in this younger uveitis population. Although inflammation should be controlled to prevent further intraocular damage, the agents used to do so are associated can increase a patient's risk of various cardiovascular disease risk factors which in turn contribute to a high risk of RVO and visual loss associated with its complications. The study also provides information on presentation and 1 year prognosis of RVO in uveitis patients.

From a population of 2023 patients with uveitis a prevalence of 1.83% for a new or previous history of RVO was found. Mean age at presentation for any RVO event in this population was 54 years. Similarities to general populations studies such as the Blue mountain eye study were found including: BRVO occur more frequently than CRVO, the superotemporal branch was the most common vein involved in BRVO, a small percentage of patients present with bilateral RVO and no relationships between eye or gender was found. Diabetes, haematological disorders and raised intraocular pressure were not common predisposing factors for the development of RVO in these uveitis patients.

Ocular features of RVO in this population included 38.24% with no associated intraocular inflammation on presentation of RVO, 55% had a history of pan or posterior uveitis. Macular oedema was present in 24% of eyes. Mean presenting visual acuity was poor in the affected eye 0.79 LogMAR and ranged from -0.1 to 2.00 LogMAR units for all RVO types. 72% of eyes saw an improvement in BCVA or stabilised by 1 year, poor visual outcome was associated with 50% of CRVO events. Treatment was used to control inflammation and reduce macular oedema with OFI or IVTA 6 months after RVO in three patients. Previous retinal injury due to uveitis and disease recurrence after RVO have a bearing on the visual prognosis for these patients.

Risk factors in this uveitis population include raised IOP 14.7%, active inflammation 44.1% and the presence of 1 CVD risk factors in 41.2%. 20% were associated with a

known previous history of oral steroid of immunosuppressant use. 38.24% were under 50 years of age and 30.77% had a history of hypertension and hyperlipidaemia. 53.85% of patients with Sarcoidosis or Behçet's disease had an associated cardiovascular disease risk factor, that could be attributable to previous steroid or immunosuppressant use.

3. Anti-phospholipid antibodies

3.1 INTRODUCTION

The retina, contains photoreceptors responsible for is the transduction of different wavelengths of light to the brain. These cells require oxygen, nutrients and a way to dispose of its cellular wastes obtained via two circulation pathways. The central retinal artery bringing oxygenated blood through the centre of the optic nerve and branches out to four quadrants of the retina and the central retinal vein facilitates the outflow of blood. The second pathway supplies oxygenated blood via the choroidal plexus that lies underneath the retina which is supplied by the posterior ciliary arteries. Blood circulates through the capillaries of the choroid, then exits the eye via the vortex veins.

Retinal ischemia is an important cause of visual loss that occurs as a consequence of various diseases and disease processes including: atherosclerotic vascular disease, diabetes, retinal vascular occlusion and retinal vasculitis. Lack of oxygen to the retina causes retinal cell death, dysfunction, and reduced vision. Retinal ischaemia can be demonstrated by areas of non-perfusion on FFA.

In response to the ischaemic retinal injury the retina promotes the expression of VEGF within the eye. The growth of new blood vessels are stimulated through the process of angiogenesis via hypoxia induced factors (PDGF, VEGF, IL6). Abnormal blood vessels (neovascularisation) grow on the surface of the retina, disc and iris from existing nearby blood vessels to deliver an alternative source of oxygen. Visual complications of neovascularisation include vitreous haemorrhage and neovascular glaucoma that develop because these new vessels are abnormal, fragile and leak. Collateral vessels should not be confused with these fragile new vessels. Instead they

are vessels that develop at the disc bypassing the vascular occlusion with the attempt of re-establishing the circulation at the disc.

The visual prognosis and recovery with extensive retinal ischaemia is very poor without treatment. Peripheral retinal scarring by argon pan-retinal photocoagulation laser, anti-VEGF and steroids injections are methods employed to reduce VEGF production and inhibit new vessel growth.

3.1.1 Anti-phospholipid antibodies (aPL)

aPL are a group of auto-antibodies that target phospholipids and phospholipid-binding proteins on cell membranes. The group of aPL antibodies are comprised of three main immunoglobulins: lupus anticoagulant (LA), anti-cardiolipin antibodies (aCL) and β-2 glycoprotein-I antibodies (aβ2GP-1). They are identified by enzyme linked immunosorbent assays (ELISA). aPL are one cause of acquired thrombophilia. Anti-phospholipid syndrome (APS) is the term used to characterise the presence of these circulating aPL with a history of recurrent arterial and venous thrombosis and pregnancy loss, which was previously referred to as Hughes' syndrome, named after Dr. Graham R.V. Hughes, a Rheumatologist in London.(79)

3.1.2 Epidemiology of aPL

Epidemiological data describing the rates of aPL and APS in populations are not very clear due to poor standardization of diagnostic tests and small population numbers used in clinical studies. From published papers, it can be considered that within a healthy general population, aPL are likely to be present in about 2–7% of young adults, where levels would be seen to rise with increasing age.(80) aPL antibodies are associated with systemic lupus erythematosus (SLE) in 34–44% of patients where 30% may not manifest any signs or symptoms of APS. (81)(82)

3.1.3 Pathogenesis of APS and thrombus formation

A thrombus can form in any organ system including the retinal vasculature through the abnormal activation of the coagulation pathway. (83) aPL antibodies are present as IgG, IgA, and IgM isforms. IgG aCL antibodies are found more frequently than

IgM isoforms. aPL are attracted to negatively charged phospholipids found in cell membranes, cardiolipin, β2GP-1 and pro-thrombin plasma proteins. β2GP-1 or apolipoprotein H inhibits coagulation, serotonin, factor 10 and protein C. aCL bind to cardiolipin, an inner mitochondrial membrane phospholipid discovered in 1906 in patients with syphilis. aCL bind using the plasma phospholipid-binding protein β2GP-1, which is specifically associated with APS and SLE, but independently in syphilis patients. In patients with syphilis the antibodies react to cardiolipin independently from β2GP-1. This became the basis of the VDRL syphilis diagnosis test and explains why patients with SLE yield positive VDRL tests in the absence of a syphilis infection. (79)

APS is an type 1 antigen specific autoimmune response involving class II molecules: Th1 CD4+ T cells and antigen presenting cells. Histopathology from patients with APS show evidence of ischaemia caused by thrombotic microangiopathy, proximal arterial thromboemboli and peripheral emboli from a vein, artery or cardiac source. Acutely, capillary congestion and intra-capillary thrombi form without the presence of inflammation. These fibrin thrombi and fragmented blood cells block vascular lumen. Vasculitis when present with thrombi are more likely to occur in patients with APS in association with SLE. Later chronic damage occurs when the lesions heal and scar causing further local ischaemic hypoperfusion, atrophy and fibrosis. The mechanisms of how aPL antibodies encourage thrombosis is not well understood and several theories exist.

One theory is based on the interaction of aβ2GP-1 bound to resting endothelial cells. It is thought that aβ2GP-1 stimulates these endothelial cells to up-regulate adhesion molecules, cytokines - interleukin-1β, interlukin-6 and 8 and the metabolism of prostacyclin. These pro-inflammatory cytokines induce thrombosis through further activation of tumour necrosis factor by monocytes and endothelial cells to initiate coagulation cascades. The aPL antibodies also disrupt phospholipid-binding proteins: pro-thrombin, protein C and tissue factors, that regulate the coagulation process. It is thought that this chronic low grade stimulation could contribute to the formation of thrombi. The aPL interact with activated platelets and apoptotic cells

that have lost their phospholipid structure, exposing anionic phospholipids that eventually promote the formation of thrombi. (84)

The second theory behind the pathogenesis of APS has been linked to atherosclerosis. Consequences of injury to vascular endothelium via oxidant mediated pathways is thought to be a cause of thrombosis in APS. Activated macrophages engulf oxidised low-density lipoprotein (LDL) causing injury to endothelial cells. Oxidised LDL serum lipoproteins contain phospholipids and modified LDL. aCL antibodies recognise both these oxidised phospholipids and phospholipid-binding proteins. Complexes are formed with aβ2GP-1 that become a target for aPL antibodies. The oxidized LDL antibodies do not directly interfere with blood coagulation but instead are involved in vascular wall inflammation present in atherosclerosis and vasculitis. Raised concentrations of IgG antibodies against oxidised LDL have been found in 80% of patients in a sample with secondary APS.(85) Raised levels of oxidised LDL and aCL antibodies could be used to predict mortality from cardiovascular disease.(86)

Associations between aPL antibodies causing thrombosis in SLE and oxidised LDL antibodies link both thrombotic and atherosclerotic processes with SLE. Perhaps within the atherosclerotic plaque, β2GP-1 or prothrombin plasma proteins might be found bound to endothelial surfaces contributing to the formation of atherosclerotic thrombosis by changing the balance of haemostasis toward a hypercoagulative state.(85)(87)

3.1.4 Classification and diagnosis of APS

The Sapporo classification criteria for APS was put together at the 8th International Symposium on Antiphospholipid Antibodies in Sapporo, Japan, 1998.(88) The criteria were later updated in 2007 in Australia due to the emergence of new clinical, laboratory and experimental advances.(89) APS is diagnosed in a patient with recurrent vascular thrombosis or pregnancy complications plus one of the laboratory criteria see Table 3-1. Patients with APS and triple positivity for aPL according to the Soporo criteria, are at a higher risk of developing future thromboembolic events. Patients with circulating aPL are 3–10 times more likely to have recurrent arterial and venous thrombosis compared to healthy individuals. (83) Reported associations

with APS in the literature not included in the above criteria include: thrombocytopenia, valvular heart disease, livedo reticular, nephropathy and neurological manifestations. (5)

APS = at least 1 clinical criteria and 1 laboratory criteria	
Vascular thrombosis	>1 clinical episode of arterial, venous or small vessel thrombosis in any tissue or organ. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
Pregnancy morbidity	>1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus or >1 premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions [11], or (ii) recognized features of placental insufficiency, or >3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria	Lupus anticoagulant (LA) present in plasma on >2 occasions at least 12 weeks apart detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)
	Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma present in medium or high titre (i.e. >40 GPL or MPL, or >the 99th percentile) on >2 occasions, at least 12 weeks apart, measured by a standardized ELISA
	Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titre >the 99th percentile) on >2 occasions, at least 12 weeks apart, measured by a standardized ELISA

Table 3-1: Diagnostic criteria for antiphospholipid syndrome

APS is sub-divided into three different categories: primary, secondary and catastrophic APS see Table 3-2. Primary APS comprise about 50% of cases and refers to the presence of idiopathic aPL in the absence of systemic diseases. The diagnosis of secondary APS is made when aPL are detected in a patient with a

collagen vascular disease such as SLE, in the presence of an infectious process or with the use of certain drugs, see Table 3-2. SLE is diagnosed based on serum ANA testing and clinical signs and associations include: a malar discoid rash, photosensitivity, ulcers, arthritis and Raynaud's. (5)

Classification	**Definition**		**Ocular features**
Primary APS	Idiopathic without clinical evidence of another autoimmune disease	Venous or Arterial thromboembolic disease, thrombotic stroke Sterile endocarditis with embolism Recurrent pregnancy failure	72.7% present with visual symptoms 86.4% normal anterior segment 68.2% posterior segment involvement venous dilatation and tortuosity. 22.7% retinal vascular occlusive disease
Secondary APS	aPL + autoimmune diseases	Systemic lupus erythematosus Rheumatoid arthritis Systemic sclerosis Behçet's syndrome Temporal arteritis Sjogren's syndrome Psoriatic arthropathy	
	aPL + infection acute self-limiting and chronic infections	Viral, e.g. HIV, varicella, hepatitis C Bacterial, e.g. syphilis Parasitic, e.g. malaria	
	aPl+drug	In drug exposure Phenothiazines Procainamide Phenytoin Quinidine Hydralazine	
Catastrophic APS	aPL + rapid organ failure due to thrombosis	Multiple vascular occlusive events in small vessels over a short period of time	

Table 3-2: Classification of anti-phospholipid syndrome(80)

The classification system has been validated for use in clinical studies of primary, secondary and lupus-like diseases.(90) The sensitivity and specificity of the system was measured as 71% and 98% respectively. The positive predictive value and negative predictive values of the classification system were 95% and 88% respectively.

3.1.5 Systemic manifestations of APS

This risk for thrombosis is higher in patients with aPL than in patients without. Thrombosis can affect any organ and involve both arteries and veins of varying size compared to most other thrombophilic states, which usually result in only arterial or venous thrombosis. Certain vascular sites are more at risk of thrombosis in APS depending on blood vessel health, size and length of the ongoing thrombotic process. Thrombotic events in smaller arterioles, venules and capillaries evolve as chronic processes causing a gradual decline in function of the target organ.

Central nervous system	**Cardiovascular system**	**Haematopoietic system**
Stroke	Hypertension	Haemolytic anaemia 14 – 23%
Transient ischemic attack	Valvular heart disease	Thrombocytopenia 40 – 50% (platelet count < 100×109/L)
Recurrent Migraine	Myocardial infarction	**Skin**
Epilepsy	Coronary thrombosis	Recurrent skin ulcers,skin nodules
Transverse myelopathy	DVT	Livedo reticularis 11 – 22%
Dementia	**Endocrine system**	**Gastrointestinal system**
Pulmonary system	Adrenal thrombosis	Hepatic thrombosis
Pulmonary hypertension	**Renal system**9%	Gut ischaemia
Pulmonary thrombosis/embolism	Renal vein thrombosis	**Pregnancy**
	Malignant hypertension with renal insufficiency	Recurrent fetal loss

Table 3-3: Systemic manifestations of antiphospholipid syndrome(82) (91)(92)

20% of patients with aPL develop systemic manifestations within 5 years such as those shown in Table 3-3. Transient rises in aPL levels pose a much lower risk of thrombosis in healthy individuals.(93) There are no significant differences in the clinical manifestations between patients with primary and secondary APS, the only difference is the association of the systemic autoimmune condition.

A meta-analysis by Wahl et al(30) of seven studies observing the risk for aPL associated venous thromboembolism in primary APS showed that the presence of LA increased the risk of venous thrombosis by 10 times. The overall odds ratio for venous thrombosis in patients with high titres of aCL and LA was 3.21 (95% CI, 1.11-9.28) and 11.1 (95% CI, 3.81-32.3) respectively. (29) Arterial thrombosis occur less frequently than venous thrombosis. 29–55% of patients with APS present with deep vein thromboses (DVT). 23% of APS thrombotic events involve coronary arteries and 27% involve subclavian, renal, retinal and pedal arteries. (91)(92) The risk of thrombosis is six times higher in patients with SLE compared to patients without LA and twice as high than those without aCL.(94) In a cohort study of patients with venous or arterial thromboembolism and catastrophic APS the cumulative incidence of thromboembolism was 12.2% after 1 year, 26.1 after 5 years and 44.2% after 10 years. (95) Recurrent thromboses tend to occur in the same vascular area as previous events.

Gender and age are associated with different systemic manifestations of aPL. Female patients with SLE, are prone to suffer from migraine, arthritis, livedo reticularis, thrombocytopenia and leucopenia. In contrast, male patients with secondary APS are more likely to present at older age and suffer from myocardial infarction, epilepsy and lower limb arterial thrombosis. Children can present with chorea and jugular vein thrombosis whereas older onset patients are more frequently associated with increased rates of stroke and angina.(82)

Secondary risk factors for thrombosis can act as an additive effect to the risk already posed by circulating aPL such as factor promoting stasis and vascular injury - oral contraceptives and atherosclerosis and disease recurrence. High risk of recurrent

infarcts of brain and eye are significantly associated with the presence of cigarette smoking and hyperlipidaemia.(96)

APS and the heart

Manifestations of the cardiovascular involvement in APS are shown in Table 3-3. The average carotid intima media thickness is greater in patients with primary APS than healthy controls.(97) It has been reported from one study that as high as 21% of young patients who suffer myocardial infarction are aPL positive. (7) LA can be found in 3% of patients diagnosed with a myocardial infarction, compared to only 0.7% of healthy individuals.(98) Cardiovascular morbidity in APS patients is increased in the presence of other known associated cardiovascular risk factors such as hypertension and hyperlipidaemia.(99) The odds ratio for myocardial infarction in patients with APS has been reported as 5.3, increasing to 21.6 in women using oral contraceptives and 33.7 in patients who smoked.(26)

APS and the central nervous system

Cerebral vessels are a common site of occlusion in APS patients, where 50% result in stroke and 2.3% a transient ischaemic attack. LA has been shown to be present in 17% of female ischaemic stroke patients.(99) The odds ratio for ischaemic stroke in patients with APS in one study was 43.1, which increased to 201.0 in women who used oral contraceptives and 87.0 in those who smoked. 6-18% of young patients who suffer a stroke have aPL.(83) Cerebral angiography of APS patients with cerebrovascular involvement can be normal or reveal large vascular occlusions or stenosis in the absence of any vasculitic changes. One-third of patients under 50 years with cerebral ischemia have aPL. Cerebral ischaemia can develop either as multiple or localised infarcts associated with dementia, epilepsy or movement. (96) Migraines may be a preceding symptom many years before diagnosing APS.(100) Other cerebrovascular disease risk factors add to the increased risk of recurrent ischemic events in the presence of aPL.

APS and the eye

Ophthalmic features in APS include thrombosis involving the vasculature of the retina, choroid, ocular motor nerves and the visual pathways. 8–88% of patients with

APS have some ocular involvement.(83) An ocular thrombotic event can be an early manifestation of the syndrome more likely in young female patients. Six to 33% of patients with ocular thrombosis have an average age of 39 years. Manifestations occur within any structure of the eye, either simultaneously or remain limited to the anterior or posterior segment. (93) The prevalence of aPL is 22.5% in patients with retinal thrombosis in the absence of any other associated thrombotic risk factor.(101) Signs and symptoms of ocular involvement in APS are shown in Table 3-4. Symptoms range from transient visual loss, diplopia, migraine, permanent visual field defects and even as severe as unilateral or bilateral visual loss.(2) Visual disturbances are associated with migraine in 10% of cases and transient losses tend to be related to disturbances within the central nervous system. Therefore it may not be common to find abnormal ocular signs in asymptomatic patients or those with transient visual disturbances. Visual impairment occurs due to ischaemia and haemorrhage from neovascularisation. (80)(93) The diagnosis of APS should be considered in all unexplained cases of retinal arterial and venous thromboses with neovascularisation at presentation. (102)

33% of patients with retinal vascular occlusions, involving both artery or vein, have aPL. Raised levels can be found in 24% of patients with RVO compared to 9% in patients with inflammation and 8% of controls. (104) Patients with circulating LA and aCL are also at a higher risk of bilateral retinal vascular disease. 15% of patients with secondary APS are at high risk of developing retinal vascular disease and ischemic optic neuropathy, a major cause of blindness in these patients.(103)

APS and pregnancy

Women with antiphospholipid antibodies have a high incidence of pregnancy complications, with about one-quarter of successful pregnancies delivering prematurely(105), The prevalence of aPL in women with recurrent miscarriage is between 7 to 42%, owing to the research variability in laboratory testing and unavoidable addition of transiently positive aPL patients. There is a 90% fetal loss rate in patients with APS, where the majority of miscarriages occur before 14 weeks of gestation. aPL are also associated with placental insufficiency and the early onset of severe pre-eclampsia. (106)

Symptoms	Anterior segment involvement	Posterior segment involvement
Reduced visual acuity (VA)	Bilateral episcleritis	Venous tortuosity
Transient visual field defects	Microaneurysms	Optic disc oedema
Monolateral/bilateral amaurosis fugax	Conjunctival telangiectasia	Optic atrophy AION
Scintillating scotoma	Limbal keratitis	Vitreous haemorrhage
Transient diplopia		Cotton-wool spots
		Vitreous bands
		Serous detachment of the macula
		Retinal capillary abnormalities
		Central retinal artery and/or vein thrombosis
		Branch retinal artery and/or vein thrombosis
		Thrombosis of the retinal arterioles and/or venules
		Retinal capillary non-perfusion

Table 3-4: Ocular manifestations of anti-phospholipid syndrome(80)(93)(103)

APS and mortality

Fewer than 1% of episodes of venous thromboembolism are fatal. The most common cause of death in APS patients is from thrombotic complications. A European cohort study of APS patients calculated a 5-year mortality rate of 5.3% in their sample population.(82) Patients with APS develop significant morbidity and mortality despite any treatment or preventive strategies. Catastrophic APS is associated with a higher mortality rate than other sub-classifications of APS due to acute multi-organ failure. 40% of the APS deaths are due to myocardial infarction, stroke and pulmonary embolism. The presence of SLE in patients with APS is a poor prognostic factor. (107) (108)

3.1.6 Differential diagnosis of venous and arterial thromboembolism (TE)

Causes of venous and arterial TE are shown in Table 3-5. Homocystein is biosynthesised from methionine, that is associated with CVD due to thrombi formation caused by endothelial damage and inflammation. Raised levels can be hereditary, or associated with increasing age, vitamin B 6,9 and 12 deficiencies and excess exercise or alcohol consumption.

Causes of venous thrombosis	**Causes of arterial thrombosis**	**Causes of arterial and venous thrombosis**
Protein C deficiency	Atherosclerosis (High serum LDL cholesterol and triglycerides)	Anti-phospholipid syndrome
Anti-thrombin III deficiency	Cigarette smoking	Activated protein C resistance
Pro-thrombin mutation	Diabetes Mellitus	Factor V Leiden mutation
Malignancy	Hypertension	Protein S deficiency
Immobilisation	High serum lipoprotein a levels	Oral Contraceptive Pill
Surgical operation	Factor VIII polymorphism	Hyperhomocysteinaemia
Congenital	Infection (Chlamydia, CMV)	MTHFR enzyme mutation
Pregnancy	Obesity	
	Congenital	

Table 3-5: Causes of venous and arterial thrombosis

3.1.7 Indications and description of laboratory testing for aPL

A thrombophilia screen should be requested to identify patients with either an inherited or acquired tendency to venous or arterial thrombosis of which aPL is one cause, see Table 3-6 and are described in Table 3-8 Thrombophilia screening for arterial thrombosis is indicated in patient < 40 years with TIA, cerebral thrombosis and MI as well as establishing other risk factors such as smoking, BP, lipids, diabetes.

Thrombophilia screening for venous thrombosis	**Thrombophilia screening for arterial thrombosis**
anti-thrombin	Antithrombin activity
protein C - Factor V Leiden,	Protein C activity
protein S - pro-thrombin gene mutation	Free protein S antigen Total protein S antigen
Activated Protein C resistance	Classic + Modified APCR
lupus anticoagulant - anticardiolipin antibodies	Anticardiolipin antibodies Lupus anticoagulant screen homocysteine lipoprotein A
	Protein C antigen*
	IgG & IgM ß2-GPI antibodies*
	Antithrombin antigen*
	Plasminogen activity*
* These assays are not part of routine first line thrombophilia testing	

Table 3-6: Thrombophilia screening for venous and arterial thrombosis

The current standard for diagnosis of APS relies on the expression of either LA by coagulation tests or aCL by solid phase immunoassays. aPL are identified using diverse laboratory procedures through solid phase testing for aCL and aβ2GP-1 antibodies and liquid phase assays for LA from a sample of a patient's blood serum. LA is an anti-phospholipid antibody so called because it was first described in association with SLE.(79) LA antibodies appear more specific and aCL antibodies more sensitive as tests predictor of APS. An average frequency of 44% for aCL antibodies and 34% for LA in patients with SLE. (109) Some patients may be negative for one test and positive for another. Laboratory tests used to confirm the presence of LA are shown in Table 3-7.

The presence of LA may be suggested by unexplained prolongation of clotting times in phospholipid-dependent coagulation tests Activated Partial Thromboplastin Time (APTT) and the dilute Russell's Viper Venom (DRVV) test without specifically inactivating any individual coagulation factor. At least one complete testing procedure (screening, mixing and confirmation) performed either with the dRVVT or the APTT-based method is sufficient to diagnose LA. Although a normal APTT does not exclude the presence of LA antibodies.

In the DRVV test the reagent contains dRVV, plant phospholipid and calcium ions. dRVV activates Factor X directly bypassing the intrinsic and extrinsic coagulation pathways. Coagulation is via the common pathway and prothrombinase complex formation which is dependent on phospholipid for thrombin generation.

The reagent is added to the patient's plasma and resulting clot formation is timed. When present aPL neutralise the phospholipid component of the reagent resulting in a prolongation of the clotting time. The DRVV test has been shown to be more specific for LA because it is not influenced by intrinsic factor deficiencies or intrinsic factor inhibitors which cause prolongation of the APTT. The result is expressed as a ratio of the patient's DRVV clotting time over the DRVV clotting time of normal plasma. If the DRVV ratio is raised, the presence of a LA is confirmed. By repeating the test using a reagent containing DRVV, calcium ions and a high concentration phospholipid which will neutralise any LA present so that thrombin formation is not inhibited. This confirmatory test is performed on patient and normal plasmas, the ratio is calculated and the result reported as the percentage correction of DRVV Test ratio.

Performance of the prothrombin time and thrombin time tests is important as the results assist in the interpretation of LA tests and evidence of an inhibitor demonstrated by mixing studies.

Upon detection, LA must be confirmed on a second occasion 12 weeks apart. No LA test consistently shows 100% specificity and sensitivity just one assay may lead to false negative aPL assessments because of the heterogeneous nature of aPLs, more than one test system should be used as a patient could be positive for LA or aCL independently of each other. Higher level of support for APS is considered when there are positive test combinations, when higher-titre aPL results are identified together with persistence in aPL. It is generally accepted that patients who are positive for both tests are at increased risk for clinical events.(110)

The aPL antibodies persist for many years and can be positive with the presence of other conditions such as cancer, haemodialysis and drug administration where IgM antibodies are present at low levels and are not significantly associated with a higher risk of thrombotic events. False results can occur as transient positive results can arise with infection but are independent of aβ2GP-1. (79)(81)(111) A positive aPL antibody test may also be associated with positive antinuclear antibodies, circulating immune complexes, complement deficiency, rheumatoid factor, thromboplastin APA(8) and C-reactive protein. (5, 9)

Conditions which require caution with results interpretation include the concurrent antithrombotic treatment (heparin, oral anticoagulants and direct thrombin inhibitors), the presence of high-titre antibodies directed against clotting factors and the close proximity to the acute thrombotic event. Aspirin and clopidogrel do not interfere with LA assays. LA detection is not recommended during or close to the occurrence of a thrombotic event. In addition to the above-mentioned interference of the antithrombotic treatment, it should also be noted that increasing levels of acute phase reactants such as factor VIII, a frequent finding during acute thrombosis, may influence the results of the APTT-based methods. (112)

LA detection tests
(APTT (plus 80:20 mix)) (Prolonged APTT that does not correct in an 80:20 mixture with normal human plasma)
Kaolin clotting time (KCT)
Dilute thromboplastin time (TDT/DTT)
Prothrombin time
dRVVT

Table 3-7: Lupus Anticoagulant (LA) diagnostic tests

		Deficiency is associated with
Anti-thrombin III	Natural inhibitor of blood coagulation proteases - thrombin, II a, X a , IX a and XI a.	A high risk of thrombosis
Protein C activity	Vitamin K dependent protein synthesised in the liver. activated by thrombin in the presence of phospholipid and calcium ions. Activated Protein C is enhanced by a co-factor, Protein S, as a blood clotting inhibitor that regulates the coagulation process by neutralising Factors Va and VIIIa.	Low levels may be inherited or acquired and predisposing patients to thrombosis.
Free Protein S	Protein S is a vitamin K dependent cofactor for the anticoagulant activity of activated protein C . Two forms of protein S are present in plasma : free protein S (40%) and protein S linked to the C4b-binding protein (60%). The free form has functional cofactor activity.	Protein S deficiency may be hereditary or acquired associated with a high risk of developing venous thromboembolism in young patients.
Activated Protein C Resistance (APCR)	Hereditary defect of the Protein C anticoagulant pathway. Plasma does not produce an anticoagulant response to activated protein C termed APC resistance VQ506 gene mutation which produces factor V Leiden, a factor V molecule which is resistant to cleavage by activated protein C.	Inherited resistance to activated protein C, associated with the factor V Leiden mutation G1691A has been shown to be present in 20-50% of individuals with DVT which results in a pre-disposition to thrombo-embolic disease.
Factor V Leiden mutation	Found by PCR testing with a reduced APCR or family history of factor V Leiden.	The Factor V Leiden genotype A/A is associated with a 50-100 fold increased the risk of venous thrombosis.
Prothrombin gene mutation (G-20210-A).	Prothrombin G20210A variant and associated high levels of factor II	(Prothrombin G20210A genotype G/A) increase the risk of venous thrombosis by up to 3 fold.

Table 3-8:Other diseases uncovered by thrombophilia testing

Inherited causes

Inherited causes that predispose to thrombosis deficiencies or abnormalities of natural inhibitor proteins of the coagulation system. These inhibitors exist to control the rate of formation of a blood clot. Causes of genetic thrombophilias are part of the differential diagnosis of APS and can coexist within some APS patients see Table 3-9.

Factor V Leiden variant	Levels of protein C	Plasminogen
Pro-thrombin mutation	free and total protein S	tissue plasminogen activator (TPA)
Factor VIII levels	Anti-thrombin	Plasminogen activator inhibitor-1
MTHFR mutation		β2glycoprotein 1 dependent anticardiolipin antibodies

Table 3-9: Inherited causes of thrombosis

3.1.8 Current opinion on the management of patients with APS

Acute thrombosis

An acute episode of thrombosis in APS should be managed the same as any other cause of thrombosis. Initial treatment includes anti-coagulation with unfractionated or low molecular weight heparin, followed by oral anticoagulation with Warfarin a vitamin K antagonist at a target INR of 2.5 (range 2-3) in the absence of contraindications. Intensity and duration of treatment should be determined on an individual basis, additional risk factors, the severity and the risk of bleeding. Management of recurrent events in patients who are already anticoagulated at a higher therapeutic INR is particularly difficult, recurrent venous thromboembolic events on treatment this group need a target INR of 3 to 4. It is recommended that anticoagulation should continue long term as patients with APS have a high risk of disease recurrence when treatment is stopped.(113) Recurrence remains frequent despite the use of oral anticoagulants.

Venous thromboembolism in APS

Long-term therapy with warfarin may be advantageous in some subjects with venous TE. Use of the combined oral contraceptive and of HRT are best avoided in female patients. (113) Patients with retinal vascular occlusions are generally started on

anticoagulation when found to be APS positive, however the long term benefit of anticoagulation in these patients still remains is unproven. (93)(114)

Arterial thrombosis

High risk of recurrence and likelihood of consequent permanent disability or death, stroke due to cerebral infarction in APS should be treated with long-term oral anticoagulant therapy. And as prohylaxsis at high risk times. Extracerebral arterial thromboembolic manifestations of APS will also warrant consideration of continuation of long-term anticoagulation with warfarin, plus management of additional thrombotic risk factors.

Thrombocytopenia

Thromboprophylaxis with warfarin may carry an increased haemorrhagic risk but should be considered where thrombosis is the principal clinical manifestation. Splenectomy has been safely and successfully performed and is appropriate treatment if clinically indicated.(115)

Pregnancy and APS

The aims of managing pregnancy in women with APS involves both prevention of maternal thrombotic complications and prevention of pregnancy morbidity, highlighting the need for close surveillance during pregnancy and ready access to a neonatal unit. Cases should be managed by a team including a haematologist, rheumatologist and obstetrician. The American College of Obstetricians and Gynecologists(116) have developed recommendations for prophylaxis and treatment during pregnancy. Female patients with aPL but no prior TE events should receive a daily prophylactic dose of Aspirin alone or along with heparin, during pregnancy and the postpartum period. However, treated pregnancies are frequently complicated by foetal growth retardation, gestational hypertension and premature delivery.

Management of systemic risk factors

In addition to the above medical therapeutic agents, patients should be screened for hypertension, hyperlipidaemia, diabetes they should be controlled in addition

increasing exercise, smoking cessation and reduction of obesity. Such cardiovascular risk factors should be aggressively managed to reduce the risk of disease recurrence, miscarriage and mortality.

3.2 METHODS

3.2.1 Aims and purpose

Retinal vascular occlusions are known ocular manifestations of aPL and APS with the potential of causing significant visual loss for patients. If suspected early Ophthalmologists play an important role in diagnosis and prevention of further associated systemic manifestations and disease recurrence. Currently there are no specific guidelines outlining when and who to investigate for aPL in patients presenting with ocular disease. The purpose of this chapter is to outline aPL testing in an Ophthalmology scenario and make recommendation for testing.

The aim of this study is to :

1. outline the characteristics and ocular findings of patients tested for aPL while comparing those with positive tests results with those with negative results.
2. identify systemic or ocular risk factors for thromboembolic events
3. outline changes in visual acuity and treatments employed

3.2.2 Patients

aPL tests were requested for 142 Moorfield's Eye patients from 1st January 2010 until 31st December 2010. Results of aPL testing for these patients were collected from a database of results from St Thomas's hospital, London, where all aPL testing for Moorfields patients are undertaken.

Patients were included if they had one or more aPL test performed and their medical records were found. 30.99% of patients were excluded due to one or more of the following reasons:

1. aPL test was requested but laboratory testing was not performed on the sample, due to miss-labelling or wrong/no sample was sent
2. No medical notes were located for the patient
3. No presenting information from when the aPL test was requested was made available

Demographic details were recorded for all patients including gender, age, eye involved and drug history. Particular interest in past medical history in particular previous thromboembolic events and presence of systemic risk factors including hypertension and hyperlipidaemia. Details of ocular examination were recorded. Data were input into a SPSS database and statistical analysis performed. Chi squared tests were performed on categorical data, t tests for continuous data sets and p values of 0.05 or less were regarded as statistically significant.

3.3 RESULTS

Medical records from 98 patients attending Moorfields Eye hospital for aPL screening tests for various ocular conditions were reviewed see Figure 3-1. Presenting demographic details are shown in Table 3-10. Patients have been grouped according to negative and positive aPL test results to allow for comparison. Patients with 2 positive aPL tests are discussed later.

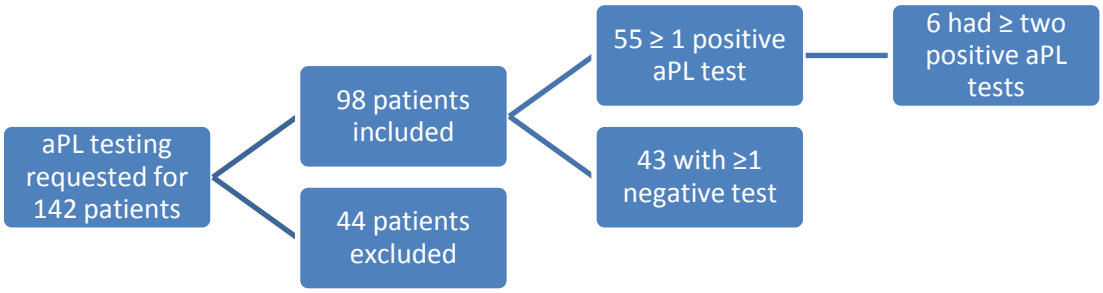


Figure 3-1: aPL test results of patients included in this study

Characteristic	Negative	≥ 1 positive
Number of patients	43	55
Age Mean	49	49
Median	47	47
Range	24-74	16-82
Standard deviation	11	16.26
95% CI	45.45 to 52.13	45.02 to 53.81
Gender (Male:female)	28:15	31:24
% Right	48.84	56.36

Table 3-10: Demographic details for aPL positive and negative patients

The variety of ocular vascular events that the consulting ophthalmologist felt warranted aPL testing are shown in Figure 3-2 and Figure 3-3 for patients with negative and positive tests. Retinal vascular occlusion accounted for 78(79.59%) of all events that aPL was tested for, 37(86.05%) and 41(74.55%) of positive and

negative groups respectively. The cause of new vessels on the retina, periphlebits and Scleritis were other diagnosis where testing was performed.

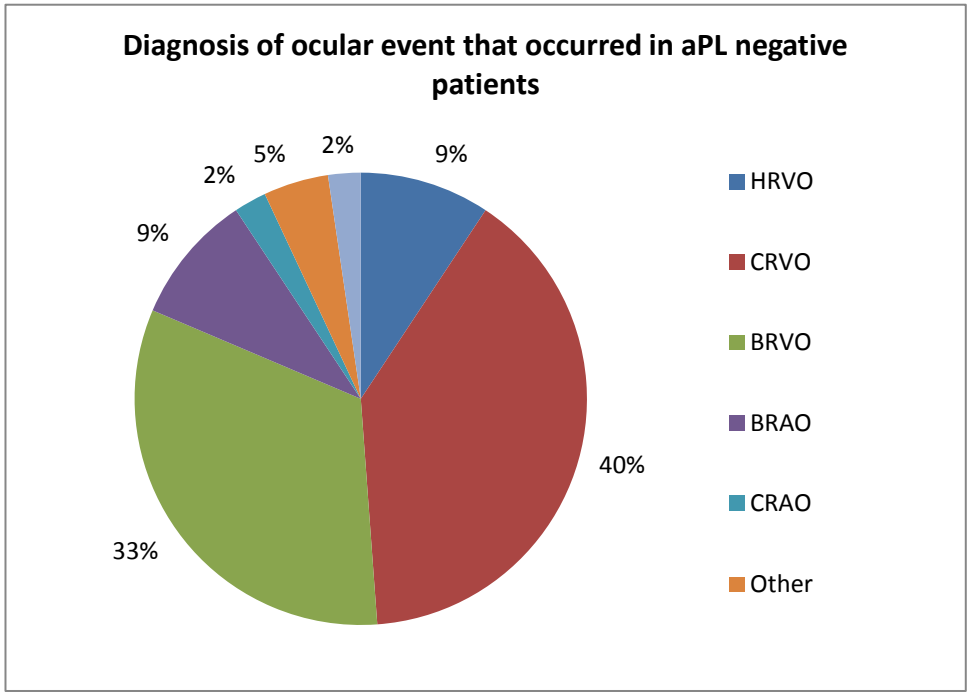


Figure 3-2: Ocular event that occurred in aPL negative patients

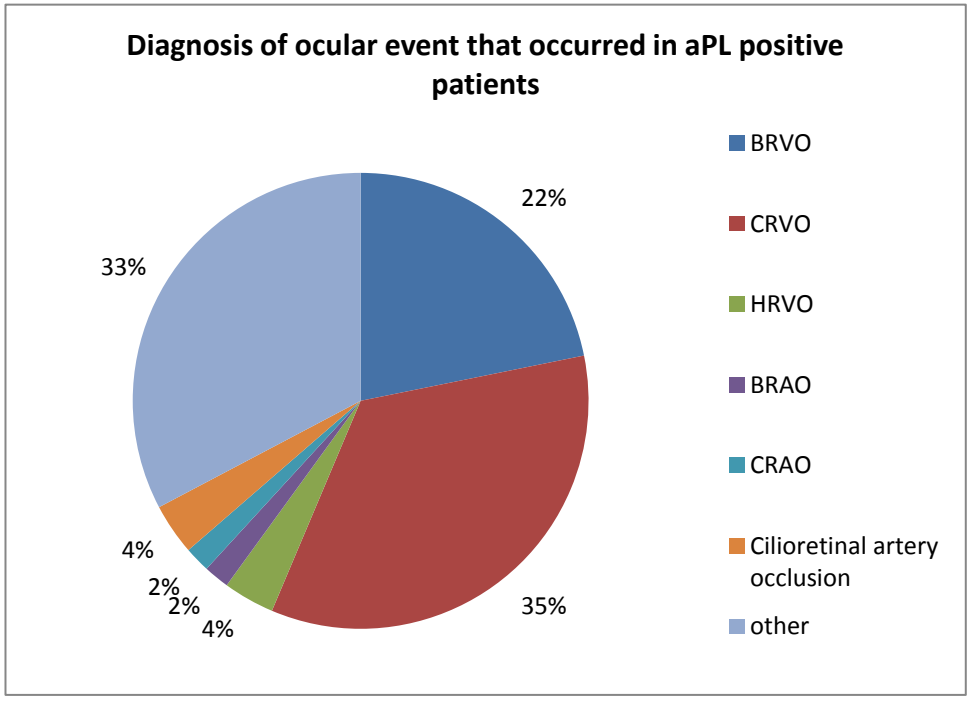


Figure 3-3: Ocular event that occurred in aPL positive patients

Ocular examination findings seen on presentation are show in Table 3-11.

	Total number of eyes	1 positive	Negative
Number of patients	104	43	55
Ischaemia	12(12%)	17(40%)	9(16%)
RAPD	15(14%)	6(14%)	9(16%)
Raised IOP at presentation	7(7%)	7(16%)	0
AC inflammation	2(2%)	2(5%)	0
Vitritis	2(2%)	2(5%)	0
VH	5(5%)	4(9%)	1(2%)
New vessels	11(11%)	7(16%)	4(7%)
Macular oedema at presentation	35(34%)	17(40%)	18(33%)

Table 3-11: Common positive examination findings seen on presentation*

(*where positive and negative findings were documented)

Associated systemic risk factors for thrombosis

Figure 3-4 and Figure 3-5 show the distribution of patients according to age and aPL test result. Table 3-12 shows the medical history of patients including cardiovascular risk factors associated with a higher risk of TE events. A higher proportion of patients with at least one positive test had a previous thromboembolic event, including RVO, CVA, DVT,PE or MI compared to the negative group.

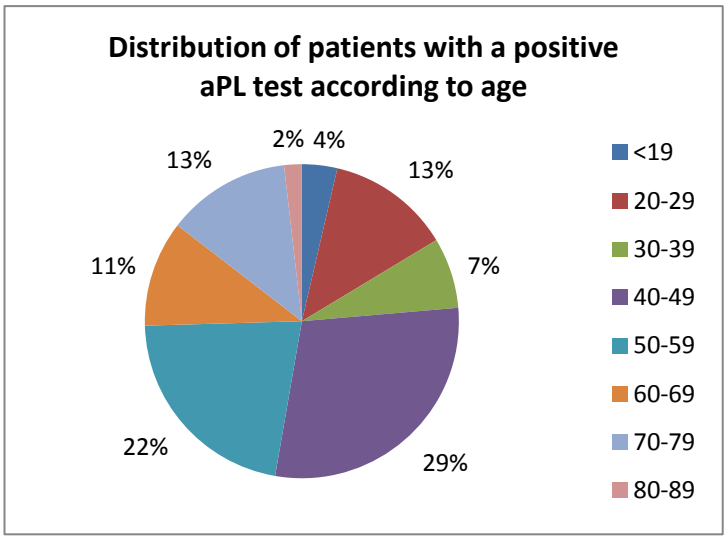


Figure 3-4: Distribution of patients with a positive aPL test according to age

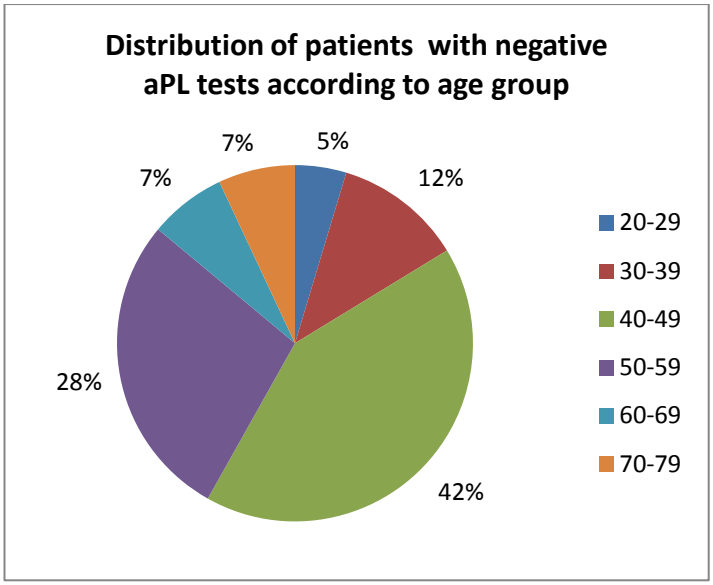


Figure 3-5: Distribution of patients with a negative aPL test according to age

Risk factor	***Total(%)***	***1 positive N=43***	***Negative N=55***	***P value***
Hypertension	44(45%)	25(58%)	19(35%)	0.0335
Antihypertensive medication	23(23%)	14(33%)	9(16%)	
Hyperlipidaemia history	18(18%)	14(33%)	4(7%)	0.0017
Smoking	17(17%)	10(23%)	7(13%)	0.1900
Diabetes	14(14%)	11(26%)	3(5%)	0.0074
Previous DVT/PE/MI/CVA/RVO	13(13%)	11(26%)	2(4%)	0.0020
Cancer	4(4%)	4(9%)	0	0.0342

Table 3-12: Systemic risk factors present in positive and negative aPL groups

Risk factors for a thrombotic event found on systemic examination at presentation are shown in Table 3-13, where tested.

Examination finding on presentation	**Total**	**positive**	**Negative**	**P value**
High blood pressure	26(27%)	16(37%)	10(18%)	0.00405
Hypercholesterolemia positive on testing	21(21%)	9(21%)	12(22%)	
Raised inflammatory markers	8(8%)	2(5%)	6(11%)	0.4597

Table 3-13: Systemic examination findings on presentation

Ocular features

Visual acuity

Presenting visual acuity (VA) are similar for both groups of patients according to aPL test results, shown in Table 3-14. This included the VA of both eyes involved in patients presenting with bilateral disease. The difference between mean presenting VA of the two groups was not significant (unpaired t test p=0.92).

LogMAR VA	1 positive	Negative
Mean	0.56	0.58
Median	0.3	0.3
Range	-0.2-3	-0.1-3
Standard Deviation	0.70	0.74
Number	61	43
95% CI	0.39 to 0.74	0.35 to 0.81

Table 3-14: Presenting LogMAR BCVA in the affected eye of all aPL positive patients

Change in VA over 1,6 and 12 months of follow up.

24 patients with a positive aPL test had 12 months of follow up data available. Mean VA from presentation (0.57 LogMAR) to 12 years (0.54 LogMAR) was 0.05 LogMAR units (paired t test p=0.59), see Table 3-15. Similarly the mean change in VA from presentation to 12 months in 28 patients from the negative group improved from 0.67 LogMAR units (SD 0.86) to 0.46 LogMAR units (SD 0.85) (paired t test p=0.11) see Table 3-16. 5 eyes with a presenting VA of worse than 0.3 LogMAR improved to better than 0.3 logMAR at 12 months. 1 eye presenting with good VA got worse at 12 months. Macular oedema was persistent in 8 eyes at 1 year, 2 developed within a year.

Treatments used to manage ocular events in patients over 1 year of follow up are shown in Table 3-17.

LogMAR VA	Presentation	1 month	6 months	12 months
Mean	0.56	0.76	0.57	0.54
Median	0.3	0.3	0.34	0.55
Range	-0.2-3	-0.1-3	-0.2-3	-0.2-1.48
Standard Deviation	0.70	1.03	0.71	0.55
Number	61	28	40	24
95% CI	0.39 to 0.74	0.36 to 1.16	0.34 to 0.80	0.30 to 0.77

Table 3-15: Change in LogMAR VA in eyes of patients that tested aPL positive over 1,6 and 12 months of follow up

LogMAR VA	Presentation	1 month	6 months	12 months
Mean	0.58	0.59	0.50	0.46
Median	0.3	0.3	0.18	0.18
Range	-0.1-3	-0.1-3	-0.1-3	-0.2-PL
Standard Deviation	0.74	0.78	0.78	0.85
Number	43	37	39	28
95% CI	0.35 to 0.81	0.33 to 0.85	0.25 to 0.75	0.13 to 0.79

Table 3-16: Change in LogMAR VA in eyes of patients that tested aPL positive over 1,6 and 12 months of follow up

Treatment administered	Negative	Positive
Laser PRP	5(9%)	11(26%)
Lucentis	1(2%)	0
Avastin	1(2%)	3(7%)
IOP lowering medication	0	4(9%)
Peripheral iridotomies performed	0	1(2%)
Blood pressure lowering medication started	1(2%)	3(7%)
Topical/oral/intavitreal implant steroid	1(2%)	3(7%)
Aspirin/warfarin	1(2%)	6(14%)
Vitrectomy	2(4%)	1(2%)

Table 3-17: Treatments administered within 1 year of follow up

Patients with two positive aPL tests

6(6%) patients had a second positive aPL test result and one patient already had the diagnosis of APS made in the past. Demographic details for these cases are shown in Table 3-18. The patient with a past history of APS did not present with a specific ocular disorder at the time of repeat testing during this year so was excluded. 4(80%) patients, mean age 43 years, presented with a unilateral retinal vein occlusion of which 2(50%) were ischaemic. The other patient presented with recurrent bilateral scleritis. LogMAR VA at presentation and follow up, are shown in Table 3-19. Mean change from presentation was 0.16LogMAR worse at 12 months in 5 patients (paired t test p=0.50). Three patients had another risk factors for TE disease, including cancer, pregnancy, hypertension and a history of smoking.

Characteristic	Patients with 2 positive aPL tests n=6
Mean age (years)	45.80
SD (years)	6.26
95% CI	38.0 to 53.6
Median (years)	44
Range (years)	40-56
Gender (%male)	2(40)
Eye (%right)	4(80%)

Table 3-18: Demographic details of patients with 2 positive aPL tests

LogMAR VA	**presentation**	**6 month**	**12 months**
Mean	0.43	0.47	0.68
SD	0.73	0.72	0.70
N	6	6	5
95% CI	0.34 to 1.2	-0.27 to 1.23	-0.19 to 1.54
Median	0	0.09	0.6
range	0-1.78	-0.1-1.48	0-1.48

Table 3-19: Changes in LogMAR visual acuity over 6 and 12 months of follow up

Patients presenting with RVO 2(50%) had macular oedema on presentation. Mean presenting LogMAR BCVA is shown in Table 3-19 Where follow up data was provided, macular oedema was persistent in both eyes with macular oedema on

presentation and 3 months later in another. New vessels had formed at the disc of one eye. Collaterals had not developed at 12 months in 3 eyes with RVO. Vitreous haemorrhage was present in one eye. One patient was treated with PRP, one was referred for haematologist review for management.

3.4 DISCUSSION

The diagnosis of APS is known to be common in younger patients without known systemic risk factors presenting with an occlusive vascular disease.(3) Only 1(1%) patient from our population from a Ophthalmology tertiary hospital population was newly referred to haematology for further management of APS with two consecutive positive aPL tests in one year.

What does a positive test mean?

A prospective study of 185 patients with primary and secondary APS (LA and/or raised aCL) from an Italian registry(92) median age 39 years, range 2 to 78 were observed. Their natural history, risk factors for thrombosis, occurrence of arterial or venous thrombosis, the outcome of pregnancies, and any severe complications leading to morbidity or mortality for a median of 3.9 years (range 0.5 to 5) was undertaken. 34 patients developed a thrombotic event, with a total incidence of 2.5%. 65% had primary APS and 35% as secondary APS of which 90% were women. Multivariate logistic regression analysis identified: a previous thrombosis (RR 4.9; 95% CI, 1.76 to 13.7; $P < 0.005$) and IgG ACA titre above 40 units (RR 3.66; 95% CI, 1.24 to 10.8; $P < 0.01$) as two independent risk factors. 18 patients died due to vascular events or haematological malignancies.

aPL occur in a variety of clinical disorders. The Montpellier study of 1014 patients admitted to a department of Internal Medicine department were tested (488 males-526 females, mean age: 66.7 years, range 18-97). 7.1% patients were found aPL positive at least once: 44 males and 28 females, mean age 69 years, range 23 to 94. 20 fulfilled the criteria of Primary APS: 10 patients were referred for DVT, 3 had history of DVT, 1 had both arterial thrombosis and a history of venous thrombosis; 2 had thrombocytopenia; 3 had stroke, 1 had a history of a stroke. The most frequent associated disease was cancer in 14 patients.(91)

Characteristics of the positive group

56.12% of patients tested positive for aPL. Patients were a mean age of 49 years. There was no significant gender difference. RVO occurred in 56.05%. A history of a previous TE event was present in 26% of aPL positive patients. 16.36% had a systemic risk factor for aPL that might had yielded a false positive result if retested. 74.55% had an associated systemic risk factor for RVO.

Characteristics of the negative group

43.88% of patients tested negative for aPL. Patients were a mean age of 49 years and 58.14% were less than 50 years old and there was a male predominance. RVO occurred in 74.55%. A history of a previous TE event was present in 4% of aPL negative patients. 6.98% had a systemic risk factor for aPL that would have yielded a false positive result if retested. 58.14% had an associated systemic risk factor for RVO

Retinal vascular occlusive events associated with a aPL

aPL were detected in 9(42.9%) patients under 50 years old with a retinal vascular occlusion without other systemic risk factors for thrombosis. Negative tests were obtained for 41(95.35%) patients with retinal vascular events, the other two negative tests included investigation into causes of peripheral new vessels and phlebitis. 13(31.71%) patients with retinal vascular events did not have a known systemic risk factor for TE of which 10(76.92%) were <50 years old.

The presence of aPL are not more likely to cause ischaemic retinal vascular occlusions or ocular conditions with a worse visual prognosis compared to aPL negative patients. Features of RVO in aPL positive patients were classical and included venous tortuosity and retinal haemorrhages. aPL do not influence the development or persistence differently in positive or negative patients.

How many positive patients were re-tested in 12 weeks?

Results of aPL testing reported by the clinical laboratory show results both as clotting times for screening, mixing and confirmatory tests with a conclusive remark

expressed as either positive or negative LA result with recommendation to retest within 12 weeks to confirm persistence of aPL. (112)(117)

A clinical audit of antiphospholipid antibody testing in a tertiary level teaching hospital over a 6 month period returned 268 hospital requests for investigation of LA and 1006 requests for aPL testing. (1) 4.1% were LA positive, 5.2% aCL positive, 45.5% of the LA-positive samples also positive for aCL. 22 patients had repeat testing, 50% repeated in less than 12 weeks. (110)

In our population only 8(19%) patients positive for LA on initial testing were re-tested for persistence of the aPL antibodies within 12 weeks despite recommendations from laboratory for all 43 positive patients. Thus comments on transient rises in aPL cannot be made on the whole sample. The reason for lack of retesting is unknown but could be due to many reasons including: results are obtained late the other laboratory samples and not checked at a later date especially if not documented in the notes that the test had been requested. Some patients may have been discharged or failure to attend further follow up before test results are obtained. Repeat testing could also have been carried out by the patient's GP which would not be available on the Moorfields database.

Calculating the sensitivity and specificity of aPL testing in our population

LA detection is a complex diagnostic procedure with varied sensitivity. None of the tests currently used are able to detect with LA types with great certainty.(117)(111) The dRVVT has been shown to be sufficiently sensitive for LA detection, but results may vary within and between laboratories as tests are difficult to standardise according to the commercial brand used for testing. (111)

Based on our population we cannot calculate accurate predictive values from sensitivity, specificity and prevalence of APS because not all patients from the positive group have a second positive result performed. The number of patients who tested positive who actually had the disease was not established nor do we know how many patients initially tested as negative would return a positive test.

Appropriate aPL testing requests

Screening can be justified in a wide range of subjects. An investigation into aPL testing behaviours calculated testing was justified in 69% of their patients where aPL were positive in 18% positive for LA. The presence of the triple aPL positivity was found only in the justified requests (118) From our population, 26(47.27%) positive aPL patients were over 50 years, of which only 4(15.38%), mean age 53.75 years, had no associated systemic risk factors for TE. It would be difficult to discriminate whether the aPL or presence of systemic risk factors in particular contributed to the vascular event in these patients. But if all patients over 50 and those at presentation or with the presence of one or more systemic risk factor for TE were excluded, then potentially 68(69.39%) of tests could have been avoided.

True analysis of false positive results relies on the repeat testing of aPL in patients with initially positive tests. To reduce false positive results, LA screening should not be performed during the acute phase after the patient presents with a clot. Haemolysis, under or overfilling of blood samples can also affect results. The relatively poor specificity of the testing procedures may increase the rate of false positive results. LA testing should be reserved in subjects with incidental prolonged APTT and those with a history of venous and/or arterial thrombosis in association with autoimmune disease, at unusual sites and in young patients.

Limitations of this study

Limitations restricted by the retrospective nature of this study include the lack of standardised documentation of a substantial medical and drug history for all patients for example with smoking history. Bias towards documenting only positive findings does not allow this study to exclude the absence of risk factors if not documented as either present or absent as the factor may not have been sort. Other known risk factors for TE such as BMI and recent non-ocular surgical history rarely documented. Pregnancy complications were also not generally documented. Another limitation was not knowing whether patients had repeat testing for aPL out with the hospital setting to confirm persistence of circulating aPL. This study was also restricted by the 12 month follow up period, thus future ocular and systemic events that patients with positive tests incur would need further investigation.

Recommendations

This study recommends guidelines are necessary to guide both clinical ordering and which tests laboratories should offer to reduce the risk of false positive and reduce the number of costly and unnecessary tests. Routine screening for aPL is not recommended at the first instance in patients over 50 years of age.

Relevant history should be documented including TE risk factors and conditions that would yield false positive results including:

- smoking history
- recent surgical history
- malignancy
- current pregnancy
- drug history including OCP and anti-coagulant use
- current infections
- previous TE events

Initial testing should investigate common causes associated with a high risk of thrombosis including:

- hypertension
- hyperlipidaemia
- diabetes
- raised IOP

In an Ophthalmology scenario aPL should be tested after the acute event so as not to yield false positive results in patients with:

- venous or arterial thromboembolism in the absence of cardiovascular risk factors such as hypertension, diabetes or hyperlipidaemia
- especially in those under 50 years of age including patients with recurrent thrombotic events
- or young patients with recurrent events in the presence of other controlled risk factors

aPL investigation in the presence of inflammation should be reserved after investigation of common causes are excluded.

Documentation of aPL requests should be specifically made in the medical notes to aid follow up of results at future visits when made available.

When requesting aPL tests:

- blood samples must be clearly labelled with the patients first name, surname, D.O.B, hospital number and the date the sample was taken.
- The details on the sample must correspond to the request form.
- Current anticoagulant medications should be specified as additional tests may be required.
- Relevant clinical details including ocular diagnosis, previous thrombosis, pregnancy and OCP use should be included.
- State the haemostasis investigation required
    - Thrombophilia profile
    - Antiphospholipid profile
    - or other specialist investigation

St Thomas's laboratory antiphospholipid antibody markers include: IgG, IgM & IgA Anticardiolipin antibodies and IgG and IgM anti-beta2-glycoprotein 1 antibodies by special arrangement. All samples negative by DRVVT and dAPTT will receive: mixing studies and a confirmatory test where indicated. Patients receiving oral anticoagulation additionally receive: TSVT, Ecarin time (ET) and mixing studies where indicated.

Ophthalmologists should remember that upon return of 1 positive test this does not diagnose APS. Requests should be made with the knowledge that repeat testing would be indicated. Repeat testing should be performed within 12 weeks to confirm persistent aPL which should be performed in the hospital setting or request to the GP if the patient has been discharged. Communication with the patients GP as to ocular events that yield positive aPL testing should be made for documenting with the patients whole medical history for analysis of future medical events or repeat testing.

If patients yield two positive results referral to a local haematology department can be made for further investigations and management of APS, ie should be a multidisciplinary approach.

3.5 SUMMARY OF RESULTS

APS is a rare diagnosis in the ophthalmology setting. The incidence of APS was 1% in our population of patients over one year. The majority of tests were performed on patients presenting with retinal artery or vein occlusions.

This study highlights changes to testing practices that should be employed when investigating for aPL, including the exclusion of common risk factors associated with thrombosis in the first instance including measuring blood pressure, cholesterol and glucose levels to diagnose diabetes. 51.9% of 17 patients with characteristics or risk factors for APS yielded positive aPL results. 72.5% of tests in our population could potentially have been avoided including one patient already known to have APS. False positive results may mean unnecessary long-term anticoagulation for some patients. Moreover, indiscriminate and inappropriate testing may lead to misdiagnosis and add to increasing health care costs where unnecessary in the majority of cases.

Repeat testing in such patients should be requested within the hospital scenario or in community within 12 weeks to confirm APS diagnosis to allow for early initiation of suitable management to prevent future events.

It is difficult to discriminate between whether retinal vascular occlusions in APS patients are caused by or are associated with an increased risk due to the aPL antibodies, if known systemic risk factors are also present.

Long term follow up of these patients would be interesting to find out results of repeat aPL testing and observe potential systemic and ocular effects in the future.

4. Ozurdex - an intravitreal Dexamethasone implant for uveitis

4.1 INTRODUCTION

Uveitis is a cause of 10-15% of irreversible blindness and visual impairment in the developed world which is frequently due to oedema accumulating at the macular. (119)(4)(120) The prevalence of macular oedema varies between 20 to 30% of uveitis cases.(6) Fluid accumulates through the complex actions of inflammatory cells involved in inflammation causing an increased production of inflammatory mediators such as cytokines, growth factors, free radicals, prostaglandins, leukotrienes, interleukins (10 and 6) and vascular endothelial growth factor. Intra-retinal fluid accumulates expanding extracellular compartments pooling in cystoid spaces due to the disruption these inflammatory cells cause, see photograph 4-1. Loss of integrity of the healthy inner retinal barrier (retinal capillary endothelial tight junctions), outer retinal barrier (tight junctions between retinal pigment epithelium cells) and dysfunction of the retinal pigment epithelium pump are seen. (6) Control over the actions of these inflammatory cells allows for the successful treatment of macular oedema in uveitis. (121)

Corticosteroids have long been used as one such treatment of macular oedema and inflammation associated with uveitis.(120) The long-term management of patients with uveitis is frequently a difficult balance of efficacy and safety. Currently the choice of which agent to use depends on the beneficial action and duration outweighing their negative side effect and cost profiles. (3)(6)(119) Systemic (oral and intravenous) and local methods (topical, peri-ocular and intravitreal) of steroid delivery are available with differing drug potency, biologic activity, duration of action, solubility and side effect profiles.

The introduction of sustained release intravitreal implant preparations have provided a new treatment alternative to deliver steroids to the posterior segment of the eye.

This introduction will highlight the current methods available for corticosteroid delivery to the eye with particular emphasis on the dexamethasone intravitreal implant and the evidence available for its use in non-infectious uveitis.

4.1.1 Modes of action of steroids

Corticosteroid actions are multifactorial, they have potent effects mediated by cytosolic glucocorticoid receptors within target cells (lymphocytes, monocytes; nonpigmented ciliary epithelium, trabecular meshwork, lens epithelium, corneal endothelium) to increase the expression of anti-inflammatory proteins that suppress the production/transcription of pro-inflammatory cytokines: interleukin 1,2,3,5, TNF-alpha, interferon gamma. Inhibitory inflammatory mediators include: prostaglandins, leukotrienes, phospholipase A2, thromboxane, histamine release and VEGF.(6)(121) Corticosteroids also reducing wound scarring/prevent healing by inhibiting fibroblasts and fibrin deposition. and stabilise endothelial cell tight junctions preventing leakage of fluid at the macula as discussed earlier. Three most commonly used steroids used in uveitic eyes include: triamcinolone acetonide, fluocinolone acetonide, prednisolone and dexamethasone, see Table 4-1. Routes of administration of the steroids are discussed below, except oral preparations discussed in the introduction to this thesis.

4.1.2 Topical corticosteroids

Topical corticosteroids are the primary form of treatment for anterior uveitis first described in the 1950s.(122) Topical routes provide direct delivery of a steroid to an eye that penetrates through to the anterior chamber. Topical preparations commonly used for anterior uveitis include: Maxidex (dexamethasone 0.1%), Pred Forte (prednisolone 1%) and Vexol (rimexolone 1%). Topical drops can be administered at frequent intervals depending on the degree of active inflammation. One major disadvantage of topical steroids are that they are inadequate when used to treat posterior segment inflammation, owing to its poor penetration abilities beyond the lens to the vitreous cavity. Side effects of topical treatments are related to the corticosteroid dose, duration, rate of penetration into the eye and systemic absorption. In general topical steroids have minimal systemic absorption rates reducing the risk of systemic side effects.(123) Local side effects associated with

topical steroids include cataract formation and increased intraocular pressure. Moreover, frequent daily topical treatments may be cumbersome for some patients when required long term. In such cases local effective steroid doses for posterior segment inflammation can be targeted via periocular or intravitreal routes.(121)

4.1.3 Peri-ocular and intravitreal corticosteroid injections

Corticosteroids can also be administered locally via trans-scleral absorption with orbital floor injections (OFI)/sub-Tenon's injection or directly as an intraocular injection into the vitreous. The latter provides a quicker response but is associated with an increased risk of ocular side effects. This route offers the advantage of delivering high therapeutic concentrations of a steroid to an inflamed eye within close proximity to the retina, macula and optic nerve. Higher local steroid concentrations are achieved compared to topical and systemic routes by bypassing the blood–retinal barrier, minimising systemic absorption rates and therefore reducing the risk of systemic steroid side effects.(2)

Triamcinolone is one such corticosteroid used via this route. (124) IVTA represents an important and recent adjunct in the management of macular oedema and vitritis in eyes with non-infectious uveitis(125) (120) (9) (126) Uses of IVTA have also been investigated in eyes with macular oedema due to diabetic retinopathy(127)(128)(129)(130) and retinal vein occlusion. The most commonly used Kenalog formulation of IVTA is delivered in a relatively insoluble crystallised form prevents its rapid clearance from the eye but clumps of which are occasionally visible to the patient. Moreover, the benzyl alcohol addition within the commercially available Kenalog formulation of triamcinolone has been linked to retinal toxicity. (131) As a suspension it is technically difficult to deliver a consistent dose of IVTA. Ober et al(132) found that 0.1 mL of well mixed IVTA (40 mg/mL) can contain anywhere from 1.4 mg to 12.9 mg of triamcinolone acetate. The steroid persists in the vitreous for approximately 90 days (mean half life of 18.6 days) in non-vitrectomised eyes and shorter in vitrectomised eyes (half life of 3.2 days).(133) Triamcinolone is cleared from the vitreous after approximately 3 months and patients often require re-treatment to sustain any further beneficial effects of the treatment.

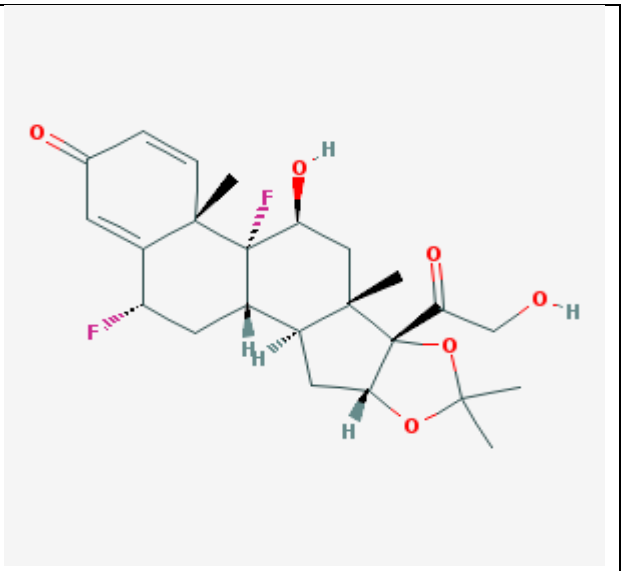
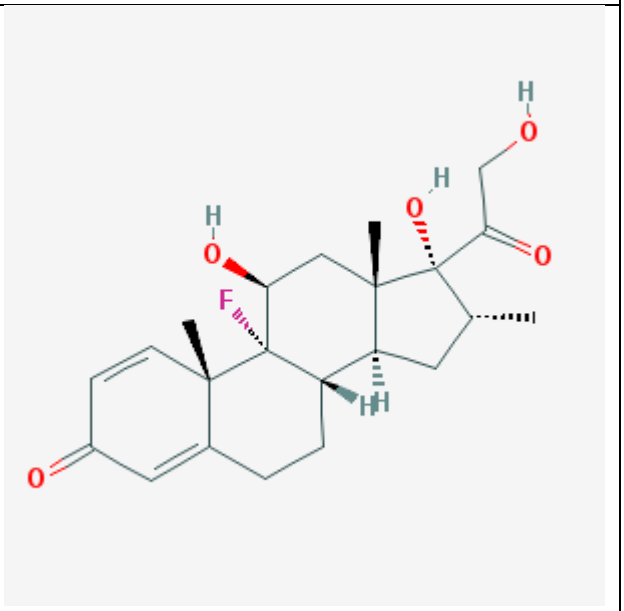
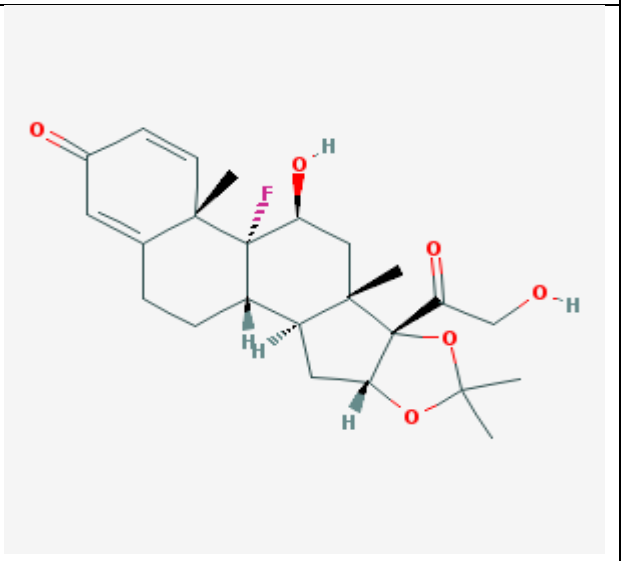
Fluocinolone	
Dexamethasone	
Triamcinolone	

Table 4-1: Molecular structure of Fluocinolone, dexamethasone and triamcinolone

Local ocular side effects occur including a fivefold increased risk of developing cataract than in the general population(121), raised IOP, endophthalmitis, vitreous haemorrhage, retinal detachment and central retinal vein occlusion.(134) Peri-ocular orbital floor injections have the added risk of inadvertent globe penetration, extra-ocular muscle injury, ptosis, orbital fat protrusion and local skin depigmentation. (121)(124)(135)

4.1.4 Intravitreal implants

The evolution of the intravitreal implant has brought about interest to supersede current short acting local drug delivery methods to overcome the difficulty of delivering effective doses of a steroid into the vitreous cavity with the ability to maintain a sustained control of intraocular inflammation. Ocular implants were developed based on the Ganciclovir intravitreal implant, Vitrasert, used to treat cytomegalovirus retinitis.(136) Steroid based implants used for uveitis are discussed below.

4.1.4.1 Retisert – Fluocinolone acetonide

Retisert (Envision TD) is a sustained release intraocular implant containing the steroid fluocinolone acetonide 0.59mg which is released over a 36-month period produced in the US by Bausch & Lomb and Control Delivery Systems for the treatment of severe, non-infectious posterior uveitis.(6)

In April 2005 Retisert 0.59mg was approved by the FDA for the treatment of chronic, non-infectious, posterior uveitis. The implant is surgically placed into the vitreous cavity at the pars plana. It slowly releases the corticosteroid at a nominal initial rate of 0.6 µg/day, decreasing over the first month to a steady state between 0.3-0.4 µg/day over approximately 30 months. The implant is not biodegradable and surgical removal of the original implant is associated with an increased risk of vitreous or retinal haemorrhage, retinal traction, and possible retinal detachment.(137)

Published data from a 3 year, multicenter, randomised trial (138) showed Retisert reduced uveitis recurrence and improved or stabilised visual acuity in subjects with

non-infectious posterior uveitis where previous treatments have failed. The prospective trial included 278 patients treated with either 0.59mg or 2.1mg strength agents. In summary uveitis recurrence was reduced from 62% to 4%, 10%, and 20% after 1, 2, and 3 years after implants were inserted, for the 0.59mg dose group and from 58% to 7%, 17%, and 41%, respectively, for the 2.1-mg dose group. Vision was improved by 0.81 logMAR units by 30 months, which was sustained for approximately 3 years. Complications including rises in intraocular pressure (≥ 10 mm Hg) occurred more frequent in treated eyes. Glaucoma surgery was required in 40% of implanted eyes vs 2% of non-implanted eyes, cataracts were extracted in 93% of phakic implanted eyes vs 20% of phakic non treated eyes. The implant decreased the need for adjunctive systemic and other local steroid treatments.(138)

4.1.4.2 Dexamethasone implants

Dexamethasone is a synthetic glucocorticoid used to treat systemic and ocular inflammatory disorders. It is a relatively small molecule, with an estimated half life of 5.5 hours in humans when injected into the vitreous, it has a significantly shorter action compared to Triamcinolone and Fluocinolone but is five times more potent and hydrophilic than Triamcinolone, which allows for a higher concentration within the vitreous. The placement of the implant in the vitreous maximises drug exposure to the macula while minimising unnecessary anterior chamber exposure with the aim of reducing the incidence of IOP rises.(3)

Preclinical studies using animal models of a non-biodegradable dexamethasone implant was first developed by Cheng et al for the treatment of experimental uveitis. A sustained release implant of dexamethasone 5 mg in the vitreous of rabbit eyes induced to have two episodes of severe panuveitis. Inflammation was reduced in treated eyes and the implant appeared to prevent ocular complications from recurrent inflammatory episodes.(139)

Surodex - dexamethasone implant

Surodex was a biodegradable dexamethasone 60 µg implant developed by Oculex Pharmaceuticals in the US (now taken over by Allergan). When inserted intra-cameraly into the anterior chamber in vivo, it was shown to significantly reduced inflammation, protein, cell infiltrates, interferon-gamma and IL-4 in rat eyes.(121) It

was tested for use to reduce post-cataract surgery inflammation in a randomised, masked, controlled trial of 104 Asian eyes post extra-capsular cataract extraction with intraocular lens implantation. Patients had two Surodex implants inserted into their anterior chamber or ciliary sulcus, which reduced flare independent of the insertion site. The implant was successful in suppressing postoperative inflammation, pain, photophobia and lacrimation after uncomplicated cataract surgery whilst also reducing the need for topical anti-inflammatory drops.(121) Moreover, when combined with phaco-trabeculectomy surgery the Surodex implant provided good control of inflammation.(140)(141)(142)

The Ozurdex dexamethasone intravitreal implant

The Ozurdex (Allergan Inc, Irvine, California, USA) biodegradable 'Novadur' polymer implant is a prolonged method of administering 0.7 mg of Dexamethasone via the pars plana to the posterior segment structures of an eye. (121)(143) This new drug delivery system contains a poly(lactic acid-co-glycolic acid) (PLGA) matrix material, which completely dissolves, omitting the need for surgical removal after the drug depletes. The implant is administered using a single use, suture less posterior segment drug delivery system applicator see photograph 4-2, which allows for the injection of the implant as an outpatient day case basis without the patient requiring admission into hospital. This novel drug delivery system is administered from the lateral aspect of the globe out of view from the patient and has been shown to be generally well tolerated. The steroid is released by diffusion in a controlled, biphasic fashion where the highest doses are provided for up to six weeks, peaking at 2 months and followed by subsequent lower doses for up to six months. Animal studies have shown that an intravitreal implant allows for a higher concentration of dexamethasone to be administered to the retina compared to oral and peribulbar routes. (144)(145)

4.1.4.3 Contraindications for Ozurdex use

Use of the implant is contraindicated in cases of advanced glaucoma and corticosteroid hypersensitivity in addition to eyes with active or suspected ocular or peri-ocular infections. Moreover, the immunosuppressive actions of the steroid

implant may enhance the establishment of secondary ocular infections caused by bacteria, fungi, or viruses.

4.1.4.4Phase II clinical trials of the Dexamethasone implant

A randomised controlled trial of a intravitreal dexamethasone drug delivery system (DDS) was tested by Kuppermann et al in patients with persistent macular oedema. (146)(147) 315 patients with a BCVA of 6/12 or worse with persistent macular oedema for over 90 days secondary to CRVO, BRVO, diabetic retinopathy, uveitis or Irvine-Gass syndrome that had not responded to laser or medical therapy. Patients were randomised into three groups: observation or 0.35 mg/0.7 mg dexamethasone implant treatment groups. The primary outcome measure was the percentage achieving a 10 letter improvement in BCVA at day 90.

In summary the primary objective was achieved more frequently in the 0.7 mg implant group for over 180 days compared to observation, regardless of the cause of macular oedema. Both treatment groups saw a significant reduction in central retinal thickness and leakage (seen on FA) after 90 days compared to the observation group. No statistically significant differences in BCVA were seen between the 0.35 mg treatment and observation groups. The implant was surgically implanted and was generally well tolerated. Cataract prevalence was not found to be statistically different between treatment and observation groups at 90 days and raised IOP (≥10 mmHg from baseline) was found in 3%, 12% and 17% in the observation, 0.35 mg and 0.7 mg treatment groups, respectively. (146)(147)

4.1.4.5Phase III safety and efficacy studies of the Ozurdex implant

In June 2009 the implant was approved by the United States FDA to treat macular oedema due to BRVO, CRVO and in September 2010 for non infectious posterior segment uveitis. The Ozurdex implant was approved by used in CRVO eyes by NICE in the UK and more recently in BRVO if and when laser photocoagulation did not prove to be beneficial or unsuitable due to excessive haemorrhage. (148) Guidelines were published in May 2011 for the treatment of macular oedema secondary to RVO in adults. For eyes with CRVO, an Ozurdex implant is required 3-

4 monthly and approximately lasts 5 months in eyes with BRVO. At the time of publication, the 700 microgram implant and applicator was £870.00. The actual number of treatments required is not known.

4.1.4.6 RCTs supporting Ozurdex for macular oedema secondary to retinal vein occlusion

Two multicentre randomised clinical trials studied the efficacy and safety of the Ozurdex implant in 1267 adult patients with macular oedema secondary to CRVO or BRVO.(63) Eyes with macular oedema persisting for between 6 weeks to 12 months were randomised into either sham or 0.35 mg or 0.7 mg dexamethasone implant treatment groups. One eye was selected for treatment according to the inclusion and exclusion criteria shown in Table 4-2. Patients were treated with an initial 6 month regime. Patients were re-treated if BCVA was measured less than 84 letters or OCT showed continual increases in central macular thickness over 250. The primary efficacy outcome was the time to reach a 15 letter improvement for both phase III studies pooled together from baseline BCVA.

In summary the results from the pooled analysis showed that the eyes receiving the Ozurdex implant achieved a 15 letter improvement in BCVA significantly greater in both implant groups and significantly faster than controls from day 30 through day 90, with the greatest response (29%) at day 60 ($P < 0.001$). The mean increase from baseline VA was also significantly greater in both implant groups than controls from day 30 through day 180 ($P \leq 0.006$), with the greatest between group difference (approximately 10 letters) at day 60. The mean decrease in CRT was significantly greater in both implant groups compared with the sham group at day 90 ($P < 0.001$) but not by day 180. The response to the implant was greater among eyes with a shorter duration of macular oedema at baseline (≤90 days) and worse if prolonged (>90 days). Eyes with CRVO did not respond as well to therapy as eyes with BRVO but did not improve with no treatment.

<table>
<tr><td colspan="3">Inclusion criteria</td></tr>
<tr><td>BCVA of 10 to 75 letters (0.2 LogMAR or worse)</td><td>Past ocular history of non-infectious intermediate or posterior uveitis</td><td>Vitreous haze score of +1.5 (on a scale of 0-4) on examination</td></tr>
<tr><td colspan="3">Exclusion criteria</td></tr>
<tr><td>BCVA <34 letters in the non study eye</td><td rowspan="4">History of glaucoma, ocular hypertension, Steroid related ocular hypertension, IOP >21 mm Hg at baseline, use of IOP lowering medications within the last month</td><td rowspan="4">OFI in the study eye 8 weeks prior to the trial
IVTA of 4mg <26 weeks prior to the trial
Previous Retisert or Ozurdex implant in the study eye
Changes to steroid medication within the first 8 weeks of the original trial</td></tr>
<tr><td>Active infectious uveitis</td></tr>
<tr><td>Uveitis unresponsive to prior steroid treatment</td></tr>
<tr><td>Uncontrolled systemic diseases</td></tr>
</table>

Table 4-2: Inclusion and exclusion criteria for the Phase III Ozurdex for retinal vein occlusion trial (63)

Open label extension of the trial observed the 12 month safety and efficacy evaluations of single and repeated treatments with the Ozurdex 0.7mg implant.

Conjunctival haemorrhage is a common adverse drug reaction due to the insertion procedure of the implant itself and not due to the effects of the steroid. With the exception of cataract, there were no statistically significant differences in the incidence of ocular adverse events between patients who received 2 implants and patients who had been treated initially with sham and received one implant at day 180 only. No surgical procedures were required in eyes treated with one 0.7mg implant or those treated later. The 12 month incidence of cataract in the single 0.7 mg and 0.35 mg implant groups were 7.6% and 7.7% respectively and 5.7% in untreated groups (P=0.849).

Overall, 32.8% of study eyes in the retreated implant group had at least a 10 mmHg increase in IOP at some point in the 12 month study resolving by 180 days managed with observation or medication. 25.5% of patients began treatment with IOP lowering medication during the masked phase of the study, and in the subgroup that qualified for retreatment and received a second implant day 180, an additional 10.3% of patients began treatment with IOP lowering medication. 14 study eyes required laser or surgery to reduce IOP compared to no patients in the observation groups.

4.1.4.7 Ozurdex for inflammation associated with non-infectious posterior uveitis

Lowder et al (119) investigated the 6 month outcomes of using the Ozurdex implant in patients with non-infectious intermediate or posterior uveitis. The main outcome measure was the proportion of eyes with a vitreous haze score of 0 at week 8. Patients were recruited from different centres according to the inclusion and exclusion criteria shown in Table 4-3.

Inclusion			
Non-infectious intermediate or posterior uveitis	Vitreous haze score of at least +1.5	Visual acuity of 10 to 75 letters	
Stable doses of topical steroids and NSAIDs for at least 2 weeks prior to the trial	20 mg/day or less of oral prednisone stable for at least 1 month prior to the trial	systemic immunosuppressants with stable doses for 3 months prior to the trial	
Exclusion			
Visual acuity of less than 34 letters in the non-study eye	uveitis unresponsive to prior steroid treatment	active ocular disease or infection	uncontrolled systemic disease
previous steroid intravitreal implant in the study eye	periocular corticosteroid injections in the study eye 8 weeks or less prior to the treatment visit on day 0	any intravitreal drug injected into the study eye <26 weeks pre-trial excluding IVTA <4mg injected 26 weeks or more	the use of IOP-lowering medications within the last month history of glaucoma, ocular hypertension, or clinically significant IOP elevation in response to corticosteroid treatment; IOP > 21 mm Hg at baseline
NSAID = nonsteroidal antiinflammatory agents			

Table 4-3: Inclusion and exclusion criteria for Ozurdex in non-infectious uveitis trial(1)

Patients were randomised into either sham or treatment groups. Patients in the treatment group were then randomised into receiving either the 0.7mg or 0.35mg

steroids implant using a 1:1:1 allocation ratio. Randomization was performed centrally and was stratified by baseline vitreous haze score of +1.5, +2 ,+3 or +4), see Table 4-4. The treatment investigator performed the implant placement and other treatment procedures and was responsible for the overall safety of study participants. All study medication information was kept confidential and the treatment investigator was not involved in the follow up visits. Patients were masked with regard to study treatment, and the key efficacy variables were collected and evaluated by follow-up investigators who were also masked with regard to study treatment. During the study the use of systemic immunosuppressive therapy or steroids (systemic, periocular, intravitreal, or topical) or surgery was prohibited unless vitally necessary and recorded. Anti-inflammatory medications could be used if haze increased.

0	no inflammation
+0.5	trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fibre layer reflex)
+1	mild blurring of the retinal vessels and optic nerve
+1.5	optic nerve head and posterior retina view obscuration greater than +1 but < +2
+2	moderate blurring of the optic nerve head
+3	marked blurring of the optic nerve head
+4	optic nerve head not visible.

Table 4-4: The standardised photographic scale for measuring vitreous haze ranging from 0 to 4(1)

Prior to each treatment, standard clinical practices for eyes undergoing intravitreal injection were adhered to and topical anaesthetics were used to prepare the eye. The implant was inserted into the vitreous cavity through the pars plana using a specialised, single use, 22 gauge applicator. The sham procedure followed the same protocol but used a needleless applicator. Patients were prescribed a post-procedural topical antibiotic prior to and 3 days after the implant/sham. Patients were followed up from baseline (date of implant/sham) and at days 1 and 7 and weeks 3, 6, 8, 12, 16, 20, and 26. Visual acuity was measured using a standardised Early Treatment Diabetic Retinopathy Study protocol and central macular thickness from OCT measurements. Adverse events were monitored which included IOP

The primary outcome measures of the original study was based on the amount of vitreous haze that reduced visualisation of the fundi at week 8.

In summary their results showed that the primary outcome was successfully maintained for 26 weeks by 47% of patients in the 0.7mg treatment group, 36% with the 0.35mg implant and 12% of controls ($p< 0.001$). Visual outcome was significantly better in the treatment groups where patients experienced a gain of >15 letters from baseline throughout the trial.

Complications from the implant were not found to be statistically significant. Common adverse events occurred in approximately 2% of eyes within the first 6 months of administration of the steroid implant, which included eye pain ($P = 0.023$) and anterior chamber cells ($P \leq 0.031$). IOP rises were seen in 7.1%, 8.7 % and 4.2% in the 0.7mg, 0.35mg and control groups respectively ($p>0.05$). The percentage of eyes receiving IOP lowering medication increased in the dexamethasone implant groups from 6% at baseline to 24% at day 180, while there was no change in the sham group. Cataract developed in 15%, 12% and 7% of 0.7mg, 0.35mg and control groups respectively ($p>0.05$). Rare complications included endophthalmitis and retinal detachment and there were no statistically significant differences between the treatment groups and the incidence of cataract.(119)

It is in this uveitis population we went on to further study the long term evaluation of patients treated with the Ozurdex implant for macular oedema and inflammation in a subset enrolled in MEH.

4.2 METHODS

4.2.1 The aims and purpose of this study

Current local steroid treatments for uveitis are short lived and are associated with significant complications that impact on patient's quality of life. The purpose of this chapter is to evaluate the long term outcome of the Ozurdex implant and the strategies employed as and when patients relapsed, comparing these outcomes with those of the Ozurdex implant.

This study aims to:

1. outline when and what additional therapies are needed after a single Ozurdex implant due to disease recurrence
2. document any differences in outcomes with alternative therapies used compared to after a single dexamethasone implant
3. outline complications associated with a single Ozurdex implant including ocular hypertension, cataract progression and surgery and compare to the additional therapies needed.

4.2.2 Patients

The patients used for this study were identified from our cohort enrolled in the HURON Ozurdex for uveitis trial (Lowder et al).(119) The original trial was a 26 week, prospective, multicenter, masked, randomised, parallel group, sham controlled clinical trial. 28 patients were identified from the Moorfield's eye hospital population that were randomised into either treatment or control arms. Notes were obtained for the patients from Moorfields hospital.

Patients were included if they were followed up for greater than 6 months after the trial period at Moorfields eye hospital. Data was collected for both treatment and sham patients. 16 patients were treated with the steroid implant upon the original trial. One patient had no follow up past 6 months and another entered another clinical trial, so both were excluded from this study.

Data about further treatments used to manage disease recurrence (inflammation and macular oedema) over 6 months to 1 year, 1 year to 2 years and 2 years to 3 years, respectively where available were documented. Specific treatments of interest include: oral steroids, OFI and IVTA.

In addition changes to doses of oral steroids and immunosuppressive agents were also documented. Details about complications such as high IOP and cataract were collected. Changes in IOP from baseline to final follow up, including occasions when IOP rose above 21mmHg and the use of medical or surgical interventions were also documented. Lens status in the study eye was documented at baseline and progression followed until final follow up including any cataract surgery performed. Any other complications that would affect the VA of the patient including retinal detachment and endophthalmitis were noted.

4.2.3 Statistics

Data was input into an Excel spreadsheet and analysed using SPSS. Visual acuity was converted from snellen to logMAR using the scale in chapter two. Tests for significance of continuous data including LogMAR visual acuity and intraocular pressure were measured using unpaired or paired t tests. Mean time for improvement in outcomes were measured from treatment date to best visual acuity and highest IOP documented. A significance level of $p<0.05$ was deemed statistically significant.

4.3 RESULTS

Demographic details were obtained for 26 patients of the original 28 patients involved in Lowder et al's trial, see Table 4-5, 15 patients received the implant.

	Sham (n=11)	**Ozurdex Treatment group (n=15)**
Mean age (years) at implant/sham(SD)	55.91 (12.05) range 34 to 77	49.6 (10.87) range 32 to 70
% >50 years	7(63.6%)	8(53.3%)
Gender, %male	36.4%	46.7%
Eye %Left	54.5%	53.3%
Uveitis diagnosis		
Birdshot Retinochoroidopathy	1 (0.9%)	0(0%)
HLA B27+ posterior uveitis	1 (0.9%)	0(0%)
Sarcoid uveitis (intermediate/posterior uveitis)	2 (18.2%)	3(20%)
Idiopathic posterior/panuveitis uveitis	5 (45.5%)	2(13.3%)
Idiopathic intermediate uveitis and vasculitis	2(18.2%)	10(66.7%)

Table 4-5: Demographic and baseline details for Ozurdex treated and sham control patients

4.3.1 Outcome results from the 26 week trial period

Of the 15 patients treated with the Ozurdex steroid implant, 29% gained ≥15 letters and 57% gained >10 letters of improvement in BCVA by the end of the clinical trial. Table 4-6 shows the change in visual acuity between baseline and 26 weeks. Vitritis was present in 10(66.67%) eyes by 26 weeks and macular oedema was present in 9(60%) eyes at baseline and completely resolved in 7(77.78%) of these eyes at 26 weeks. 2(13.33%) eyes however had macular oedema that persisted to 2 years of follow up.

	BASELINE	***6 MONTHS***
Mean LogMAR VA	0.45	0.39
Standard deviation	0.31	0.47
Range	0.1 to 1.25	-0.2 to 1.20

Table 4-6: Change in LogMAR visual acuity from baseline and at 6 months of follow up of Ozurdex treated eyes

4.3.2 When were additional treatments required?

Patients with a mean follow up of 25 months after the initial 26 week trial are shown in Table 4-7.

	6 months	1 year	2 years	3 years
Ozurdex treatment group	15	14	10	6
Sham Group	11	9	4	2
*until data collection ceased 2011				

Table 4-7: Patients with follow up appointments at Moorfields eye hospital after the initial trial*

The persistence of vitreous cells was seen in 10 treated eyes after the 26 week end point of which two eyes had persistent macular oedema. The two eyes with macular oedema required additional IVTA injections and two eyes with vitreous cells required OFI. More than one treatment was required in one eye to settle the inflammation (IVTA then OFI).

Disease recurrence characterised by the development of posterior segment inflammation and macular oedema was seen in 3(20%) eyes within one year and one eye within two years after the Ozurdex implant. IVTA was used to manage inflammation and macular oedema in 3(20%) eyes, where one patient required repeat injections within the same year.

In the sham group 5 eyes required rescue treatments during the 26 week trial to control inflammation and/or macular oedema where 80% had IVTA injections. Disease recurrence was documented in 5(45%) eyes during 1 year.

4.3.3 Did additional interventions improve visual acuity and inflammation

In this sub-group of 4 patients in the treatment arm that required further steroid treatments (OFI or IVTA) Table 4-8 mean improvement in BCVA was matched by further interventions but starting BCVA was worse. Macular oedema, where present in eyes requiring further interventions improved 2 months after IVTA. Vitreous cells persisted in 75% of cases.

	Ozurdex N=10	Ozurdex + IVTA/OFI N=5
Mean improvement (LogMAR)	0.26	0.22
Pre-treatment BCVA (LogMAR)	0.71	0.85
Post-treatment BCVA (LogMAR)	0.45	0.63
t test significance in mean change in BCVA	p=0.0014	p=0.1477

Table 4-8: Change in visual acuity in Ozurdex treated eyes compared to eyes that required further IVTA/OFI

4.3.4 Oral steroid and second-line immunosuppressive agents

13(86.67%) patients started the initial trial without oral Prednisolone or second line immunosuppressive agents and they were not required on completion of the trial or at subsequent follow up periods over 1,2 or 3 years of follow up (where data available) (excluding pre-cataract operation doses).

Details for the medication changes for two patients that did require oral prednisolone and a second line immunosuppressants are shown in Table 4-9. These two patients experienced disease recurrence after Ozurdex treatment. One patient was managed with a maintenance dose throughout 3 years of follow up with the addition of IVTA injections. And the second saw a reduction in second agent and prednisolone dose over three years with the addition of IVTA for disease recurrence. The Ozurdex implant did not removed the need for oral prednisolone or immunosuppressant requirements after the trial period in patients that were taking them during the trial.

	Ozurdex	Ozurdex + IVTA/OFI	Sham	Sham + IVTA/OFI
Start of study number of patients taking oral prednisolone<10mg + immunosuppressant therapy*,**	0	2	1	1
Start of study number of patients taking oral prednisolone<10mg	0	0	0	1
Post-26weeks number of patients that required increase in oral prednisolone dose (excluding pre-cataract extraction)	0	0	0	3
Number of patients on oral prednisolone and immunosuppressant therapy after the 26 week trial *,**	0	2	0	1
* MMF - Mycophenolate mofetil, **MXT - Methotrexate				

Table 4-9: Oral steroid and immunosuppressant use in eyes before, during and after the 26 week trial

In the sham group, two patients required oral prednisolone <10mg a day in addition to immunosuppressants prior to entry in the trial. After additional treatments with IVTA or OFI two eyes required increases in oral steroid doses to manage inflammation and/or macular oedema but were reduced to ≤10mg within the same year.

4.3.5 Cataract formation/progression

In the Ozurdex treatment arm, 7(46.7%) had a clear lens, 6(40%) had lens opacities and 2(13%) were pseudophakic prior to entering the trial compared to 1(9%), 6(55%) and 4(36%) in the sham control group. Changes in lens status according to treatment and retreatment groups are shown in Table 4-10.

	Lens status	Ozurdex implant N=10	Ozurdex + IVTA/OFI N=5	Sham N=7	Sham + IVTA/OFI N=4
Baseline	% clear lens	7(70%)	0(0%)	0(0%)	1(25%)
	% lens opacities	2(20%)	4(80%)	3(43%)	3(75%)
	% pseudophakic	1(10%)	1(20%)	4(57%)	0(0%)
6 month post-treatment	% clear lens	5(50%)	0(0%)	0(0%)	1(25%)
	% Lens opacities	4(40%)	4(80%)	3(43%)	3(75%)
	% pseudophakic	1(10%)	1(20%)	4(57%)	0(0%)
1 year post-treatment	% clear lens	3(33%)*	0(0%)	0(0%)	1(25%)
	% lens opacities	3(33%)*	3(60%)	3(43%)	0(0%)
	% pseudophakic	3(33%)*	2(40%)	4(57%)	3(75%)
* of 9 patients with follow up for 1 year					

Table 4-10: Change in lens status in treatment and sham groups over 1 year post-trial

During the post-trial period to 12 months of follow up, 22%, 25%, 0% and 75% of phakic patients required cataract surgery from the Ozurdex, Ozurdex +IVTA/OFI, sham and Sham + IVTA groups respectively. Adjunctive steroids were provided for all patients undergoing cataract extraction in the form of pre-op oral steroids or intra-operative IVTA injections. 2 patients who received peri-operative IVTA treatments developed sterile endophthalmitis immediately after. Details of cataract surgery in Ozurdex treated eyes are shown in Table 4-11.

	At 6 months	At 1 year	At 2 years	At 3 years
Number of eyes	15	14	10	6
Number of phakic eyes	13(86.67%)	9(64.29%)	3(30.00%)	1(16.67%)
Eyes requiring cataract extraction	0	6(42.86%)*$	1(10.00%)	0
* 1 Patient had Vitrectomy post implant prior to cataract extraction $1 patient had Retinal detachment surgery post implant prior to cataract extraction				

Table 4-11: Cataract extraction required in Ozurdex treated eyes

Visual acuity declined from baseline to pre-cataract extraction date by a mean 0.65 LogMAR units (95% CI 1.12-0.18) (p=0.0152)(Paired samples t test). Post-cataract extraction, visual acuity improved by a mean 0.84 LogMAR units (95% CI 0.31-1.37) (p value = 0.0080)(paired samples t test) see Table 4-12.

	Baseline BCVA pre-treatment	**BCVA prior to cataract extraction**	**Best BCVA post implant**
Number of eyes	7*	7	7
BCVA mean	0.4	1.05	0.21
Range	0.1-0.7	0.5-1.78	-0.1-0.3
Stdev	0.22	0.49	0.15
* Total excluding 6 Phakic eyes that had not had removal of a lens at final follow up and 2 Pseudophakic prior to the trial			

Table 4-12: LogMAR BCVA improvement in Ozurdex treated eyes after cataract extraction

4.3.6 Intraocular pressure

Table 4-13 shows mean highest IOP after steroid implant and IVTA/OFI interventions. 8(53.3%) eyes in the treatment arm experienced raised IOP (>21mmHg) after an average of 47.25 days (range 7 to 112) during the initial 26 week trial.

Mean highest IOP was greater in the Ozurdex treatment arm compared to the sham control during the 26 week trial t test p=0.0056. 3(37.5%) eyes saw an increase over 30mmHg. Mean IOP at baseline in eyes treated with the Ozurdex implant was 13.93mmHg (SD 1.91). A significant rise in IOP of 9.87mmHg (95% CI 7.72-12.01)(p value 0.0001) (paired t test) was seen from baseline to highest IOP reading. 60% of eyes commenced on topical IOP lowering treatments in the Ozurdex arm continued during the post-trial period. No patients required surgical interventions.

6(40%) eyes in the Ozurdex group that required further interventions experienced raised IOP during the post trial period, 4(66.67%) eyes were associated with IVTA treatment, 1(16.67%) eye post OFI and 1(16.67%) with uveitis recurrence, see Figure 4-1. 2 patients were newly started on IOP lowering medication during this period. 2 eyes were already on treatment from the trial period. Mean highest IOP was

greater in sham eyes that required further interventions (t test p=0.1283). Topical IOP lowering treatment was started in 5 of these eyes.

	Ozurdex treatment arm	Sham control	Ozurdex + IVTA/OFI	Sham + IVTA/OFI
Mean highest IOP (mmHg)	23.80	18.18	20.60	24.00
Median	23	18	22	20
Range	18-32	12-30	12-29	18-42
Standard deviation	4.66	4.62	8.29	10.12

Table 4-13: Highest intraocular pressure (IOP) in different treatment and sham groups

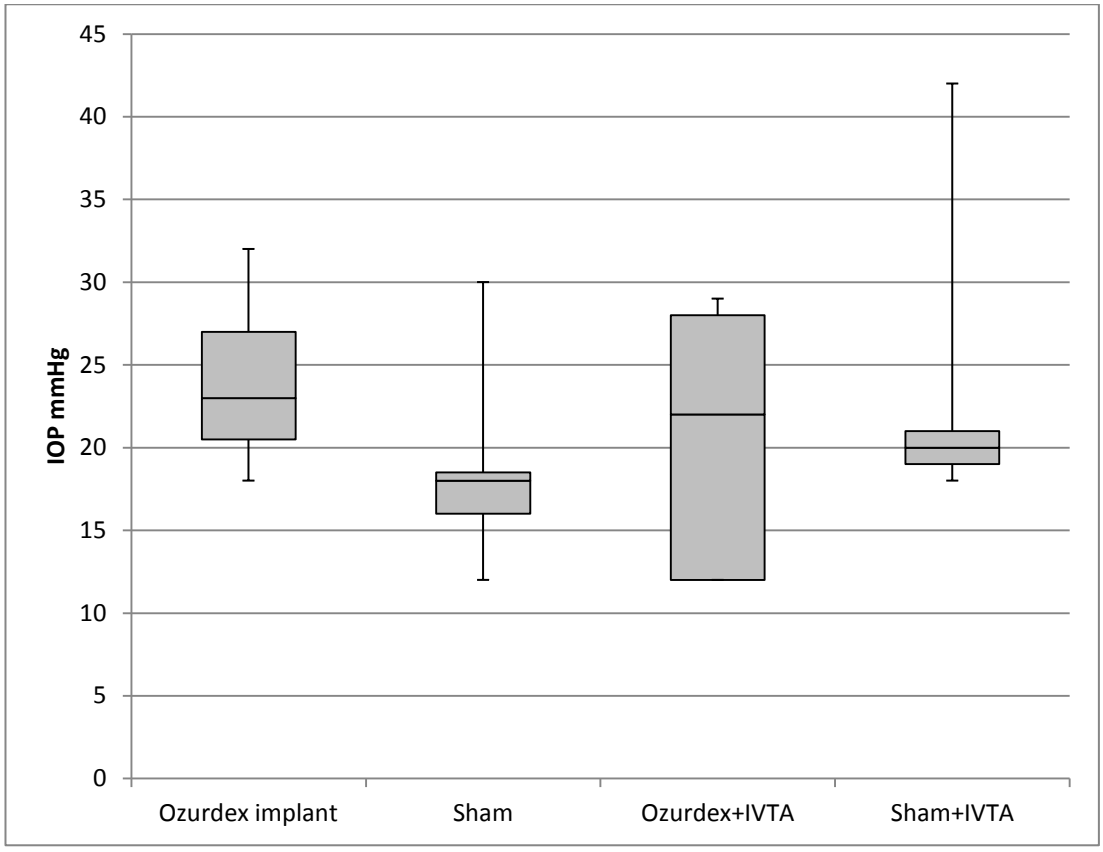


Figure 4-1: Box plot showing mean highest IOP in eyes treated with one Ozurdex implant during the 26 week trial, Sham, and eyes that required further IVTA/OFI

On comparison of mean highest IOP in eyes treated with the Ozurdex implant and eyes later treated with IVTA/OFI in the Ozurdex and sham groups the difference was found not to be statistically significant, (23.80mmHg vs 22.30mmHg t test p=0.5862).

4.4 DISCUSSION

This study demonstrates that 13% of eyes with uveitis treated with an Ozurdex implant may require additional treatment for macular oedema and 13% for persistent vitreous cells within one year. Moreover, disease may recur in 20% of eyes within one year.

Intravitreal triamcinolone - IVTA

Habot-Wilner et al showed IVTA is an effective adjunct to systemic therapy for the treatment of uveitic macular oedema. On review of the literature there were 4 studies investigating IVTA treatment in eyes with non-infectious uveitis. (125) (120) (9) (126)

In summary from the literature IVTA has been shown to improve visual acuity in 85%. Mean improvement of 0.26 to 0.33 LogMAR units, by mean 4 to 6.2 weeks has been shown. (120)(9) Resolution of macular oedema can be seen in 88% of eyes but 26-50% may persist or relapsed (126) after a mean 4.2 months (range 2.5-5.5) (120). The effects of an IVTA injection are better if macular oedema is present for less than 12 months and in patients less than 60 years old. (9) Dosage of oral corticosteroids and/or second-line immunosuppressive medication can be reduced or stopped in 54.5%(9) - 82.8%(120) of cases after single or multiple IVTA injections. IVTA (2 or 4 mg) has been shown to improve macular oedema secondary to non-infectious uveitis in eyes of children in 3 weeks (range, 1-24 weeks) where 31% disease relapsed after 7 months (range, 3-13 months).(149)

In our sample population of uveitis patients, visual acuity was improved by a mean 0.22 LogMAR units with an IVTA injection compared to mean 0.26 LogMAR units with a single Ozurdex implant. 33% and 45% of eyes in the Ozurdex and sham groups respectively needed further IVTA/OFI treatments within 1 year of starting the trial to manage inflammation and/or macular oedema.

Macular oedema persisted in two(22%) eyes at 6 months after Ozurdex insertion treated with IVTA with which 50% resolved with one treatment. 4 eyes required

IVTA injections to control inflammation and/macular oedema of which 2(50%) required repeat treatment.

The study shows that with a single Ozurdex implant systemic corticosteroid use and other immunosuppressive agents can be decreased or oral prednisolone doses maintained less than 10mg. The implant allows for oral steroid and immunosuppressant agents to be kept at a low maintenance dose for up to 3 years shown in two cases. Disease recurrence in these patients were managed with IVTA injections.

Complications associated with the dexamethasone implant include Vs IVTA

Corticosteroids increase the IOP by increasing the resistance of the aqueous humor outflow facility, which is mediated by alteration of the mechanical structure of the trabecular meshwork, extracellular matrix deposition in the trabecular meshwork, and reduction of the functional and phagocytic activity of the trabecular cells. (150) responding worse in eyes with prior compromised aqueous outflow pathway systems. Steroid response in a normal population is shown in Table 4-14. IVTA is known to be associated with a higher side effect profile including ocular hypertension and cataract progression compared to other ocular treatments such as anti-VEGF agents and laser photocoagulation. (127)(128)(129)(130)

Type of responder	**Distribution in a normal population**	**IOP increase**
High responders	5%	>15 mm Hg and >31 mm Hg after daily corticosteroid use for 4 - 6 weeks. (37-38)
Moderate responders	Approximately 1/3	6 to 15 mm Hg and had IOP between 20 and 31 mm Hg. (37-38)
Non-responders	Approximately 2/3	<6 mm Hg and IOP of <20 mm Hg. (37-38)

Table 4-14: Intraocular pressure response to topical steroids (41)

IVTA can cause a mean rise in IOP by 10.3 mmHg where raised IOP over 21mmHg can occur in 32-49% of cases. (9)(151) Except for in steroid responders, raised IOP with IVTA treatment is transient in most cases and responds well to topical

medications. (9)(126)(151) 51% of eyes require topical anti-glaucoma medications for raised IOP for a mean 17.4 weeks. (9) Drainage or glaucomatous tube surgery may be required. 83% raised IOP at 10 weeks (125) Rises in IOP greater than 15 mm Hg were noted in 31% of eyes of children. (149) Over half of patients treated with an Ozurdex implant might experience raised IOP greater than 21mmHg within two months. IOP rises can be managed with topical lowering medications however, 60% of patients may required treatment lasting longer than 6 months. Known steroid responders were excluded from this trial.

Steroid induced cataract progression is likely in 17 - 20% of eyes treated with IVTA. (126)(120). Cataract was observed in over half (55%) of children in one small study of 15 eyes. (149) Patients treated with either Ozurdex, IVTA or OFI in this study were more likely to see progression of cataract. This study also showed that cataract surgery is likely in 31% of eyes treated with the Ozurdex implant within one year and an additional 31% will see progression in lens opacities compared to untreated uveitis patients.

The complications associated with the Ozurdex implant such as raised IOP and cataract progression is greater when IVTA is used in conjunction. There is also an additional risk of post-operative complications such as sterile endophthalmitis when IVTA is used as steroid cover during cataract surgery.

Comparison with OFI in uveitis

A retrospective cohort study by Leder et al(152) studied the effects of OFI when used to manage macular oedema due to non-infectious causes of uveitis in 126 patients with anterior uveitis, intermediate uveitis and panuveitis. Patients were re-treated if they had evidence of persistent macular oedema for more than 1 month after the first OFI. Macular oedema resolved in 53% at 1 month and 57% at 3 months but recurred in over half by a median 20.2 weeks. 26% required retreatment, 81% after subsequent OFI had no macular oedema at 1 month, 48% had no macular oedema at 3 months and 15% did not respond.

A retrospective comparative study of OFI and IVTA by Roesel et al(153) studied their differences in cases of chronic non-infectious uveitis. 97 patients received a single injection of either IVTA or OFI. A summary of results are shown in Table 4-15. Both IVTA and improved BCVA and macular oedema in eyes with chronic non-infectious uveitis, where IVTA significantly improved macular oedema compared to OFI at3 months. Effects were more effective in eyes treated with IVTA but were transient for both treatments as initial improvements in BCVA at 3 months were not maintained at 1 year. A retrospective study by Roesel et al(124), followed up 94 eyes of 86 patients with acute non-infectious uveitis over 6 months after one OFI 40 mg. They found OFI improved AC and vitreous inflammation P<0.01, but BCVA did not differ before and after. Macular oedema at 6 months was unchanged in 59% and worse in 14%. Ocular hypertension was noted in 8% of eyes and cataract progression in 29% at 6 months.

	IVTA (n = 48)	**OFI (n = 49)**	**Significance**
BCVA improvement of ≥2 lines at 3 months	50%	34%	p = 0.23
BCVA improvement of ≥2 lines after 12 months	18%	20%	
Improvement in macular oedema within the first month	100%	76%	p = 0.36
Improvement in macular oedema after 3 months	100%	20%	p < 0.01
Cataract progression at 1 year	68%	27%	p < 0.01
Raised IOP at 4 weeks	21%	0%	p <0.01

Table 4-15: Results from Roesel et al OFI vs IVTA for chronic non-infectious uveitis

Use of OFI in eyes of children with uveitis

A retrospective non-comparative interventional case series 15 consecutive children (19 eyes) with various forms of uveitis treated with OFI of 40 mg/ml methylprednisolone acetate or a combination of 20 mg/0.5 ml Triamcinolone and 2 mg/0.5 ml dexamethasone.(154) The mean LogMAR BCVA improvement of 0.18 was achieved (p<0.001) at mean of 6 weeks (range, 4-20), 4-7 weeks post-OFI (median of 4 weeks) 74% had significant improvement in inflammation. Effects were transient, half of patients experienced a relapse of uveitis after a median time of 4 months (range, 2-5 months). 21% of eyes required further injections. Adjunct

immunosuppressive systemic therapy was reduced or stopped in half of patients. Cataract was present in 21% of eyes approximately 5 months post-injection.

Ozurdex verses Retisert

There are many advantages of the dexamethasone implant including its biodegradable properties. The implant can be inserted in an outpatient setting in comparison to the surgically implanted polymer ease of sequential implants compared to Retisert and potentially lowers the cost of implantation without the need to surgically remove older devices. The actual cost of the dexamethasone implant is significantly lower than the cost of Retisert by approximately 65%. This cost approximation also does not take into consideration cataract extraction and glaucoma filtering procedures that may be necessary as a result of complications from the steroids and the disadvantage of chronic ocular inflammation requiring multiple implants per year.

It is difficult to compare the efficacy and safety profile of the dexamethasone intravitreal implant with other sustained release corticosteroid implants, specifically Retisert given the different pharmacokinetic properties and duration of effect half-lives of the two implants and the current lack of a randomised controlled trial to compare them.

Limitations of this study

The major limitation of this study was that we were not able to differentiate between which patients received the 0.7mg and 0.35mg dexamethasone implants to discern any differences between the various outcomes measured. Other limitations include the retrospective nature of the study. There was no control over examination findings and drugs and doses documented at various time points of follow up. Another disadvantage of the retrospective nature of this study included the lack of control over when and what additional treatments were administered by medical staff at follow up after the 26 week clinical trial ended. As no guidelines were stated or followed IVTA, OFI, systemic steroid or IS treatments were given based on the decision made by the consulting Ophthalmologist.

4.5 SUMMARY OF RESULTS

There is significant visual loss associated with uveitis due to macular oedema associated with posterior segment inflammation. Macular oedema is thought to improve in eyes with a good presenting BCVA when treated within 12 months from onset. Corticosteroids administered systemically and locally have been used to reduce inflammation, macular oedema and prevent long term visual loss in patients with non-infectious uveitis but are associated with significant adverse effects.

The Ozurdex dexamethasone drug delivery system is a novel approach to the treatment of uveitis and has been shown to be efficacious in the treatment of non-infectious uveitis with potentially fewer adverse effects than other steroids with ease of use in an outpatient setting. Advantages of the polymer structure design of the dexamethasone implant include its slow and consistent effects to last longer at the back of the eye than a typical bolus IVTA injection requiring less frequent injections, less patient discomfort, hospital visits and reduced risk of endophthalmitis.

Future studies will need to determine the relative long term efficacy and safety profiles among the different intravitreal steroid implants and the long term effects of repeated use of the dexamethasone implant in the treatment of recurrent uveitis in order to be able to effectively compare adverse effects to other longer acting steroid implants.

5. Conclusions

The overall purpose of this thesis was to document retinal vascular involvement in uveitis and new treatment options, specifically the intraocular Ozurdex steroid implant. The aims were to: 1) determine the relationship between exposure to steroid treatments and other immunosuppressive agents, cardiovascular disease risk factors and retinal vein occlusion events in patients with uveitis. 2) outline anti-phospholipid antibody testing in an Ophthalmology scenario and make recommendation for testing and 3) provide information about the long term outcome of the Ozurdex implant and the strategies employed as and when disease relapsed, comparing these outcomes with those of the Ozurdex implant.

This study outlines demographic and clinical findings and presentation and 1 year of follow up. Clinical features of retinal vein occlusion in uveitis patients are similar to the general population, including examination findings and complications. Uveitis patients with a retinal vein occlusion presented with poor visual acuity of mean 0.79 logMAR units where over half improved over a year. Risk factors such as raised intraocular pressure and haematological conditions for vein occlusions were rarely associated with this population. Worse presenting visual acuity and visual outcome at one year was seen in eyes with a central retinal vein occlusion. Over half of eyes with branch retinal vein occlusions seen an improvement in visual acuity over 1 year. Macular oedema, vitreous haemorrhage and signs of ischaemia were seen in under half of eyes at presentation or during 1 year of follow up. 10% of eyes experience disease recurrence in the same or fellow eye.

Steroid and immunosuppressant treatments are used to manage inflammation and macular oedema associated with uveitis in the form of different systemic and local preparations. Such treatments have extensive ocular and systemic side effect profiles including inducing hyperlipidaemia, hypertension and diabetes. Moreover, these systemic conditions increase a patient's risk of suffering from a retinal vein occlusion associated with sight threatening complications such as macular oedema, vitreous haemorrhage and ischaemia. This study shows that uveitis patients are at a higher

risk for retinal vein occlusion not as a direct consequence of inflammation but likely due to the above systemic cardiovascular disease risk factors induced by previous or current steroid and immunosuppressant use.

The characteristics of these high risk group of uveitis patients are in their early 50s or younger and who would normally be classed as low risk for cardiovascular disease based on their relatively young age are less likely to be commenced on prophylactic medication according to current cardiovascular disease risk guidelines. Therefore it is postulated from the results of this chapter that uveitis patients that require systemic steroid or immunosuppressant treatments, especially those on long term regimes, be assessed as high risk for cardiovascular disease and risk factors such as hyperlipidaemia, hypertension and diabetes, be diagnosed and managed aggressively to prevent cardiovascular disease events. Managing these risk factors would therefore aim to reduce visual loss in this population due to retinal vein occlusion and its sight threatening complications.

Secondly, the presence of anti-phosphlipid antibodies are a known risk factor for sight threatening vascular occlusions thus Ophthalmologists play a role in investigation and diagnosis of the disease as ocular presentation may be the initial vascular event. Testing for the presence of these autoantibodies is made through laboratory testing of serum blood samples taken from the patient and diagnosis is based on two positive samples taken 12 weeks apart in association with a thromboembolic or pregnancy loss event. The presence of these autoantibodies are not specific for antiphospholipid syndrome and can be raised in the presence of infection and cancer for example. Currently there are no specific guidelines outlining which patients and who should be performing these investigations in an ophthalmology setting. This study shows that over a year a very small percentage of patients presenting to Moorfield's eye hospital with a retinal vascular event are diagnosed with circulating antiphospholipids. Less than 20% of patients who had circulating aPL were re-tested as per laboratory request/guidelines. Recommendations for testing for aPL have been made based on patient characteristics and clinical features on presentation of an ocular event and serum blood test result. Due to the small percentage of patients that would be diagnosed

with APS in an ophthalmology setting it is recommended that aPL testing be performed in young patients under 50 years of age, with unilateral or bilateral retinal vascular disease once all other common systemic and ocular risk factors are rules out with repeat testing after 12 weeks to confirm the diagnosis either on further follow up in the Ophthalmology department or through communication with the patients GP. Thereafter prophylactic management of APS upon diagnosis can be initiated by a Haematologist and follow up for ocular complications can be managed by the ophthalmologist. Patients with concurrent infections, cancer that would yield high false positive rates as results cannot be interpreted correctly and haematological opinion be sort. Patients on anti-coagulation should be clearly stated on request forms. Guidelines for aPL testing for Ophthalmologists would help reduce the cost of unnecessary laboratory tests and clear outlining of patient and clinical details upon request for aPL investigations would assist interpretation of results and the need for further testing.

Thirdly, the innovation of the Ozurdex intravitreal dexamethasone implant has brought about a new drug delivery system to manage inflammation and macular oedema associated with visual loss in non-infectious intermediate, posterior and panuveitis. The implant also allows for oral steroid and immunosuppressant doses to be kept to low maintenance doses or were not required in some patients.

After a single Ozurdex implant, 33% of eyes will require further IVTA or OFI due to disease recurrence or persistent macular oedema. Intraocular treatments such as IVTA or OFI can match the improvement in visual acuity but repeat treatments within a year are required in most eyes to maintain this.

The implant is not without side effects, approximately 22% of phakic patients will require cataract extraction within one year after implant insertion, which increases to a quarter of patients that have additional IVTA or OFI treatments. Raised intraocular pressure is common in half of eyes within the first two months from implant insertion, patients are managed with topical IOP lowering medication which continue for over 6 months. IVTA or OFI are associated with higher IOP rises in a

higher percentage of eyes compared to the Ozurdex implant alone, which again require topical IOP lowering medication.

Future considerations based on the results of this study

Data on more than one Ozurdex implant for the treatment of non-infectious uveitis and head to head studies of other steroid treatments will provide long term information and efficacy of the implant. Steroid have uses in managing macular oedema due to diabetes as well, and results of the Ozurdex implant alone or in combination with current laser and or anti-VEGF treatments are awaited, although the Iluven steroid implant has been shown to improve vision in such eyes. The use of intraocular implants for long term delivery of drugs to the posterior segment of the eye are in progress and will be of use in other ocular conditions such as age related macular degeneration and diabetes.

Changes in practice for the diagnosis of APS in the ophthalmology setting should be made and investigation into the long term outcomes of these patients should be investigated as well as the outcomes for patients as a result of guideline implementation.

Moreover the outcome of aggressive management of cardiovascular disease risk factors in uveitis patients taking systemic steroid and immunosuppressants on visual outcome and frequency of retinal vein occlusion events should be investigated.

In conclusion this thesis provides results and discussion of methods and a new treatment to reduce the risk and manage visual loss in specific sub-groups of Ophthalmology patients with uveitis and those at high risk of retinal vascular occlusion.

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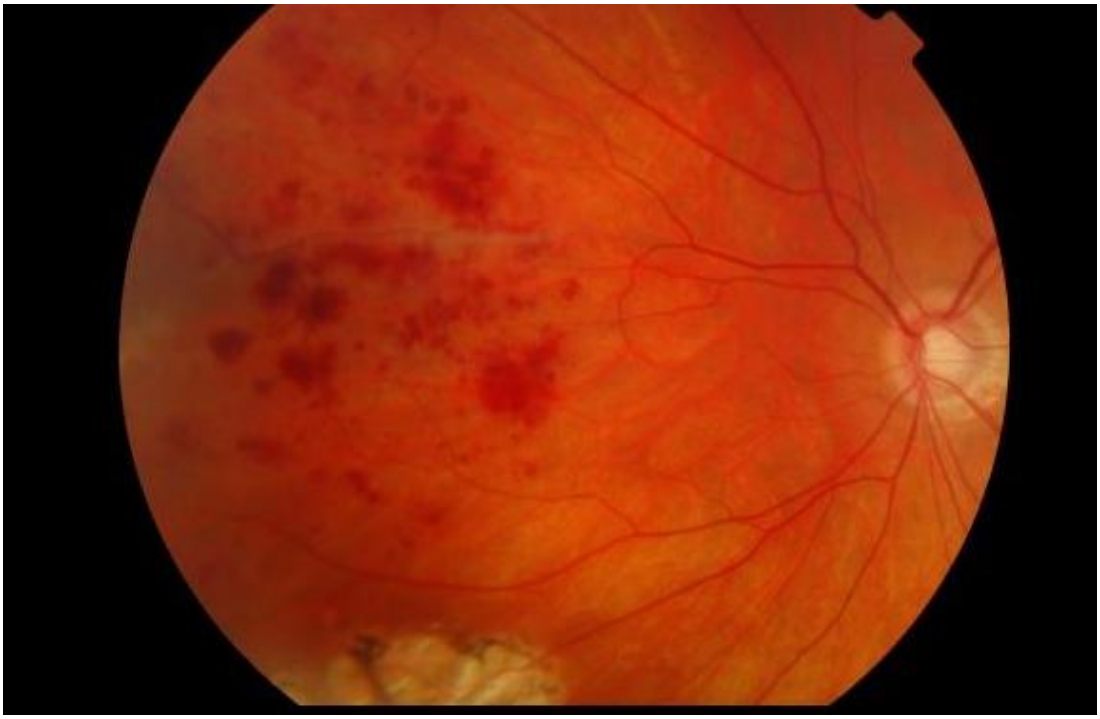
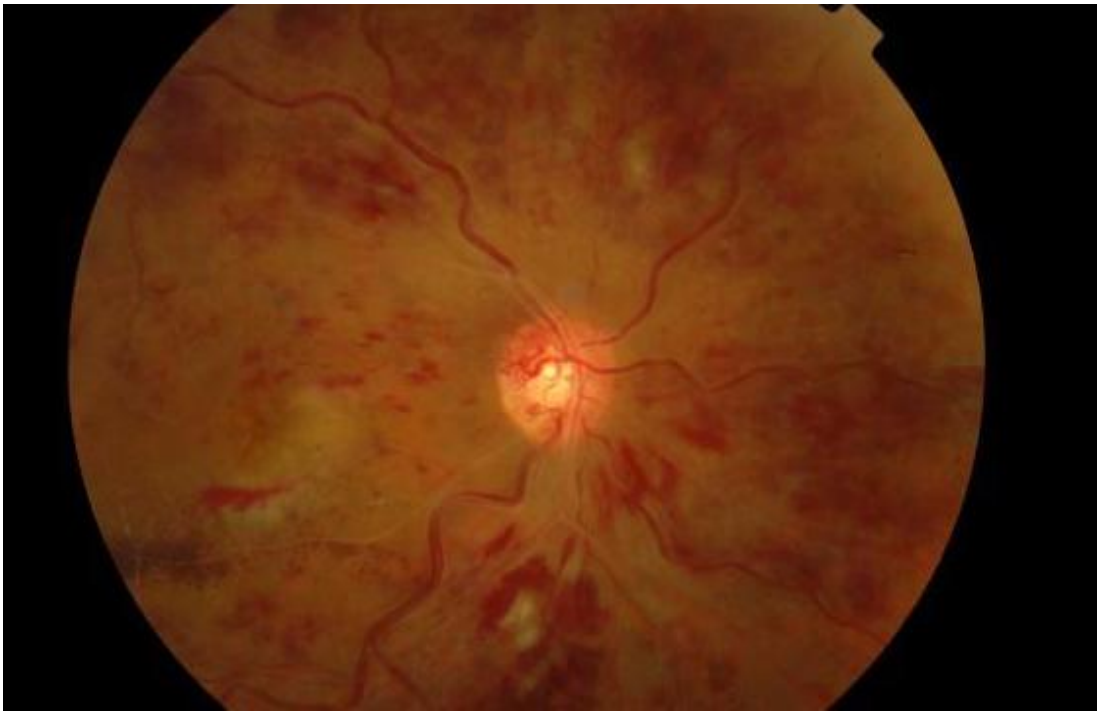
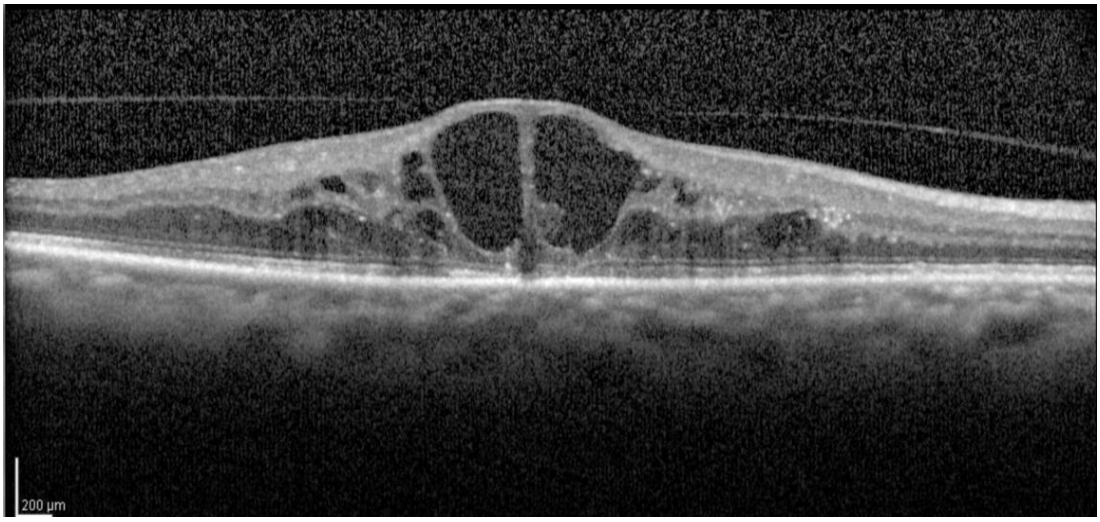
Photographs



Photograph 2-1: Colour fundus photo of a branch retinal vein occlusion



Photograph 2-2: Colour fundus photo of a central retinal vein occlusion



Photograph 4-1: OCT image of macular oedema

Photograph 4-2: Ozurdex dexamethasone intravitreal implant drug delivery system