Preface

Ophthalmologists within Scotland with an interest in uveitis met in January 2005 to consider how the care of patients with sight-threatening uveitis could be delivered in a more uniform manner. A decision was made to develop a Scottish Uveitis Network involving clinicians and the Uveitis Information Group, a United Kingdom based patient organisation. Since then, the group has developed as a National Managed Clinical Network, under the auspices of National Services Division, NHS National Services Scotland. As part of its remit it has set out to develop guidelines for the management of uveitis.

The aim of this document is to help guide ophthalmologists as to which patients require referral to a uveitis specialist and aid in the prescription of immunosuppressive therapy for ocular inflammatory disease.

This document does not replace the advice given by the British National Formulary, nor the advice given by manufacturers.

Introduction

Despite the relatively limited evidence for the efficacy of immunosuppressive treatment in uveitis(1) it is generally accepted that delay in referral to a uveitis specialist, delay in commencement of immunosuppression or inadequate immunosuppression all result in poorer visual prognosis of ocular inflammatory disease (2)

‘Early on you regret too little, late on you regret too much’. (Andy Rees).

Central to the management of ocular inflammatory disease and the use of systemic immunosuppression is the patient’s understanding of the disease and its treatment. All these therapies have potentially life-threatening complications and by educating patients about their treatment and re-enforcing the importance of regular blood tests where appropriate, hopefully if complications do arise then they will be identified early.

All immunomodulatory drugs used in ocular inflammatory disease were initially developed for use in other medical specialities, either as chemotherapeutic agents or for immunosuppression in transplant medicine. Although all these medications are licensed for other indications none are currently licensed for ocular inflammatory disease and are used at the discretion of the prescribing consultant. It is important that the patient is aware and accepting of this prescribing situation.
Immunomodulatory drugs have different side effect profiles and so the treatment regime needs to be planned for each patient aiming to produce a treatment regimen that is well tolerated and is able to suppress the ocular inflammation.

The document is intended as a guideline rather than a set of protocols. The aim is to assist the ophthalmologist in making decisions about when to initiate treatment and which type of treatment is appropriate. It is expected that ophthalmologists will refer on to a uveitis specialist or ask for assistance from physician colleagues if they do not feel competent to move on to the appropriate step in the treatment pathway.

Although the guidelines are primarily intended for the use of ophthalmologists, they may be found helpful by some patients, general practitioners and optometrists in gaining a greater understanding of uveitis management.

The majority of patients with uveitis will have acute anterior uveitis which settles promptly with topical treatment. However, the guidelines appropriately cover in greater detail the minority who require systemic therapy and who generally have more sight-threatening disease.

These guidelines do not apply to infectious uveitis, which should always be considered, along with malignancy, in patients presenting with uveitis.

In unilateral disease intra-orbital or intra-vitreal steroid may be considered as an alternative to systemic steroids.

The points emphasised in the treatment pathways such as macular oedema, retinal vasculitis and steroid dose should be considered ‘red flags’ highlighting indicators of sight threatening uveitis and of systemic complications of therapy.

**Uveitis Treatment Pathways**

The following flow diagrams aim to simplify and demystify the treatment of uveitis. By providing a clear route for treatment we would hope to identify those patients with sight-threatening uveitis at any earlier stage. These pathways are intended for use by ophthalmologists involved in the management of patients with uveitis. This will allow prompt, appropriate referral to a uveitis specialist for consideration of systemic immunosuppression.

**These pathways are not applicable to infectious uveitis**
Anterior Uveitis

Macular oedema

Yes

Systemic and topical steroids
Topical mydriatic

No

Posterior synechiae

No

Topical steroid
Topical mydriatic

Yes

Try staged mydriasis. If fails then subconjunctival steroids and Mydricaine.

Resolving?

No

Yes

Taper therapy

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Intermediate Uveitis

Macular oedema

Yes

Intra-orbital or intravitreal steroids

No

Systemic steroids

Vitritis causing reduced vision

No

Topical steroids

Observation only
Posterior/Panuveitis

Retinal vasculitis

Yes

Occlusive

Non-occlusive

Central

Peripheral

If observation not appropriate

Systemic steroids

No

Macular oedema

No

Vitritis causing reduced vision

Yes

Vitritis causing reduced vision

No

Observation may be appropriate
When to immunosuppress?

Which immunosuppressive agent to use?

Immunosuppressive therapy should be considered in the following situations:

- All patients requiring chronic steroid therapy greater than 7.5mg a day (osteoporosis guideline) should be considered for immunosuppressive therapy to allow reduction in the steroid therapy.

- Most patients requiring systemic steroid therapy who relapse on steroid withdrawal will require systemic immunosuppression to reduce long-term steroid exposure.

- Early indications for immunosuppression would be ineffect of prednisolone despite adequate dosing.

- Reactivation while reducing the steroid therapy usually requires an increase in the prednisolone dosage to ensure rapid control of the disease.

- Immunosuppression is recommended at the outset in a number of inflammatory eye diseases due to the chronicity and potentially poor prognosis that these conditions have if untreated.

- Patients requiring ongoing systemic steroid therapy do so because they have disease that is either steroid-dependent, steroid-resistant or relapsing disease.

- When starting immunosuppression it is important to determine whether the patient requires a steroid sparing agent or an agent to induce remission of disease as agents differ in their ability to induce disease remission.
**Summary of side effect profiles**

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<tr>
<th>Immunosuppressive agent</th>
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### Summary of side effect profiles

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Uveitis NMCN Treatment Guidelines
Revised September 2010
Immunosuppressive Therapy

- Immunosuppressive therapy may be effective in the longer term management of inflammatory eye disease for some patients. The aim of therapy is to allow a reduction in the steroid dosage while maintaining disease control. Most drugs are well tolerated but all carry a small risk of severe side effects which may be potentially life-threatening.

- As most immunosuppressive drugs take several weeks to be effective, reduction of the oral prednisolone, even in patients with controlled ocular inflammation may need to be deferred for several weeks after commencement of the immunosuppressive agent.

- In active disease, high dose prednisolone is often required at the same time as commencing immunosuppressive therapy.

- Pregnancy and breast feeding are relatively contraindicated while on immunosuppressive therapy.

- It is important to ensure adequate contraception being used. See appendix for teratogic risks.

- To minimize the risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using sunscreen with a high protection factor.

- Once a treatment plan is agreed this should be actioned as promptly as possible.

- If an agent is not effective, provided an adequate period of treatment has been adhered to, then there should not be unnecessary delay (max 2 Weeks) in either switching or adding further therapy.

- When a decision is made to commence biologic therapies, treatment should begin within 2 weeks of that decision.

This document does not replace the advice given by the British National Formulary, nor the advice given by my manufacturers.
Prednisolone

**Indications**

Corticosteroids are the initial mainstay of treatment in inflammatory eye disease. Almost all patients with sight-threatening uveitis will require systemic steroids at some point.

Systemic steroids are effective in the short and longer term management of inflammatory eye disease. They are usually well tolerated, but do have a number of side-effects, most of which are predictable.

**What to do**

- Consult BNF.
- Ensure no potential interaction with other medications.
- Check baseline U+E, LFTs, FBC, serum glucose, urinalysis and blood pressure.
- Consider what is the most appropriate route of administration (Steroids may be administered topically, intra-orbitally, intra-vitreally or systemically).
- Initial treatment may depend on consultant and patient preference.
- Many authors would advocate initial dosing of prednisolone at 1mg/kg, however it is our experience that a starting dose between 40mg and 60mg is usually required for patients with uveitis, depending on severity and type of uveitis.
- If rapid disease control is required then methylprednisolone may be given at a dose of 1g pulses per day over 3 consecutive days. This would be followed by high-dose oral prednisolone.
- High dose oral steroid therapy does not increase the risk of ulcer disease and therefore the routine use of proton pump inhibitors (PPI) or histamine H2 blockers is not necessary. However many patients complain of dyspepsia when commenced on steroids and PPIs or H2 blockers may have a role in these patients. Patients should be started on a PPI if they are also taking non-steroidal anti-inflammatory drugs (NSAIDS) as this combination of therapy has been associated with a fourfold increased risk of gastric ulceration.

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Revised September 2010
• Bone densiometry should be considered for any patient on any dose of oral prednisolone for longer than three months or where the patient is likely to require prednisolone for at least three months due to the risk of osteoporosis. The college of physicians guidelines are summarized on the following website http://www.rcplondon.ac.uk/pubs/books/gluocorticoid/

• Patients on corticosteroid for longer than 3 weeks, treatment must not be stopped abruptly. Adrenal suppression can last for a year or more after stopping treatment and the patient must mention the course of corticosteroid when receiving treatment for any illness or injury.

• Unless patients have had chickenpox, patients receiving oral or parenteral corticosteroids should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.

• Mood and behaviour changes. Corticosteroid treatment, especially with high doses, can alter mood and behaviour early in treatment—the patient can become confused, irritable and suffer from delusion and suicidal thoughts. These effects can also occur when corticosteroid treatment is being withdrawn. Medical advice should be sought if worrying psychological changes occur.

• Steroid Treatment Cards should be issued to all patients.

**Side Effects**

Side effects include acne, atherosclerosis, avascular necrosis of femoral head, cataract, delay in pubertal growth, diabetes mellitus (up to 30%), dyslipidemia (up to 30%), heart failure, hypertension (up to 85%), infection, osteoporosis, raised intraocular pressure (IOP), serious psychosis (up to 5%), sleep disturbance.
Antimetabolites

Azathioprine

Indications

Azathioprine may be used as a steroid sparing agent.

Evidence in Inflammatory Eye Disease

- A recently published retrospective cohort study found 69% of patients with intermediate uveitis, 44% of patients with posterior or panuveitis and 24% of patients with anterior uveitis patients had control of their ocular inflammation within 6 months of treatment with azathioprine\(^{(10)}\).

- The only randomized, placebo-controlled, double-blind trial of azathioprine was in patients with Behcet disease. This trial found azathioprine to be effective in the treatment of chronic uveitis and in reducing incidence of second eye involvement when used in combination with prednisolone\(^{(11)}\).

- Azathioprine has also been shown to provide effective long-term control of uveitis associated with Behcet disease\(^{(12,13)}\) but newer drugs are likely to be more effective. See section on interferon alpha and tumour necrosis factor alpha inhibitors.

- There are a number of case series illustrating the efficacy of azathioprine in the treatment of chronic uveitis in patients with eye disease\(^{(13,14,15)}\).

- Azathioprine has been shown in case series to be useful in the treatment of serpiginous choroiditis, multifocal choroiditis tubulointerstitial nephritis and panuveitis when combined with prednisolone or ciclosporin A\(^{(16,17,18,19)}\).

What to do

- Consult BNF.

- Ensure no potential interaction with other medications.

- U&E, LFT and FBC should be checked before commencing therapy, then weekly for the first month of therapy and at least three monthly thereafter.
The enzyme thiopurine methyltransferase (TPMT) metabolises azathioprine; the risk of myelosuppression is increased in those with a low activity of the enzyme, particularly in the very few individuals who are homozygous for low TPMT activity. Normal levels: normal dose. Medium levels (heterozygous for TPMT mutation): reduce dose. Very low levels (homozygous for TPMT mutation): low dose or avoid use.

If Allopurinol is co-prescribed the dose of Azathioprine should be reduced by 75%.

If on warfarin then close monitoring of INR is advised as azathioprine may alter anticoagulant effect.

Azathioprine may be started at a dose of 50mg/day and if tolerated increased to 100mg after a week.

Dosing usually needs to be adjusted based on the clinical response and side effects.

Dose may be increased to a maximum of 2.5mg/kg/day.

In practice, this will rarely exceed 150mg/day.

**Side effects**

Side effects are common and in one study 24% patients stopped azathioprine due to side effects \(^{10}\). These include generalised muscle aches, fatigue and headache. Slow titration of the dose reduces the chance of these side effects and if they do occur then dose reduction is often enough for symptoms to resolve. Regular blood monitoring is required to identify liver dysfunction and bone marrow suppression. These effects usually resolve on stopping the azathioprine. Gastrointestinal upset is relatively common. A recent retrospective review would suggest that there is no increased cancer-related mortality in patients treated with azathioprine for ocular inflammatory disease \(^{20}\).
**Methotrexate**

*Indications*

- Most frequently used in disease in association with connective tissue disorders as a steroid sparing agent.
- May be used in combination with infliximab for idiopathic inflammatory eye disease.

*Evidence in Inflammatory Eye Disease*

- Methotrexate has been show in several large studies to be effective in the treatment of uveitis\(^{18,22,23,24,25,26,27}\) with one large study showing remission in 76% patients \(^{22}\).
- A recently published retrospective cohort study found 55.6% of patients with anterior uveitis, 47.4% of patients with intermediate uveitis and 24% of patients with posterior or panuveitis had control of their ocular inflammation within 6 months of treatment with methotrexate \(^{21}\).
- This however appears not to be the case in Scottish clinical practice and methotrexate is rarely used except in patients requiring some form of immunosuppression while on infliximab and all other immunosuppressants have been either ineffective or not tolerated.

*What to do*

- Consult BNF.
- Ensure no potential interaction with other medications.
- Full blood count and renal and liver function tests before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2–3 months.
- A baseline CXR is required.
- Patients should be advised to report all symptoms and signs suggestive of infection, especially sore throat
- Not suitable for patients with either significant renal or liver disease.
• 16% patients (21) are intolerant of this drug.

• Commence at 7.5mg/week (as single dose).

• Dose may be increased by 2.5mg increments every 6-8 weeks (available in strengths of 2.5mg and 10mg).

• The maximum dose is usually 15-25mg/week.

• Nausea, diarrhoea and mouth ulcers may respond to folic acid 5mg once a week 3 days after methotrexate.

• Respiratory symptoms should be investigated with a CXR and pulmonary function tests as there is a risk of pulmonary fibrosis.

• **Side effects**

• Regular blood monitoring is important as hepatoxicity and bone marrow suppression may occur. These usually resolve on stopping the methotrexate. Nausea, diarrhoea and mouth ulcers are relatively common but usually respond to treatment. Conception must be avoided for at least 3 months after administration has ceased for both males and females. May cause reversible sterility in males. Hair loss or rash may occur. It is important to get medical review urgently if a rash develops. Hair loss generally improves on stopping methotrexate. Irreversible lung changes may occur (interstitial disease).
Mycophenolate mofetil

Indications

Used as a steroid sparing agent.

Evidence in Inflammatory Eye Disease

- In a number of published case series mycophenolate mofetil appears to be effective in the treatment of ocular inflammatory disease \(^{(28,29,30)}\).

- In one retrospective case series 64.3% patients achieved long term disease control with mycophenolate mofetil \(^{(31)}\).

- A recently published retrospective cohort study showed mycophenolate was associated with a greater level of treatment success at six months than azathioprine and methotrexate (70%, 58%, 42% respectively) \(^{(32)}\).

What to do

- Consult BNF

- Ensure no potential interaction with other medications.

- U&E, LFT, lipid profile and FBC should be checked before commencing therapy.

- FBC should be checked weekly for the first month, then twice a month for the second and third months, then every month in the first year. Thereafter monitoring every two to three months may be appropriate.

- U&E, LFTs and blood pressure should also be monitored regularly.

- Avoid clozapine and mycophenolate together as there is an increased risk of agranulocytosis.

- Use cautiously in renal impairment or gastrointestinal disorders.

- Commence orally at 1g twice a day.

- May be increased up to 1.5g twice daily if clinically indicated.

- A negative pregnancy test is essential prior to commencement of therapy.
Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding

- **Mycophenolate should not be prescribed concomitantly with azathioprine.**

**Side effects**

Side effects include generalised muscle aches, fatigue and headache and gastrointestinal upset. May be reduced by titrating the dose slowly. If side effects do occur then dose reduction is often enough for symptoms to resolve. Regular blood monitoring is important to identify liver dysfunction and bone marrow suppression. These effects usually resolve on stopping the drug. A recent retrospective review would suggest that there is no increased cancer-related mortality in patients treated with mycophenolate for ocular inflammatory disease \(^{(20)}\).
T-cell inhibitors/Calcineurin Inhibitors

Ciclosporin

**Indications**

Ciclosporin may be used as a steroid sparing agent.

**Evidence in Inflammatory Eye Disease**

- Case series have suggested that ciclosporin is an effective monotherapy for the treatment of uveitis at a dose of 10 mg kg/day \(^{(33)}\). This is much higher dose than that currently used.

- Several studies in uveitis have shown its efficacy and safety \(^{(34,35,36,37,38,39,40)}\).

- In a randomized controlled trial involving 56 patients with uveitis, ciclosporin had similar efficacy to oral steroids \(^{(41)}\), though greater efficacy was noted in combination.

**What to do**

- Consult BNF.

- Ensure no potential interaction with other medications.

- Baseline FBC, LFTs, U&E (x2), lipids, urinalysis and blood pressure.

- U&E, LFTs and FBC should then be checked fortnightly until dose stable for 3 months, then monthly thereafter.

- Lipids should be checked every six months.

- BP should be checked at each monitoring visit.

- There is no indication for routine monitoring of serum concentrations of the drug as they do not correlate well with efficacy. May be useful if compliance in question.

- Because of differences in bioavailability, the brand of oral ciclosporin to be dispensed should be specified by the prescriber

- **Doses given for Neoral.**
• Commence at 2mg/kg twice a day (4mg/kg/day) orally.

• Dose adjusted dependent upon clinical response and side effects.

• Nephrotoxicity is relatively uncommon on doses of 2-5mg/kg/day. Treatment contraindicated in patients with evidence of moderate or severe renal impairment.

• **Do not prescribe concomitantly with tacrolimus.**

• The concomitant use of nifedipine or colchicine should be avoided.

• Potassium sparing diuretics, ACE inhibitors, Angiotensin-II receptor antagonists and potassium salts should be used with caution.

• Grapefruit juice should not be taken at the same time as ciclosporin.

**Side effects**

• Frequently causes hirsutism and therefore less favoured in women. Not generally a problem in men

• Gum overgrowth may occur. Does not generally resolve on stopping ciclosporin and may require surgery to correct.

• Regular blood monitoring usually allows early identification of liver or kidney impairment. These effects may resolve on stopping the ciclosporin.

• High blood pressure and high cholesterol may result in an increased risk for stroke and heart disease. Both of these side effects are monitored for and are potentially treatable with further medication.

• Low magnesium levels may occur with ciclosporin. Occasionally these may cause muscle aches or numbness. If these are problematic then the magnesium levels usually return to normal on stopping the ciclosporin.

• Pregnancy and breast feeding relatively contraindicated while on ciclosporin.

• Tremor if not well tolerated may require cessation of treatment.

• Mild nephrotoxicity often responds to dose reduction. Ciclosporin should be stopped if nephrotoxicity moderate or worse. Nephrotoxicity (42). All patients on 10mg/kg/day
will develop evidence of nephrotoxicity. This is significantly reduced on doses of 2-5mg/kg/day.

**Tacrolimus**

*Indications*

Used as a steroid sparing agent.

*Evidence in Inflammatory Eye Disease*

- Small case series have suggested tacrolimus is effective in the treatment of uveitis, achieving between 62% to 76% control \(^{43,44,45,46}\).

- One prospective randomized controlled trial has shown tacrolimus to be as efficacious as ciclosporin but with a better side effect profile \(^{47}\).

*What to do*

- Consult BNF

- Ensure no potential interaction with other medications.

- Baseline FBC, LFTs, U&E and creatinine, lipid profile, blood glucose, coagulation screen and ECG.

- Once on treatment U&E, creatinine, LFTs, FBC and blood pressure, should be checked weekly for 4 weeks then fortnightly for 2 months then monthly.

- Lipid profile and blood glucose should checked regularly.

- Monitoring the blood concentration of tacrolimus is not essential when using low doses. However, trough tacrolimus levels are useful when considering increasing the tacrolimus dose, for ensuring that maintenance doses are not toxic and as a measure of compliance.

*Recommended doses given for Prograf*

- An initial dosage of 0.05 mg per kg per day may be effective for uveitis.

- Usual effective dose 1-2mg twice daily.
• Dosing should be based on achieving disease control with minimal side effects.

• **Do not prescribe concomitantly with ciclosporin.**

• Grapefruit juice should not be taken at the same time as tacrolimus.

• Potassium sparing diuretics and potassium salts should be used with caution.

**Side effects**

• Regular blood monitoring usually allows early identification of liver or kidney impairment. These effects may resolve on stopping the tacrolimus.

• May cause hypertension and hypercholesterolaemia which potentially may result in an increased risk of stroke and ischaemic heart disease. Both of these side effects are monitored for and are potentially treatable with further medication.

• Tacrolimus is associated with diabetes.

• Low magnesium levels may occur with tacrolimus and may result in muscular aches. If these are problematic then magnesium supplements may be tried. The magnesium levels usually return to normal on stopping the tacrolimus.

• Gastrointestinal upset including abdominal pain, nausea, vomiting, and diarrhoea may occur. Slow dose increase reduces the chance of these side effects and if they do occur then dose reduction is often enough for symptoms to resolve.

• Tremor occurs in some patients but stops with treatment cessation.

• Due to reports of reversible cardiomyopathy in children receiving tacrolimus following cardiac transplant, it is recommended that children have regular echocardiograms (reference to BNF). However, screening is generally not undertaken in adults.

• Occasionally headache can be a problem.

• Pregnancy and breast feeding relatively contraindicated while on tacrolimus. Avoid steroid based contraceptive agents as tacrolimus may alter their metabolism.

• Adverse effects generally resolve or improve when tacrolimus is stopped or when the dosage is reduced.
Alkylating Agents

Cyclophosphamide

Indications

Essential therapy in some forms of inflammatory disease especially if systemic disease involvement. Used as an induction therapy.

Evidence in Inflammatory Eye Disease

- The majority of data on cyclophosphamide use in ocular inflammatory disease comes from uncontrolled case series \(^{50,51,52,53}\).

Intravenous pulsed cyclophosphamide has fewer side effects, but is less efficacious than the preferred oral route \(^{52}\).

What to do

- Consult BNF
- Ensure no potential interaction with other medications.
- U&E, LFT, FBC and urinalysis and pregnancy test (if appropriate) before commencing treatment.
- Once treatment commenced, U&E, LFT, FBC and urinalysis weekly for the first month, two weekly for the second and third month and then monthly thereafter.

Doses given for oral route of administration.

- Starting dose orally, 1 to 3 mg/kg/day.
- Usual starting dose 100-150mg/day.
- Use with caution in elderly population (start at 50mg/day).
- Dose may be adjusted depending on response and toxicity.
- If toxicity occurs, dose may be decreased by 25 to 50 mg.
- Dosage reduction may be necessary in renal impairment.
should not be given concurrently with allopurinol as this increases bone marrow suppression, or sulphonylureas due to the increased risk of hypoglycaemia.

- Opportunistic infections are more common with oral daily cyclophosphamide compared to intravenous “pulse”, with 30% of patients on oral regimen developing Pneumocystis carinii pneumonia in one study \(^{(48)}\). Intermittent intravenous administration is increasingly favoured by rheumatologists \(^{(49)}\).

- Pneumocystitis carinii pneumonia prophylaxis should be considered for all patients commencing cyclophosphamide. Septrin 960mg three times a week is recommended. (see BSR guidelines)

- Patients should be asked about the presence of sore throat, rash, abnormal bruising or oral ulceration at each visit.

- If a patient has haematuria on a urine dipstick they should be advised to increased fluid intake. Monitor closely.

- If a patient develops macroscopic haematuria or haematuria with dysuria the drug should be stopped.

**Side effects**

- Bone marrow suppression is dose dependent, reversible and more common in the elderly.

- It is important that the patient is aware of signs and symptoms of bone marrow suppression. They should be instructed to stop the cyclophosphamide and to seek urgent medical advice if they develop a sore throat, rash, abnormal bruising or oral ulceration.

- Relative increased risk of cancer (especially bladder and bone cancer), however most patients receiving this treatment do not develop cancer.

- Hair loss, usually recovers.

- Cystitis due to cyclophosphamide irritating bladder (high fluid intake reduces risk).

- Blood in urine, may be microscopic or macroscopic and is more common in patients with inadequate fluid intake. Patients should stop treatment and seek medical advice immediately if macroscopic haematuria occurs.
• Nausea and vomiting.

• Cyclophosphamide is contraindicated during pregnancy and lactation and should be withdrawn at least 3 months prior to conception.

• Amenorrhoea and azoospermia may occur in patients taking cyclophosphamide.

• May result in primary ovarian failure in over 70% patients \(^{(53,54,55,56)}\).

• Patients should be offered sperm banking/ cryopreservation of oocytes.
Biological therapies

Biologic therapies currently have a role in treating sight threatening uveitis refractory to conventional immunosuppression. They may be used as steroid sparing agents or where other immunosuppressive agents are poorly tolerated as well as when ocular inflammation remains uncontrolled. There remains some uncertainty about the long term consequences of biologic therapy and so they should not be used as first-line treatment at present. There are considerable cost implications to these therapies, but they may be sight-saving, and in patients where the more ‘traditional’ approaches have failed, expense should not prevent appropriate treatment. Common and important side effects of medication are discussed here but please consult the British National Formulary and product datasheets for more complete information.

The aim of biological immunosuppressive therapy is to control ocular inflammation and allow the oral prednisolone dosage to be reduced below 7.5mg. The overall duration of treatment is dependent on the individual and their disease. At present there are no large studies comparing biological treatments in inflammatory eye disease. The use of biological therapy for treating inflammatory conditions is changing rapidly and as our understanding of immune mechanisms contributing to ocular inflammation improves we should aim to target our therapies more precisely.
Tumour necrosis factor (TNF) alpha inhibitors

The tumour necrosis factor (TNF) alpha inhibitors comprise adalimumab, infliximab and etanercept. Adalimumab and infliximab are being used for the short and long term treatment of refractory ocular inflammatory disease and are discussed below but etanercept appears to be ineffective. Adalimumab offers the advantage of being delivered via a subcutaneous injection whereas infliximab is given as an infusion. However, there is currently more experience with infliximab than with adalimumab in treating uveitis.

The anti-TNF therapies can:

- Can unmask previously unidentified multiple sclerosis.
- May reactivate tuberculosis.
- Allergic-like reaction may occur during infusion (infliximab). Slowing infusion or pre-treating with hydrocortisone often effective in preventing this during further infusions.
- Sudden death has been reported in patients with known heart problems.
- Pregnancy and breast feeding relatively contraindicated.
- Injection site reactions may occur. It has been reported that cooling the site prior to administering the injection reduces pain associated with the injection.
- Infection including histoplasmosis and other invasive fungal infections.
- SLE and lupus like syndrome.
- Hepatitis B reactivation has been reported in patients on infliximab.
- Patients with hepatitis B should be referred to a gastroenterologist to consider antiviral prophylaxis prior to starting anti TNF alpha therapy.
- Lymphoma has been reported but the incidence was not higher than would be expected for that population.
- Haematologic reactions including pancytopenia and aplastic anaemia are rare.
- Although adverse effects may be severe, they are relatively rare and should be compared with those associated with other immunosuppressive agents.
**Adalimumab**

*Indications*

- It is recommended that adalimumab should be used as an adjunctive therapy for refractory cases of uveitis rather than as a first-line treatment.
- Can be used as either a steroid sparing agent or an inducing agent.
- Adalimumab has not been licensed for use in inflammatory eye disease

*Evidence in Inflammatory Eye Disease*

- There are a number of moderate sized case series, and one open label prospective trial looking at adalimumab in paediatric uveitis. These have reported an improvement in ocular inflammation (57,58,59,60), reduction in the use of topical and systemic medication (57,59) and a low rate of uveitis flares (61) in children, the majority of whom had juvenile idiopathic arthritis associated uveitis.

- There is one open label prospective trial of patients with uveitis refractory to therapy treated with adalimumab for 12 months. This reported a reduction in macular oedema, ocular inflammation and immunosuppression but 42% of patients had relapses requiring periocular steroid injections (62).

- There is one small case series showing maintenance of remission of Bechet’s uveitis in patients on adalimumab (63).

*Practical Considerations*

Prior to commencing therapy:

- Consult BNF.
- Ensure no potential interaction with other medications.
- Medical history and examination looking for evidence of infection or malignancy.
- Full blood count (FBC), urea and electrolytes (U+E), liver function tests (LFTs), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), double stranded DNA (dsDNA).
- Consider testing for hepatitis B.
• Consider investigating for central nervous system (CNS) demyelination in patients with intermediate uveitis or a history of optic neuritis.

• Chest X-ray (CXR) to exclude tuberculosis (TB). Patients with an abnormal CXR, history of TB or TB treatment should be referred to a TB specialist.

• Patients at high risk of TB eg. black African aged over 15 years and all South Asians born outside the UK should be considered for TB chemoprophylaxis.

• Urinary pregnancy test as appropriate.

Short and longer term

• Usual adult dose is 40mg subcutaneous administered 2 weekly. May be increased to 40mg weekly if required. There is no data looking at the optimum dose of adalimumab in uveitis.

• Dose for child ≤30kg is 20mg 2 weekly. Child ≥30kg is 40mg 2 weekly.

• Patients may be taught to self-administer adalimumab.

• Blood monitoring (FBC, U+E, LFT, CRP and ESR) should be performed 4 to 8 weekly.

Adalimumab as a monotherapy

• Adalimumab has been successfully used as a monotherapy in patients with ocular inflammatory disease\textsuperscript{(59,61)} although in the majority of reported cases it has been used in combination with systemic steroids and/ or other immunosuppressive agents.

• In rheumatoid arthritis, a combination of methotrexate and adalimumab has been found to be superior to adalimumab alone\textsuperscript{(64)}.

• There is currently no data on anti-adalimumab antibody formation in patients with uveitis.

Contra-Indications/drug interactions

• Avoid concomitant use of adalimumab with other biological therapies.

• Avoid live vaccines (www.humira.com)
• Breast feeding. It is not known whether adalimumab is excreted in breast milk (www.humira.com).

• Pregnancy. The effect of adalimumab on the fetus is unknown. (www.humira.com)

• Active infection including tuberculosis (www.humira.com)

• Demyelinating CNS disorders (65).

**Side Effects**

• Injection site reactions (10.6%). It has been reported that cooling the site prior to administering the injection reduces pain associated with the injection (61).

• Infection including histoplasmosis and other invasive fungal infections (65,66).

• Reactivation of tuberculosis (61).

• Demyelinating disease (61).

• SLE and lupus like syndrome (61).

• Hepatitis B reactivation has been reported in patients on infliximab (66,67). Patients with hepatitis B should be referred to a gastroenterologist to consider antiviral prophylaxis prior to starting anti TNF alpha therapy (68).

• Lymphoma has been reported but the incidence was not higher than would be expected for that population (65).

• Congestive cardiac failure (65). Use with caution in patients with known cardiac failure (www.humira.com).

• Haematologic reactions including pancytopenia and aplastic anaemia are rare (www.humira.com).
**Infliximab**

*Indications*

- It is recommended that infliximab should be used as an adjunctive therapy for refractory cases of uveitis rather than as a first-line treatment.

- Can be used as either a steroid sparing agent or an inducing agent.

*Evidence in Inflammatory Eye Disease*

- In one prospective open label trial infliximab in patients with refractory uveitis, clinical success was achieved in the majority of patients (17 out of 23 patients) at 10 weeks although by one year the numbers of patients considered a success had fallen to 7 out of 14 patients \(^{(69)}\).

- There are a number of prospective open label trials of patients with refractory Behcet’s uveitis showing rapid control of inflammation with infliximab \(^{(70,71,72)}\), a significant reduction in uveitis flares \(^{(72,73)}\) and of systemic steroid dose in patients treated with infliximab compared with the pre-treatment period \(^{(73)}\).

- There are case series reporting success in controlling ocular inflammation in childhood uveitis \(^{(60,74,75,76)}\).

*Practical Considerations*

- Consult BNF.

- Ensure no potential interaction with other medications.

- Hepatotoxicity has been reported. Infliximab should be stopped if liver function tests become elevated to >5 times normal levels.

- Haematologic reactions including pancytopenia and aplastic anaemia are rare.

- Infusion hypersensitivity reaction – 10% of patients. May be severe and delayed.

- Although adverse effects may be severe, they are relatively rare and should be compared with those associated with other immunosuppressive agents.
Prior to commencing therapy:

- Medical history and examination looking for evidence of infection or malignancy.
- FBC, U+E, LFTs, CRP, ESR, ANA, dsDNA.
- CXR to exclude tuberculosis (TB). Patients with an abnormal CXR, history of TB or TB treatment should be referred to a TB specialist.
- Patients at high risk of TB eg. black African aged over 15 years and all South Asians born outside the UK should be considered for TB chemoprophylaxis.
- Consider testing for hepatitis B
- Consider investigating for CNS demyelination in patients with intermediate uveitis or a history of optic neuritis.

**Short and longer term**

- Usual dose is 5mg/kg administered as an intravenous infusion but doses of up to 20 mg/kg may be given.
- After the initial dose a second dose may be given after two weeks and then at 6 weeks.
- Further doses may be given up to 6 to 8 weekly dependent upon clinical response.
- Blood monitoring (FBC, U+E, LFT, CRP and ESR) should be performed 4 to 8 weekly.

*Infliximab as a monotherapy*

- Infliximab has been used successfully as a monotherapy in uveitis (71,72), although in the majority of reported cases it has been used in combination with systemic steroids and/ or other immunosuppressive agents.
- Studies of patients with rheumatoid arthritis have shown that the formation of anti-infliximab antibodies is greater in patients on infliximab alone compared with those on infliximab combined with methotrexate (77). The formation of anti-infliximab antibodies has been associated with a loss of clinical response and an increased rate of infusion reactions (78).
• There is currently no data on anti-infliximab antibody formation in patients with uveitis. However, it is recommended that infliximab is used in combination with another immunosuppressive agent where this is tolerated.

Side Effects

• Infusion hypersensitivity reaction – 10% of patients (79). May be severe and delayed.

• Infection, including histoplasmosis and other invasive fungal infections.

• Reactivation of tuberculosis (80).

• Demyelinating disease (81).

• Optic neuropathy (82).

• SLE and lupus like syndrome (83).

• Hepatitis B reactivation (66,67). Patients with hepatitis B should be referred to a gastroenterologist to consider antiviral prophylaxis prior to starting infliximab (68).

• Lymphoma has been reported but it is unclear whether the incidence is higher than that in the general population (84).

• Congestive cardiac failure. Both exacerbation of existing heart failure and new-onset heart failure reported (85,86).

• Hepatotoxicity has been reported. Infliximab should be stopped if liver function tests become elevated to >5 times normal levels (www.remicaide.com).

• Rare reports of haematologic disorders including leucopenia, neutropenia, thrombocytopenia and pancytopenia (www.remicaide.com).
Interferon α

**Indications**

- It is currently recommended that Interferon-α is used only in cases of uveitis refractory to conventional immunosuppressive therapy.

- Can be used as either a steroid sparing agent or an inducing agent.

**Evidence in Inflammatory Eye Disease**

- Both interferon alpha 2a (Roferon A®) and interferon alpha 2b (Intron A®, Viraferon®) have been used in uveitis.

- A large prospective case series of patients with Behcet’s disease reported that 92% patients responded to treatment. This effect appears to be prolonged with 40% remaining inactive for 7 to 58 (mean 29.5) months after stopping treatment \(^{(87)}\).

- Interferon alpha has been used to treat children with uveitis associated with Behcet’s disease, and a corticosteroid sparing effect has been reported in one case series \(^{(88)}\).

- Case series of patients with idiopathic uveitis, predominantly posterior and panuveitis, refractory to conventional immunosuppression have demonstrated a beneficial effect of interferon-α on uveitis in 59 to 83% of patients \(^{(89,90)}\).

- Refractory uveitic cystoid macular oedema responded to interferon alpha with complete resolution in 6 out of 8 patients in a prospective pilot study \(^{(91)}\).

**What to do**

**Pre-treatment**

- Consult BNF.

- Ensure no potential interaction with other medications.

- Medical history and examination, including history of mental illness.

- Prior to administration of the first dose, the following investigations should be performed: FBC, U+E, LFTs, CRP, ESR, thyroid function tests (TFT), autoantibodies.
including dsDNA and thyroid autoantibodies, coagulation screen, lipid profile, urinary pregnancy test as appropriate.

- The patient’s weight should be recorded.
- Base line ECG for patients with cardiovascular disease.
- Chest X-ray.
- Steroid dose should be no greater than 15 mg prednisolone daily when interferon treatment commenced, and ideally reduced to 10mg or less.
- Other immunosuppressive drugs should be stopped prior to starting interferon therapy.

**Short and longer term**

- Starting dose 3 million units once daily for Intron A.
- Maximum dose of Intron A used in ocular inflammatory disease is nine million units daily.
- Administered as a subcutaneous injection daily before bed as patients may feel tired after the injection.
- Paracetamol should be given 500mg tds for days 1-3.
- The following blood tests should be monitored during treatment at weeks 1, 2, 4, 8 and every month thereafter: FBC, U+E, LFTs, CRP, ESR, TFT and lipid profile
- Weight should be recorded at each clinic visit.

**Contra-Indications/drug interactions**

- Avoid concomitant use of interferon alpha with other immunosuppressive agents. Low doses of steroids may be used in combination with interferon alpha.
- Avoid live vaccines.
- Breast feeding. It is not known whether interferon alpha is excreted in breast milk. ([http://www.introna.com](http://www.introna.com)).
• Pregnancy. The effect of interferon alpha on the fetus is unknown. ([http://www.introna.com](http://www.introna.com)).

• History of severe depression.

• Hypersensitivity to interferon alpha ([http://www.introna.com](http://www.introna.com)).

• Autoimmune hepatitis ([http://www.introna.com](http://www.introna.com)).

• Decompensated liver disease ([http://www.introna.com](http://www.introna.com)).

• Uncontrolled thyroid disease ([http://www.introna.com](http://www.introna.com)).

**Side Effects**

• Flu-like illness (fatigue, headache, arthralgia, fever) occurs in almost all patients ([87,88]) ([http://www.introna.com](http://www.introna.com)). It is most predominant in the first two weeks of therapy and may be improved by taking regular paracetamol ([http://www.introna.com](http://www.introna.com)).

• Fatigue may persist during therapy ([90]).

• Anorexia and weight loss - 33% ([90]).

• Bone marrow toxicity resulting in myelosupression ([87,89]) and rarely aplastic anaemia ([http://www.introna.com](http://www.introna.com)).

• Injection site reaction. 25% ([90]) - 100% ([87]).

• Alopecia. 24% ([96]). Hair growth returns when interferon alpha is stopped ([http://www.introna.com](http://www.introna.com)).

• Hepatotoxicity ([91]). If the ALT rises to greater than 5 times normal, interferon should be withheld. It may be later re-introduced at 50% of the initial dose. If the ALT rises to greater than 10 times normal, interferon should be stopped and not re-started ([http://www.introna.com](http://www.introna.com)).

• Regular blood monitoring usually allows early identification of liver disturbance and bone marrow suppression. These effects should resolve on stopping the interferon.

• Depression may be dose related and improve as the dose is reduced ([89]). Selective serotonin re-uptake inhibitors have been used to treat interferon-induced depression in a case series of patients ([92]). Depression may be severe and suicidal ideation has
been reported (88,90). Patients with severe or worsening depression should have their therapy stopped (92).

- Pruritis 24% (87)
- Diarrhoea
- Hypertriglyceridaemia, which may cause pancreatitis (http://www.introna.com).
- Retinopathy manifesting as cotton wool spots and retinal haemorrhages (90).
- Acute hypersensitivity reactions. Drug should be stopped if an acute reaction develops (http://www.introna.com). The risk of development of hypersensitivity reactions may be greater with second and subsequent treatments.
- Thyroid dysfunction, which may not be reversible when the drug is stopped (http://www.introna.com).
- Psoriasiform rash (90)
- Seizures (87)
- Interferon alpha may impair fertility (http://www.introna.com).
- The patient should be made aware of the possibility of delayed adverse reactions and should be advised to report any symptoms which may give them cause for concern.
- Not recommended in pregnancy or breast feeding.
- Women of childbearing age should use effective contraception during treatment and for four months after.
Daclizumab

**Indications**

- It is recommended that Daclizumab is used only in cases of uveitis refractory to conventional immunosuppressive therapy.
- Humanised IgG monoclonal antibody that binds CD25 of the human IL-2 receptor.
- Mechanism of action may be via induction of natural killer (CD56\textsuperscript{bright}) cells.

**Evidence in Inflammatory Eye Disease**

- Daclizumab has been found to be effective in the treatment of intermediate and posterior uveitis in a small open label study. Eight out of ten patients maintained remission of uveitis over 4 years and were able to withdraw concomitant immunosuppressive medications with 2 to 4 weekly infusions of daclizumab \(^{(94)}\).
- High dose intravenous daclizumab has been used successfully as an induction therapy for active sight-threatening uveitis in a small open label study with control of uveitis in 4 out of 5 patients at 4 weeks \(^{(95)}\). Standard dose daclizumab (1mg/kg) improved ocular inflammation in 59% of eyes in one case series \(^{(96)}\).
- Two-weekly subcutaneous administration of daclizumab has also been shown to be effective in maintaining remission of uveitis in a small 26 week open label trial \(^{(61,97)}\).
- A retrospective case series of patients with birdshot retinochoroidopathy showed an improvement in clinically observed ocular inflammation with daclizumab, but electroretinography parameters declined in some patients \(^{(98)}\).
- Three out of five children with ocular inflammatory disease responded to daclizumab in one series but there were a number of adverse events with three children developing transient leukopenia, one nausea, and one myalgia and fatigue \(^{(60)}\).
- A small randomised controlled trial of daclizumab use in patients with Behcets disease did not show any benefit of intravenous daclizumab over placebo in preventing ocular attacks of Behcet’s disease \(^{(99)}\).
Practical Considerations

- Consult BNF.

- Ensure no potential interaction with other medications.

- Infusion hypersensitivity reaction. If a severe reaction occurs, daclizumab should be discontinued.

- Fatigue may occur.

- Infection. An increased risk of death from sepsis was observed in a trial using daclizumab for cardiac transplantation but these patients were on up to 5 immunosuppressive agents \(^{(93)}\).

- Skin rash, liver disturbance, painful muscles, lymphadenopathy and leucopenia have been reported.

- An increased risk of malignancy has not been found in studies of renal transplant patients, but there is a theoretical increased risk of malignancy with immunosuppression.

- Side effect profile should be discussed explaining that although adverse effects may be severe, they are relatively rare and should be compared with those associated with other immunosuppressive agents.

- Prior to commencing therapy:
  
  - Medical history and examination looking for evidence of infection or malignancy.
  
  - U+E, LFTs, CRP, FBC, ESR
  
  - CXR to exclude tuberculosis (TB). Patients with an abnormal CXR, history of TB or TB treatment should be referred to a TB specialist.

  - Urinary pregnancy test as appropriate.

Short and longer term

- Blood monitoring (FBC, U+E, LFT, CRP and ESR) should be performed 2 to 4 weekly prior to administering infusion.
Daclizumab as a monotherapy

- Daclizumab has been used effectively as a monotherapy for uveitis. In a four year open label study, patients were tapered off other immunosuppressive agents and maintained on daclizumab alone \(^{(94)}\).

Side Effects

- Infusion hypersensitivity reaction. If a severe reaction occurs, daclizumab should be discontinued \((\text{http://www.rocheusa.com/products/zenapax/})\).

- Infection. An increased risk of death from sepsis was observed in a trial using daclizumab for cardiac transplantation but these patients were on up to 5 immunosuppressive agents \(^{(93)}\).

- Skin rash \(^{(100)}\).

- Hepatic dysfunction \(^{(98)}\).

- Leucopenia \(^{(96,98)}\).

- Lymphadenopathy \(^{(94)}\).

- Fatigue \(^{(60)}\).

- Myalgia \(^{(60)}\).

- An increased risk of malignancy has not been found in studies of renal transplant patients \(^{(101)}\), but there is a theoretical increased risk of malignancy with immunosuppression \((\text{http://www.rocheusa.com/products/zenapax/})\).

Short and longer term

- The dose regime for transplantation is an intravenous infusion of 1mg/kg two weekly for 5 doses.

- In uveitis, induction doses of 8mg/kg have been used intravenously with a second dose of 5mg per kg at 14 days \(^{(95)}\).

- Maintenance intravenous dose is 1mg per kg (up to 100mg). Administer 2-4 weekly \(^{(94)}\).
• Although subcutaneous daclizumab has been used in trials at a dose of 1 to 2mg/kg, 2 to 4 weekly (maximum 200mg)\(^\text{94,96}\), there is not currently a commercial product for subcutaneous use.

**Campath (Alemtuzumab)**

*Indications*

• It is currently recommended that Alemtuzumab is used only in cases of uveitis refractory to conventional immunosuppressive therapy.

• Can be used as either a steroid sparing agent or an inducing agent.

• Is a humanised mAb which binds to CD52, the pan-lymphocyte antigen.

*Evidence in Inflammatory Eye Disease*

• One case series of ten patients showed Campath-1H to be effective in the treatment of refractory ocular inflammatory disease with initial improvement in all patients. Eight patients had control of ocular inflammation lasting 5 months or longer\(^\text{102}\).

• Campath-1H has also been used effectively in the treatment of a Mooren’s ulcer\(^\text{103}\).

• A case series of patients with Behcet’s syndrome were treated with Campath using a total of 134mg administered over 5 days. Details of eye involvement is limited in the paper but there were four patients with active ocular disease prior to receiving Campath, and at 6 months two were in remission and two in ‘partial remission’\(^\text{104}\).

*Practical Considerations*

**What to do**

*Pre-treatment*

Prior to commencing therapy:

• Consult BNF.

• Ensure no potential interaction with other medications.
• Medical history and examination looking for evidence of infection or malignancy.

• FBC, U+E, LFTs, CRP, ESR

• Baseline cytomegalovirus serology.

• CXR to exclude tuberculosis (TB). Patients with an abnormal CXR, history of TB or TB treatment should be referred to a TB specialist.

• Consider HIV test.

• Urinary pregnancy test as appropriate.

• Ensure adequate contraception is used for at least 6 months following the infusions.

**Short and longer term.**

• Patients should be pre-treated with steroid, paracetamol and anti-histamine e.g. 1g oral paracetamol, 100mg hydrocortisone and 10ml chlorpheniramine 30 minutes prior to the infusion.

• Patients should receive anti-infective prophylaxis against Pneumocystis jiroveci pneumonia (e.g. trimethoprim/ sulfamethazole 1 tablet twice daily, 3 times weekly) and an oral anti-herpes agent such as famciclovir 250mg bd while on therapy and following treatment for a minimum of two months after treatment or until the CD4+ count has recovered to 200 cells/μl (whichever occurs later). ([www.campath.com](http://www.campath.com)).

• Patients should have daily monitoring of full blood count and platelet count during therapy with Campath and at 1, 2 and 4 weeks post therapy and at intervals thereafter until haematological indices have recovered. Thyroid function should be monitored.

Contra-Indications/drug interactions

• Breast feeding. It is not known whether Campath is excreted in breast milk ([http://emc.medicines.org.uk/](http://emc.medicines.org.uk/)).

• Pregnancy ([http://emc.medicines.org.uk/](http://emc.medicines.org.uk/)).

• Active infection ([http://emc.medicines.org.uk/](http://emc.medicines.org.uk/)).

• HIV ([http://emc.medicines.org.uk/](http://emc.medicines.org.uk/)).
• Use with caution in patients with ischaemic heart disease, angina and patients on antihypertensives. (http://emc.medicines.org.uk/). Myocardial infarction following a Campath infusion has been reported \(^{104}\).

• Avoid live vaccines (www.campath.com)

**Side Effects**

• Infusion reactions due to cytokine release causing rigors, fever, nausea, vomiting and skin rashes are common. Severe reactions with bronchospasm, syncope, acute respiratory distress syndrome, myocardial infarction and death have been reported. Infusion reactions may be minimised by dose-escalation and by pretreatment with oral antihistamines, paracetamol, and corticosteroids (http://emc.medicines.org.uk/).

• Haematological toxicity. Lymphopenia occurs in all patients. Neutropenia, thrombocytopenia \(^{106}\), anaemia (www.campath.com), and coagulopathy \(^{107}\) may occur.

• Severe infections, some resulting in death, have been reported in patients with haematological malignancies treated with Campath, although these patients received higher doses than are used for ocular disease and had received other immunosuppressive agents. Opportunistic infections included cytomegalovirus, aspergillosis, cerebral toxoplasmosis and progressive multifocal leukencephalopathy \(^{108}\). There have been no reports of significant opportunistic infections in patients treated with Campath for ocular inflammatory disease but experience of Campath treatment in ocular disease is limited \(^{109}\). Patients should be advised to report symptoms of infection e.g. pyrexia (www.campath.com).

• Myocardial infarction post-infusion has been reported in the oncology literature \(^{105}\).

• Hypothyroidism developed in 2 out of 18 patients with Behcet's disease following Campath infusions (http://emc.medicines.org.uk/). Thyroid dysfunction, usually associated with thyroid autoantibodies, developed in 22% of patients with multiple sclerosis and occurred up to 30 months after the last infusion. Some patients required long term treatment for thyroid disease \(^{110}\).
• Campath is administered as an intravenous infusion over 2 hours ([www.campath.com](http://www.campath.com)). The reported regimen for ocular inflammatory disease is daily infusions for five days (102).

• The initial dose is 3mg. If tolerated this may be increased to 5 mg on the second day and then up to 10mg. The maximum reported dose for treating ocular inflammatory disease is 10-12 mg daily (102).

• One paper on Campath use in systemic Behcet’s disease, which included patients with ocular disease, used an escalating regimen of 4mg, 10mg, 40mg, 40mg and 40mg infusions on consecutive days (104). Doses of up to 30mg daily or 90mg weekly are used for B cell chronic lymphocytic leukaemia ([www.campath.com](http://www.campath.com)).

• If blood products are required following Campath therapy, these should be irradiated while the patient remains lymphopenic because of the risk of graft versus host disease ([http://emc.medicines.org.uk](http://emc.medicines.org.uk/)).

**Rituximab**

*Indications*

• Can be used as either a steroid sparing agent or an inducing agent.

• Is a monoclonal antibody that binds to CD20 on mature B lymphocytes.

• Depletes CD20+ B cells by antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis.

• Significant reduction in peripheral blood B lymphocytes occurs for 6 to 12 months.

**Evidence in Inflammatory Eye Disease**

• There are isolated case reports showing a benefit in anterior uveitis(112), scleritis associated with Sjögrens syndrome (113), and scleritis (114) and peripheral ulcerative keratitis (115) associated with Wegener’s granulomatosis. Rituximab has been used in the treatment of retinal vasculitis (116).

• A number of small uncontrolled studies and case reports suggest that rituximab may be effective in systemic lupus erythematosus (117) and systemic vasculitis (118).
Practical Considerations

What to do

Pre-treatment

- Consult BNF.
- Ensure no potential interaction with other medications.
- U&E, LFT, FBC before commencing treatment.
- Four rituximab infusions (375mg/m²) intravenously at 4 weekly intervals effective in treatment of anterior scleritis. So far no information or data for its use in uveitis. It may be that this could be reduced further.
- Administration of IV administration of corticosteroids prior to the first dose of rituximab reduces the incidence of infusion reactions. Infusion reactions less common after the second rituximab dose, compared with the first.
- It may be that this could be reduced even further as an on-going dose-ranging trial for the use of Rituximab in RA suggests dosing at day 1 and 15 at either 500mg or 1000mg proved efficacious (111).

Short and longer term

- U&E, LFT, FBC weekly for the first 2 months and 4 weekly thereafter.
- Human antichimaeric antibodies against rituximab have been detected, although despite these patients were successfully retreated.
- Regular blood monitoring usually allows early identification of liver impairment and bone marrow suppression with increased risk of infection and bleeding.

Contra-Indications/drug interactions

- Breastfeeding.
- Recent MI.
- Severe arrhythmias.
• Uncontrolled CCF.

• Women of childbearing age should use effective contraception during treatment and for twelve months after.

**Side Effects**

• Up to 94% patients have reported adverse events during clinical trials for Rituximab (119).

**Infusion related reactions**

• Transient flu-like symptoms during first infusion (50-87%). Normally resolves within 3 hours. May require paracetamol and/or antihistamine (120,121,122,123,124,125).

• Up to 10% patients also experienced bronchospasm, hypotension or severe cytokine release syndrome during first infusion.

• Generally treatment can be completed after symptoms resolved.

• Administration of IV corticosteroids prior to the first dose of rituximab reduced the incidence of infusion reactions. Infusion reactions less common after the second rituximab dose, compared with the first (121,123).

• Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred 1–2 hours after infusion of rituximab (0.04–0.07% of patients) in patients treated for AML and CLL.

• In the vast majority of cases these adverse effects are reversible with interruption or discontinuation of rituximab along with supportive care severe consequences of infusion-related reactions have been reported, including pulmonary infiltrates, acute respiratory distress syndrome and cardiovascular events. Multi-organ failure can occur. Infusion-related fatalities with rituximab have been rare (126).

• Transient hypotension frequent during infusion. Recommend withholding antihypertensives for 12 hours prior to infusion.

• Cardiac arrhythmias (2%) (121).

• Angina pectoris.
• Syncope.
• Anaphylaxis.
• Urticaria \(^{(127)}\).
• Stevens-Johnson syndrome \(^{(127)}\).
• Human antichimaeric antibodies (HACA) against rituximab were detected in <1% and patients were successfully re-treated with the drug after developing HACA \(^{(124)}\).
• Anaemia (Hb<10 g/dl) (10%) \(^{(121)}\).
• Thrombocytopenia (2%) \(^{(121)}\).
• Leucopenia \(^{(121)}\).
• Neutropenia (0.5-1.5x10^9 cells/L) (10%) \(^{(121)}\).
• These mild haematological abnormalities resolved spontaneously in 4 to 8 days (relationship to treatment not reported) \(^{(121)}\).
• All side effect information available is for use in AML and CLL therapy where dosing regimens more aggressive and therefore we would hope the type and severity of adverse reactions would be much less with this dosing regimen.
• Two dose-ranging studies have shown no relationship between side effects and administered dose \(^{(120,122)}\).

**Anakinra**

*Indications*

• May be used as a steroid sparing agent or an inducing agent.

*Evidence in Inflammatory Eye Disease*

• Anakinra is an anti-IL-1 agent.
• There is one case report of successful treatment of a child with uveitis associated with the CINCA syndrome using anakinra \(^{(128)}\). There is also a report of scleritis responding to anakinra in two patients with rheumatoid arthritis \(^{(129)}\).
Although anakinra has been shown in several randomized, controlled, double-blind clinical trials to be effective in the treatment of rheumatoid arthritis, there are no human studies for its use in ocular inflammatory disease.\(^{130,131}\)

**Practical Considerations**

**What to do**

- Consult BNF.
- Ensure no potential interaction with other medications.
- Monitor neutrophil count before treatment, then every month for 6 months, then every 3 months—discontinue if neutropenia develops.
- Dose 100mg subcutaneous once a day.
- Alternating injection site recommended.
- Supplied in pre-filled syringe.
- Use cautiously in patients with a history of asthma (risk of serious infection).
- Patients should be instructed to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat, infection) develop.

**Contra-Indications/drug interactions**

- Predisposition to infections.
- History of asthma (risk of serious infection).
- Renal impairment. Manufacturer advises caution if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute.
- Despite animal model studies suggesting a benefit of combination therapy with anakinra and anti-TNF-\(\alpha\) in inflammatory arthritis, a safety study, though showing increased efficacy, identified a high rate of adverse effects\(^{132}\). A further study looked at the additional benefit of anakinra and etanercept versus etanercept alone in patients with rheumatoid arthritis but didn't show any additional clinical benefit\(^{133}\). Combination therapy is therefore not recommended.
Side Effects

- Injection site reactions (70%) ([http://www.kineretrx.com/#](http://www.kineretrx.com/#)).
- Serious infection (mainly bacterial) ([http://www.kineretrx.com/#](http://www.kineretrx.com/#)).
- Neutropaenia (<1 x10^9/L) (0.4%) ([http://www.kineretrx.com/#](http://www.kineretrx.com/#)).
- Increased lymphoma (3.6 fold increase) and melanoma rates (3 fold increase) ([http://www.kineretrx.com/#](http://www.kineretrx.com/#)).
- Unlike anti-TNF-α therapies, there has been no report of increased incidence of tuberculosis or opportunistic infections in patients treated with anakinra.
- Regular blood monitoring usually allows early identification of bone marrow suppression with increased risk of infection.
- Patients should be instructed to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat, infection) develop.
- Relative increased risk of cancer (especially lymphoma and melanoma), however most patients receiving this treatment do not develop cancer.

Other biological therapies

Etanercept

Etanercept appears to be ineffective as an agent for the treatment of uveitis. While an early report suggested a benefit in children with uveitis ([134] ) the majority of these patients had an incomplete treatment response and small randomised controlled trials looking at the role of etanercept in preventing relapse of uveitis ([135] ), controlling juvenile idiopathic arthritis associated uveitis ([136] ) and ocular sarcoidosis ([137] ) have shown no benefit over a placebo. Retrospective comparison of infliximab and etanercept in controlling uveitis have found the former to be superior ([138,57] ). There are also case reports of new onset uveitis occurring in patients on etanercept for other conditions ([139,140] ). Etanercept is not currently recommended for use as treatment for eye disease.
Summary of use of second line and biologic agents

- The aim of immunosuppressive therapy is to control disease and allow the oral prednisolone dosage to be reduced to 7.5mg or less.

- Cystoid macular oedema is the leading cause of visual loss in uveitis and systemic treatment should be considered in ALL patients with cystoid macular oedema.

- Having achieved disease control, immunosuppressive therapy is usually continued for at least 6 months.

- The overall duration of treatment is dependent on the individual and disease activity.

- Treatment may be required in the long-term or possibly even life-long depending on the underlying condition.

- Once the prednisolone dose below 7.5mg and provided ocular inflammation remains controlled then immunosuppressive therapy is slowly withdrawn.

- Dosage reductions are usually made every 4 to 6 weeks, and complete withdrawal of therapy may take up to 12 months.

- At present there are no large studies comparing treatment efficacies.

- Individual treatment plans often initially the result of a patients preferred side effects rather than on evidence-based decisions.

- Mycophenolate or tacrolimus are often the first choice agents with the choice of agent based on likely efficacy and tolerability.

- T-cell inhibitors (ciclosporin or tacrolimus) are often the first choice agent for T-cell mediated disease (retinal vasculitis, Vogt-Koyangi-Harada disease, sympathetic ophthalmitis).

- Frequent review and early identification of treatment failure is important to allow appropriate therapeutic changes to reduce morbidity and improve long-term visual outcomes.

- The aim of biological immunosuppressive therapy is to control ocular inflammation and allow the oral prednisolone dosage to be reduced below 7.5mg.
- Biological therapies are associated with significant systemic side effects. The long term effects of biological therapies are still unknown and so these drugs should not be used as first line agents.

- The overall duration of treatment is dependent on the individual and their disease.

- At present there are no large studies comparing biological treatments.

- The use of biological therapy for treating inflammatory conditions is changing rapidly and as our understanding of immune mechanisms contributing to ocular inflammation improves we should aim to target our therapies more precisely.
Combination Therapy

- As with all treatments for inflammatory eye disease, the concept of combination therapy was adopted from allied specialities.

- This strategy has a long and proven history in the treatment of cancer.

- Due to the many pathways involved, a ‘two-pronged’ approach affecting different parts of the immune system may be more effective than individual therapies.

- As the drugs have different side effect profiles, combination therapy may allow lower individual doses to be used and so may be better tolerated than monotherapy.

- Although in other specialities large randomized controlled trials have been undertaken to show the benefits of combination immunosuppressive therapy over monotherapy (141,142,143), there are currently no randomized clinical trials making such comparisons (1).

- In practice, immunosuppressive therapy is usually prescribed in combination with oral prednisolone, the exception being interferon, where it is felt that combination therapy actually reduces its efficacy. If prednisolone is used in combination with interferon then the dose of prednisolone should be 10mg or less.

- In one case series combining methotrexate, ciclosporin and corticosteroid was shown to be beneficial (144).

- Triple therapy in the form of azathioprine, cyclosporine and corticosteroid appears to be more effective than monotherapy in the treatment of serpiginous choroidopathy (16).
Appendices

Appendix 1: Posterior Uveitis requiring early immunosuppressive therapy

Immunosuppression is recommended at the outset in a number of inflammatory eye diseases due to the chronicity and potentially poor prognosis that these conditions have if untreated. These conditions include ocular Behçet’s disease, birdshot retinochoroidopathy, multifocal choroiditis with panuveitis, serpiginous choroidopathy, Vogt-Koyangi-Harada disease and Sympathetic ophthalmitis.

A number of these specific conditions and their treatment guidelines are presented below. Where possible evidence for the efficacy of therapy is provided but due to the relative scarcity of some of these conditions the evidence base is limited. It is important to realise that many of these conditions have been treated under the blanket of sight-threatening uveits, the individual conditions being lost within the study’s statistics. In practice therefore where evidence doesn’t exist for specific disease-directed therapy then the therapy should be directed by the disease activity.

Behçet’s disease

Treatment guidelines

- The acute presentation should be controlled with high dose oral prednisolone (1 to 1.5 mg/kg/ day).

- Sight-threatening disease may warrant urgent high dose pulsed methylprednisolone of 1g per day for 3 days.

- Corticosteroids rarely prevent recurrences and are therefore used in combination with immunosuppressive agents \(^{145,146,147}\).

- Second line immunosuppresion should be started as soon as the diagnosis is confirmed.

- Treatment choice will depend on the individual patient circumstances and disease activity, both ocular and systemic.

- Chlorambucil and cyclophosphamide are effective in disease control in this condition \(^{148}\) (case series). Chlorambucil is usually commenced at 0.1 mg/kg/day \(^{149}\) and it may take up to 3 months to be effective.
Both ciclosporin and tacrolimus have been used widely for the treatment of uveitis in patients with Behçet’s disease \(^{(34,150,44,46)}\). Ciclosporin has been shown to be more effective than colchicine and cyclophosphamide in the treatment of ocular Behçet’s disease \(^{(151,52,36)}\).

Tacrolimus may be effective in patients with posterior uveitis refractory to ciclosporin \(^{(151)}\).

Ciclosporin and tacrolimus are not recommended in patients with central nervous system involvement as they may potentiate this \(^{(152)}\).

Azathioprine (dose of 2.5 mg per kg per day), has been shown to be effective (controlled trial), although 22% patients developed disease while on azathioprine \(^{(11)}\). Other groups have also reported favourable results \(^{(153)}\).

Biologic agents, specifically interferon \(\alpha\) and infliximab have recently been shown to be effective in the treatment of ocular Behcet’s disease \(^{(154,155,156,157,70,96)}\).

Interferon \(\alpha\) has been shown to produce remission, even in previously refractory disease \(^{(96)}\). In one study 92% patients with previously refractory disease responded to treatment. This effect appears to be prolonged with 40% remaining inactive 14 months after stopping treatment \(^{(96)}\).

The results of infliximab in ocular Behcet’s disease appear very promising. In one study, 24 of 25 patients had went immediate remission after a single treatment \(^{(70)}\) and remission was attained for over six months in 60% patients who had further dosing. Numerous other studies have shown favourable results for the use of infliximab in ocular Behcet’s disease \(^{(155,156,158,159)}\).

Infliximab should be used as an adjunctive therapy for refractory cases rather than as a first-line treatment \(^{(70,159)}\). Etanercept has not been shown to be effective \(^{(135)}\).

For refractory ocular disease biologic agents should be considered.

**Birdshot Retinochoroidopathy**

*Treatment guidelines*

- Ciclosporin may be effective in the treatment of birdshot retinochoroidopathy \(^{(36,160,161)}\) (case series, no controlled trials).
• Ciclosporin is more efficacious than corticosteroid therapy alone. Disease control was achieved in 85% patients compared to 46% respectively over a follow up period of between 24 and 48 months (160).

• Another case series has shown in individual patients ciclosporin, mycophenolate mofetil, azathioprine, methotrexate, and daclizumab to be effective (162).

Multifocal Choroiditis with panuveitis

_Treatment guidelines_

• Oral corticosteroids are effective in up to 50% patients (163) in treatment of cystoid macular oedema, dense vitritis or macular choroidal neovascular membrane (164).

• Consider immunosuppressive therapy, although there is no evidence at present to suggest the efficacy of this (165).

Serpiginous Choroidopathy

_Treatment guidelines_

• Ciclosporin in combination with oral prednisolone has been advocated for early treatment of this condition (166,167). (Case series, no controlled trials)

• Other authors have found this treatment ineffective (168) and some have recommended a triple therapy regimen (16,17) involving concurrent administration of prednisone, ciclosporin and azathioprine.

• Alkylating agents have been shown to be effective in an uncontrolled case series (169).
Appendix 2: Treatment of Inflammatory choroidal neovascularization (CNV)

Inflammatory choroidal neovascularization (CNV) is a comparatively rare complication of uveitis, occurring in 1.9% of patients with uveitis (12 of 648) in one large retrospective review \(^{(170)}\). However, inflammation is the third most common cause of choroidal neovascularization, after age related macular degeneration (AMD) and pathological myopia, and CNV of any aetiology can lead to severe visual loss \(^{(170)}\).

Inflammatory conditions with a high incidence of CNV include punctate inner choroidopathy (PIC), multifocal choroiditis with panuveitis, ocular histoplasmosis, serpiginous choroiditis, Vogt-Koyanagi-Harada disease and ocular toxoplasmosis. CNV can develop during an episode of active uveitis or in eyes with signs of previous uveitis but no active inflammation at the time of visual loss from the CNV. In a recent multicentre treatment study of inflammatory ocular neovascularization, 26% of eyes (26 of 99) had signs of active uveitis, whereas in 74% of eyes (73 of 99) the uveitis was inactive \(^{(171)}\).

The following treatments for inflammatory CNV have been used either as monotherapy or in combination: argon laser photocoagulation, surgical excision, corticosteroids (local injections or systemic), second line immunosuppressive agents, photodynamic therapy (PDT) and intravitreal anti-vascular endothelial growth factor (VEGF) agents.

Laser photocoagulation of subfoveal CNV causes immediate loss of vision and is therefore counterproductive. In cases of juxtafoveal or extrafoveal CNV, laser photocoagulation can reduce the risk of severe loss of vision; however, enlargement of the subsequent scar, and recurrence of neovascularization at the edge of the scar, often causes late visual loss \(^{(172)}\).

The Submacular Surgery Trials Research Group presented a randomized comparison of surgery vs observation for subfoveal CNV in eyes with ocular histoplasmosis or idiopathic cause \(^{(173)}\). At the 24-month follow-up, median BCVA was 6/75 (20/250) in the observation arm and 6/48 (20/160) in the surgery arm. CNV recurred in 58% of surgically treated eyes. Overall this study did not show a significant benefit for surgical excision.

A tapering course of high dose oral prednisolone monotherapy has been shown to stabilize or improve vision, in the short term, in the majority of patients with inflammatory CNV due to PIC or multifocal choroiditis \(^{(174)}\). However, some patients fail to respond to systemic immunosuppression \(^{(175)}\), or develop recurrences when immunosuppression is reduced.

The Verteporfin in Ocular Histoplasmosis Study treated 22 patients showing subfoveal CNV with an average of 3.9 sessions of PDT \(^{(176)}\). At the 24-month examination, the median
improvement was 1.2 lines. PDT has been used to reduce CNV activity and improve vision when initial treatment with systemic immunosuppression has failed. In a small study of 5 patients with CNV secondary to PIC, combination therapy with PDT and systemic corticosteroids, led to an average improvement of 9 ETDRS letters at 12 months follow up (177).

Multiple recent studies have reported a beneficial effect with intravitreal bevacizumab (Avastin) for inflammatory CNV (171,178). A large multicentre retrospective study of 99 eyes with inflammatory ocular neovascularization treated with intravitreal bevacizumab has recently reported 12 month and 24 month results (171). (6 out of 99 eyes had new vessels at the disc or elsewhere rather than CNV). Forty-one patients (44 eyes) were also taking oral, periocular, or intraocular corticosteroids or other immunosuppressive agents. Thirty-three eyes received 0.1ml (2.5 mg) of intravitreal bevacizumab and 66 eyes received 0.05 ml (1.25 mg). The majority of centres treated with single intravitreal injections as required, although some centres gave a monthly injection for 3 visits and then subsequent injections as required. Ninety-five eyes completed the 12-month follow-up with a mean gain of 2.5 lines and an average of 2.3 (+/- 1.8) bevacizumab injections (range 1–12). Best corrected visual acuity (BCVA) worsened in 14 eyes (14.7%). So far 27 eyes have completed the 24-month follow-up with a mean gain of 2.2 lines and an average of 3.6 (+/- 4.2) bevacizumab injections (range 1–21). BCVA worsened in 5 eyes (18.5%).

In summary, recent evidence suggests that anti-VEGF therapy provides superior results at 2 years than previous therapies. The most commonly used protocol is to give single injections of 0.05ml (1.25mg) of bevacizumab (Avastin) on an as required basis depending on activity of the CNV. If there is active uveitis then concurrent treatment with systemic steroids or other immunosuppressive agents should be included in the regime. If there is no active uveitis then monotherapy with intravitreal bevacizumab is reasonable. There have been no reports of intravitreal ranibizumab (Lucentis) therapy for inflammatory CNV, but on the basis of the wet AMD trials there is likely to be a similar treatment effect. For patients who decline, are not suitable for, or fail to respond to anti-VEGF therapy, PDT is a reasonable alternative. It must be remembered no drug treatments have been licensed for the treatment of inflammatory CNV and patients should be counseled to this effect. Many patients with inflammatory CNV are young women and all of the above drug treatments should be avoided, if possible, in pregnancy or when breast-feeding.
Appendix 3: Management of uveitis-associated glaucoma

Glaucoma in association with uveitis is relatively common. One retrospective study identified a prevalence of 22.3% in patients with chronic uveitis at 10 year follow up \(^{(179)}\). Glaucoma is commoner in specific uveitic syndromes including Fuchs’ heterochromic cyclitis \(^{(180)}\), sarcoidosis, herpes simplex keratouveitis \(^{(181)}\), and herpes zoster associated uveitis \(^{(181)}\).

Most of the ocular hypotensive agents can be used for the treatment of uveitis-associated glaucoma, in some patients topical carbonic anhydrase inhibitors appear be very effective \(^{(182)}\). Prostaglandin analogues are relatively safe and appear to increase the uveitis activity in only a minority of patients \(^{(183,184,185)}\). They should however be used with caution in patients with a history of cystoid macular oedema \(^{(186,187,188)}\) or herpetic disease \(^{(189,190)}\). Cyclodiode laser has a high rate of hypotony in uveitis (19\%) \(^{(191)}\).

Laser iridotomy may provide temporary relief in secondary angle closure glaucoma, although longer term failure rate is relatively high due to on-going inflammation. Surgical iridectomy may be necessary. Filtration surgery is appropriate if intraocular pressure remains high despite maximum medical therapy \(^{(192,193,194,195)}\).

Ideally, ocular inflammation should be controlled prior to any surgery. Anti-proliferative agents should be used with trabeculectomy. Good results have been obtained with glaucoma drainage implant devices \(^{(196,197,198,199)}\).
Appendix 4: Management of uveitis in the perioperative period

Ideally ocular surgery should only be performed when the inflammation has been controlled for a period of at least 3 months. Control may mean 1+ cells in the anterior chamber. Ensure intraocular pressure is adequately controlled prior to surgery.

Although most uveitis specialists would agree that the use of steroid perioperatively is efficacious, there currently doesn’t appear to be any consensus as to what this should entail. Whether this should be oral or intravenous, pre, peri, or post-operative and if oral steroids should be continued for a prolonged post-operative period.

One study involving 40 patients found that a two week course of oral prednisolone prior to surgery resulted in less blood aqueous barrier break down than a single dose of intravenous methylprednisolone in the perioperative period (200).

One author recommends 2 hourly steroid drops for the 2 weeks preceeding surgery for patients with relatively inactive anterior segment disease. In patients with chronic inflammation whether or not they are already on systemic immunosuppression, he recommends intensive topical corticosteroids as above plus a pulse of iv methylprednisolone 500mg in the immediate pre-operative period. Post-operatively 2 hourly topical corticosteroids for a minimum of 4 weeks before considering a slow reduction. Early regular review is important (201).

Another opinion is that in general old anterior uveitis that has been quiet for years requires no treatment. If quiet posterior/intermediate uveitis off immunosuppression, give one dose of 500mg IV methylprednisolone intraoperatively. Patients with uveitis on immunosuppression give 3 doses of IV methylprednisolone 500mg day before, day of and day after surgery.
Appendix 5: Immunosuppression during pregnancy

As the highest incidence of uveitis occurs in the working population\(^{(202)}\), a large proportion of women with sight-threatening uveitis will be of child-bearing age. Conception, pregnancy, foetal development, and lactation may all be affected by the medications used to treat inflammatory eye disease. It is important that the physician caring for these women is aware of the potential side effects of these treatments. The risk of impaired fertility and congenital abnormality should be explained to any woman of childbearing age prior to commencing immunosuppressive therapy. Effective contraceptive measures should be used by all patients on immunosuppressive therapy.

Pregnancy itself may have an immunosuppressive effect and it may be possible to lower immunosuppression without relapse during this period. If immunosuppression is required during pregnancy then it should be explained to the mother that although there can be no guarantee that the foetus will be unharmed the risk to the baby is probably small. It is also important to remember immunosuppressive agents may cause infertility and potentially teratogenic in men\(^{(203,204)}\).

Azathioprine and ciclosporin appear to be safe for men wishing to father children on therapy\(^{(205)}\). Methotrexate may cause reversible sterility in men\(^{(206,207)}\).

The U.S Food and Drug Administration (FDA) utilises a rating system for ranking pregnancy risks associated with medications as outlined below.

<table>
<thead>
<tr>
<th>FDA pregnancy category</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well controlled studies have failed to demonstrate a risk to the foetus.</td>
</tr>
<tr>
<td>B</td>
<td>Lack of well controlled studies in human but animal studies so far demonstrate no risks to the foetus.</td>
</tr>
<tr>
<td>C</td>
<td>Animal studies had shown adverse outcome on the foetus OR animal studies are lacking and no well controlled human studies exist; hence foetal risk cannot be ruled out.</td>
</tr>
<tr>
<td>D</td>
<td>Evidence of human foetal risk but potential benefits may warrant the use of this medication in pregnant women.</td>
</tr>
<tr>
<td>X</td>
<td>Use contraindicated as studies in animals, human or both have shown foetal abnormalities and the foetal risk clearly outweigh the benefits of its usage in pregnant women.</td>
</tr>
</tbody>
</table>
**NSAIDS**

- Can be used during pregnancy until the last 6 weeks of gestation \(^{(208,209)}\).
- Felt to be safe while breast feeding \(^{(210,211)}\).

**Prednisolone**

- FDA pregnancy category B.
- Increased risk of cleft lip and cleft palate \(^{(212)}\).
- Important to limit to the lowest effective dosage or if possible, avoid during the first trimester while hard palate is forming.
- After the first trimester, can be used for sight-threatening disease.
- Require “stress doses” of hydrocortisone for any emergency surgery, caesarean section or prolonged labour.
- Monitor babies in the neonatal periods for infection or possible adrenal insufficiency \(^{(213)}\).
- Not contraindicated in breast feeding \(^{(214)}\).
- Avoid breast feeding for 4 hours immediately following maternal ingestion will reduce the amount of glucocorticoid in the milk \(^{(214)}\).

**Antimetabolites**

**Azathioprine**

- FDA pregnancy category D.
- No significant teratogenic effect on the foetus \(^{(215)}\).
- Prematurity, foetal growth restriction, adrenal hypoplasia and reduced serum immunoglobulin levels have been reported \(^{(216,217,218)}\).
- Transient neonatal leucopenia and thrombocytopenia. Reduction of dosage at 32 weeks’ gestation may decrease the risk.
- Felt to be safe in breast feeding (219,220,221,222).

Methotrexate

- FDA pregnancy category X.
- Teratogenic and therefore absolutely contraindicated in pregnancy (223,224,225)
- Reversible sterility in males.
- Discontinue at least 3 months prior to conception (214).
- If conception occurs while on treatment, methotrexate should be stopped immediately and patient given folic acid to reduce risk of neural tube defects.
- Contraindicated in breast feeding.

Mycophenolate mofetil

- FDA pregnancy category D.
- Associated with congenital malformations and spontaneous abortions (226,227).
- Contraindicated in pregnancy.
- A negative pregnancy test is essential prior to commencement of therapy.
- FDA recommends the use of 2 reliable forms of contraception 4 weeks prior to treatment, during treatment and 6 weeks after discontinuation of treatment.
- Contraindicated in breastfeeding.

T-cell inhibitors/Calcineurin inhibitors

Ciclosporin

- FDA pregnancy category C.
- No specific pattern of congenital malformations detected (205).
- No significant increased risk of foetal malformations (228).
- Acceptable immunosuppressant in pregnancy (229).
The American Association of Paediatrics warns against breast feeding while on treatment.

Tacrolimus

- FDA pregnancy category C.
- Small increase in foetal malformations but no consistent pattern (230).
- Incidence of gestational diabetes and transient neonatal hyperkalaemia reported (231).
- Transient neonatal immunosuppression.
- Safe to be used during pregnancy at therapeutic level (232).
- Secreted in breast milk and no adequate studies to determine the safety of breast feeding, therefore breast feeding not recommended.

Alkylating agents

Cyclophosphamide

- FDA pregnancy category D.
- Teratogenic therefore contraindicated in pregnancy (233).
- Discontinue at least 3 months prior to conception.
- May result in primary ovarian failure in over 70% patients (53,56).
- Cryopreservation of oocytes should be considered.
- Contraindicated in breast feeding (234).

Biologics

Knowledge of the safety of these agents in human pregnancy is very limited and therefore only consider these agents if benefits outweigh the potential risks.

Infliximab

- FDA pregnancy category B.
• Felt to be safe in pregnancy based on limited data.

• No increased risk of teratogenicity (TREAT registry and Infliximab Safety Database) (235).

• Should be stopped during the 3rd trimester when transplacental transfer is at its greatest (237).

• Reports of decreased sperm motility and morphology (235).

• Infliximab is undetectable in breast milk of nursing mother, felt to be safe in breast feeding (236,237).

Adalimumab

• FDA pregnancy category B.

• Limited data but the OTIS registry and published case reports do not suggest an increased risk for adverse pregnancy outcomes during the 1st trimester exposure (238,239,240).

• Limited data on breast feeding, but case report shows no adverse effects to infant whose nursing mother was on medication during pregnancy and post delivery (239).

Rituximab

• FDA pregnancy category C.

• Few case reports show low levels of B lymphocytes during the first 6 months of life, but no reported adverse pregnancy outcome (241).

• Should only be used if benefits outweigh risks.

• Limited data on breast feeding, therefore breast feeding not recommended.

Interferon alpha

• FDA pregnancy category C.

• Limited human case reports which demonstrate no increased risk of teratogenicity (242).
• Reported cases of neonatal lupus and intrauterine growth restriction \(^{(243)}\).

• Compatible with breast feeding \(^{(214)}\).

**Campath**

• FDA pregnancy category C.

• Contraindicated in pregnancy.

• FDA suggests that women and men should use effective birth control during treatment with Campath and for 6 months after stopping treatment.

• FDA warns against breast feeding during treatment and 3 months after stopping treatment.

**Anakinra**

• FDA pregnancy category B.

• Animal studies show no evidence of foetal harms but no controlled data in human pregnancy, therefore only recommended when benefits outweigh risks.
Appendix 6: Paediatric guidelines


This document gives guidance on the screening for Juvenile Idiopathic Arthritis associated Chronic Anterior Uveitis (JIA CAU), and the management of JIA CAU and idiopathic paediatric uveitis (IPU).

Very rarely uveitis occurs in children with other disease associations, such as Behcet’s disease, sarcoid, inflammatory bowel disease, and other rare causes. The management of these conditions is poorly evidence based, and is best done by experts with the greatest possible knowledge of these conditions, but it is expected the management should adhere to the principles of good uveitis and paediatric care and care pathways inherent in this document.

Rationale

Asymptomatic CAU associated with JIA has long been recognised as an important cause of visual loss in childhood (244,245) with high levels of complications compared to other forms of anterior uveitis. The incidence of bilateral disease is between 67-85% (246,247,248,249), and complications are reported in 20-40% of children at presentation and steadily accumulate over the first two decades of life, especially in those with persistently active disease (247,248,249,250,251,252). In order to reduce the ocular complications early, regular screening by slit lamp examination has been recommended for many years, but the incidence of a poor visual outcome remains high (16-38%) (246,247,253,254). The current screening advice (255), albeit based on limited evidence is the basis for the current screening guidance in this document, and is in line with other guidance (256). It has not been possible to demonstrate unequivocally that screening programmes have reduced the frequency of either complications at presentation, or long-term visual loss (257,258,259), but it is becoming clearer that early diagnosis, and early immunosuppression with an aggressive approach to removal of inflammation are important (1, 246, 251, 253, 260, 261, 262, 263, 264, 265, 266). Some medication choices may be important risk factors for developing uveitis (61, 57, 134, 135, 136, 137, 138, 139, 140, 267, 268, 269, 270). Other risk factors are not yet clearly elucidated, poorly controlled uveitis and chronicity of inflammation themselves presents a significant risk of cataract and glaucoma in 10- 50% of patients in many series, and are increasingly common with longer follow-up (47, 251, 253, 261, 263).
Persistent ongoing application of topical steroid is also associated with cataract and glaucoma. There is growing evidence for the value of early introduction of disease modifying anti-rheumatic therapies (DMARD), particularly methotrexate and mycophenolate, and for early introduction of biologic therapies, namely infliximab or adalimumab. The majority of children with uveitis have JIA, and paediatric rheumatology services in Scotland already manage and prescribe these drugs for the other organ manifestations of JIA. This includes access to specialist paediatric nurses with a remit to manage and educate about these drugs for children and parents.

These guidelines are based on an agreement between SPARN and the Uveitis Network that joint working between these teams is a useful way forward, and that paediatric rheumatology services are happy to support the use of these complex drugs in all children with uveitis, including those who do not have JIA, including providing paediatric nurse specialist support for ophthalmology services. Whilst the networks accept this guidance is not fully evidence based they are current best practise and are adopted by both networks until more definitive, evidence based guideline is developed.

**Core principles:**

**Communication**

In each region key personnel caring for paediatric uveitis and providing screening should be clearly identified through both SPARN and the uveitis network.

- For eye screening identified paediatric ophthalmologists would usually be the key lead for each region.

- The management of paediatric uveitis is expected to be undertaken by an ophthalmologist who has expertise in the management of uveitis, but who should be properly supported by paediatric services, including specialist paediatric nursing support in line with current standards of care. This will usually be through the local paediatric rheumatology service. In some regions the same individuals may provide both screening and uveitis care. It is essential that all children are seen in an appropriate paediatric environment supported by appropriately trained paediatric staff, even where occasional component of care takes place unavoidably in an adult setting. In many regions paediatric
ophthalmologists may do the screening, day to day uveitis care, liasing with uveitis experts as required.

- Rapid, consistent and complete two way communication between the ophthalmologist and the paediatric rheumatologist / paediatric rheumatology services is key to an effective screening service. Both services will need to have good knowledge of the screening guidelines, with awareness of decisions that alter the screening requirements for an individual patient.

- Uveitis care requires the same high level of communication.

- Planned transition to adult services aims to involve both adult rheumatology and ophthalmology services (285).

- The following is considered a core set of information to be included in all correspondence, or immediately accessible from shared clinical notes, from both ophthalmologists and rheumatologist includes:

  - Next planned appointment
  - All systemic and topical medication, whether or not given for eyes. Systemic treatment given for JIA or other systemic disease association should be recorded in the ophthalmology notes whether or not it is given for eye complications.
  - All changes in systemic and topical medication particularly cessation of treatments.
  - Ophthalmologists should record at each visit in the clinical notes, and where the clinical notes are not shared with the rheumatology team, communicate the following to the rheumatology team in numerical values, vague or descriptive terms should be avoided: visual acuity, the presence and absence of uveitis, and the severity of uveitis using the SUN criteria (289) recording the actual number of cells using a 1mm circular beam set at 45 degrees, bright light and high magnification. Flare should be recorded. For the measurement of intraocular pressures proxymetacaine should be used and a gentle examination performed. Goldman is preferred (290). This may be difficult in the very young and the failure to record pressures should be documented. The appearance of the optic disc, and the macular if the vision
Those providing screening should be able to provide rapid access to examination under anaesthetic where examination is difficult in line with current standards of care \(^{255}\). To minimise the number of general anaesthetics ideally a shared general anaesthetic with rheumatology services providing joint injections wherever possible.

Rheumatologists should urgently highlight to the ophthalmologist any changes in medication or diagnostic details that materially alter the screening programme required \(^{255}\). The paediatric rheumatologist should be aware of the implication to the management of the eyes that changes in treatment for other aspects of JIA care will make, and where this is unclear should make this decision in conjunction with the ophthalmologist.

It should be avoided that ophthalmologists and rheumatologists are both prescribing disease modifying drugs (DMARDS) or biologics for different aspects of JIA care. The lead clinician for prescribing should be formally identified, and should normally be the paediatric rheumatologist unless otherwise agreed in writing, and appropriate paediatric nursing support provided.

All communication should be sent within two weeks of clinical review in line with current guidance.

**Uveitis Screening**

JIA CAU Screening guidelines have been produced jointly by BSPAR and the RCPOphth in 2006 \(^{255}\) (appendix 7). Whilst these are not fully evidence based they are current best practise and are adopted by both networks until more definitive, evidence based guideline is developed. Both rheumatology and ophthalmology services should be aware of these guidelines, and ensure changes in diagnosis or management are effectively communicated to the other services to facilitate adherence to these guideline. In Scotland geographical issues are not an acceptable barrier to meeting screening needs. Where screening is provided by training ophthalmology doctors they should be aware of their responsibilities under the screening guidelines, and should not deviate from the screening guideline unless this is a consultant led decision and communicated to the paediatric rheumatology team.
Management of JIA CAU and IPU

The management of paediatric uveitis differs from adult uveitis in that an earlier and more aggressive approach to the introduction of DMARDS and biologics is found \(^{(47, 57, 58, 59, 60, 62, 74, 75, 76, 140, 259, 269, 271, 272, 273, 276, 277, 278, 280, 281, 282, 283, 284)}\). The algorithm demonstrates the key pathways agreed includes time lines for rapid progression through treatment regimes but acknowledges the lack of evidence base for this \(^{(1, 246, 251, 253, 261, 262, 263, 264, 265, 266, 271)}\). Key red flags for concern are considered to be:

- Persistent requirement of topical steroids after 4 months, with or without a DMARD
- Presence of macular oedema or posterior involvement.

**Detailed discussion points from the algorithm:**

Differences between the management of uveitis in adults and children include:

1) Steroids

   a. In children a very cautious approach to even low dose topical steroid is usually taken (because of the risk of glaucoma and cataract) \(^{(135, 246, 251, 253, 261, 263, 264, 291, 292)}\). In severe inflammation where high dose frequent application of topical prednisolone is required earlier introduction of DMARDS or more rapid progression through the algorithm is appropriate.

   b. Once control is achieved it is expected that low dose topical and systemic steroid will be withdrawn before weaning off the second line agent. The second line agents are usually given for a longer time period than is usual in adult uveitis, and may be required indefinitely.

2) Biologics: In children progress to a biologic agent is usual after the first second-line agent has failed.

**Paediatric Nursing Care**

Children receiving DMARDS or biologic agents are expected to have

- Access to identified trained paediatric nursing care with expertise in the management of these drugs including skills in education, monitoring and training of families appropriate for the care of children \(^{(286, 287, 288)}\).
The paediatric nurse has a key role in coordinating both the PR and ophthalmology teams. One team (usually paediatric rheumatology because of their role in prescribing immnosuppression for other organ involvement) is formally responsible for the monitoring and prescribing of these drugs.

**Drug Monitoring**

DMARDs and biologics are expected to be formally monitored. The BSPAR and RCN guidelines on the use of these drugs, including doses and monitoring guidelines, are appropriate guidance to follow for these patients (287, 288, 293).

**Choice of DMARD**

The usual choices of DMARD would be methotrexate or mycophenolate (259, 276, 277, 278, 279, 280, 281). The rationale for the choice may be influenced by the other features of JIA, such as joint involvement where methotrexate is usually the preferred choice, mycophenolate has poorer efficacy for synovitis (281), whereas where eye features predominate mycophenolate may be the preferred choice. Whichever is chosen first if the response to DMARD treatment is unacceptable a biologic would usually be the next choice rather than the other DMARD. Methotrexate is also used as the first choice in conjunction with the biologic agents infliximab and adalimumab to reduce allergic reactions, and may improve the efficacy of these drugs for JIA and uveitis (57, 61, 269) although adalimumab is licensed for use on it’s own.

**Choice of Biologic**

The current first choices for which there is evidence of efficacy are of an anti-TNF. The choice is between infliximab (75, 76, 282, 283, 284) or adalimumab (57, 58, 59, 60, 61, 62, 76, 269, 282, 283). There is a current lack of evidence base to guide choice between either of these, and practical or patient related issues around administration often influence the choice. The licences suggest these should be given with a DMARD, usually methotrexate. Where the response to one is inadequate or significant side-effects occur the other may be tried. The anti-TNF etanercept should be avoided in uveitis because of lack of efficacy and some suggestion that it might worsen inflammation in uveitis (57, 61, 135, 136, 137, 138, 139, 140, 252, 267, 268, 269, 270).

**Macular oedema**

The assessment of macular oedema is difficult in children. If the vision is reduced it is appropriate to assume that macular oedema is present, until proven otherwise. Initially oral steroid can be given, but in severe cases intravenous pulsed methylprednisolone may be
most appropriate. Concurrent commencement or escalation of DMARDs or biologics is appropriate.

**Time lines for moving through the algorithm**

These are the longest time periods felt acceptable before moving through the algorithm. Where severe disease persists, vision is threatened, glaucoma has developed, or unacceptable doses of topical or systemic steroids are required it is appropriate to move more rapidly to the next stage of the algorithm.
JIA associated chronic anterior uveitis or idiopathic paediatric uveitis

Introduce corticosteroid treatment

**Anterior Chamber involvement only**
- Topical prednisolone

Wean topical prednisolone to zero over 4 months.
- If activity recurs or is not controlled add DMARD

**DMARD**
- Usually methotrexate or mycophenolate

Failure to wean topical or systemic corticosteroids to zero over 12 weeks despite optimisation of dose and route of DMARD progress to biologic therapies

**BIOLOGICS**
- Usually adalimumab or infliximab

**Macular oedema**
- Start steroids and a DMARD +/- topical steroids

DMARD and biologic use requires the support of a trained paediatric nurse

Communication between named personnel in rheumatology and ophthalmology services

**Revised September 2010**
Appendix 7: Guidelines for Screening for Uveitis in Juvenile Idiopathic Arthritis (JIA)

Produced jointly by BSPAR and the RCPOphth 2006

Aim of the screening programme

To reduce the incidence of visual impairment among children and young people with juvenile idiopathic arthritis (JIA) by early detection through screening allowing for early intervention.

Background

The prevalence of uveitis in JIA overall is approximately 8-30%, but in young oligoarticular onset group (ie arthritis in which up to 4 joints are involved) it may be as high as 45-57%. The annual incidence of JIA in the UK is 1:10,000 with a prevalence of 1:1000. The type of arthritis and age at onset dictates the risk of developing uveitis. Only the highest risk groups are included in the regular screening recommendations below. However, late onset of first uveitis can occur even in young adults and cases have been reported in systemic JIA so it is important to make clinical referrals for ophthalmology assessment in patients where there are clinical concerns even if the patient is not specifically covered by these screening guidelines.

The uveitis in JIA is asymptomatic and therefore screening by slit-lamp is essential for diagnosis. Visual impairment arises mainly from complications of the uveitis including cataract, glaucoma, macular oedema and hypotony. Once complications have arisen they are often irreversible. Early detection and treatment can prevent the development of complications and can prevent permanent visual impairment. These complications are more frequent and more severe in younger children and are often asymptomatic. The most frequent cause of avoidable morbidity remains missed or inadequate examinations in the first year of disease and all efforts must be made to achieve early and thorough early examinations.

Principles

1) Initial screening examination Uveitis often starts soon after onset of arthritis but may also start before the arthritis. The initial screening examination is therefore a clinical priority and should occur as soon as possible and no later than 6 weeks from referral. (Reference the BSPAR Standards of Care.)

2) Symptomatic patients or patients suspected of cataracts or synechiae should be seen within a week of referral.
3) **Difficult examinations** If the patient is uncooperative at initial screening or for an urgent symptomatic examination in a young child an examination under anaesthetic should be considered.

4) **Parent information** Parents and carers of children with JIA need to be fully informed about the possibility of uveitis and that this is usually an asymptomatic condition until complications arise. They need to be told that a high street optician assessment is not an adequate examination to exclude uveitis. They should be instructed to seek medical assessment **urgently** if their child develops visual symptoms or signs. These include red eyes, photophobia, abnormal pupils, corneal clouding, or visual impairment. In younger children this may be manifest by unusual blinking, eye rubbing, visual inattention or preferential attention on auditory signals, or a new onset squint.

5) **Missed appointments** Parents and carers must be fully informed about the method of screening and the need to attend for specific uveitis screening examinations on a regular basis. Arrangements need to be in place to give priority to rebooking of any missed appointments in this group with a system of contacting non-attenders.

6) **Training** Ophthalmologists and other health professionals carrying out uveitis screening should be appropriately trained and experienced. They should have facilities to audit the outcomes of their screening program.

7) **Older patients** Older teenage patients need to be told to return quickly should they become symptomatic. If there is concern about their reliability, e.g. in developmental delay, then they should be considered for longer term less frequent screening. After discharge from the screening programme an annual check by an optometrist is a useful adjunct to self-monitoring for symptoms.

8) **On stopping immunosuppressant treatment such as Methotrexate**

Patients who have been treated with methotrexate for their arthritis may not have developed uveitis due to drug suppression. However after methotrexate is stopped uveitis may flare. Screening should therefore restart at 2 monthly intervals after stopping Methotrexate or any other immunosuppressant therapy during the period of maximum risk for 6 months before reverting to the previous screening arrangements.

**Scottish addition:** Where a child is started on etanercept alone in the absence of methotrexate the ophthalmologist should be aware of the possible increased risk in
developing uveitis, or worsening severity of pre-existing uveitis and return to 2 monthly screening for 6 months.

Specific Screening Schedules

These schedules are the best recommendation possible with current data and are focused on the highest risk groups.

First screening within 6 weeks of referral

Two monthly intervals from onset of arthritis for 6 months

*Scottish simplification: Then 3-4 monthly screening until their 12th birthday.*

Older patients presenting for the first time after the age of 11, should undergo one year of screening.

*When a patient is discharged* from the regular screening program it is vital to stress to them that they and the family are now deemed able to detect any changes in their vision which may signify a new onset or flare of uveitis. It does NOT mean that their risk of uveitis has gone completely. A tip for family self monitoring is to remind the young person to check his or her vision uniocularly- eg by reading small print with each eye once a week.

Monitoring may need to continue indefinitely if there are other reasons such as learning difficulties or treatment non-compliance when the young person may be unable to detect a change in vision or unwilling to seek re-referral.

Systemic onset JIA and definite rheumatoid factor positive polyarticular JIA patients are at very low risk of uveitis. However, there may be delay in being certain about the diagnosis or exact category of JIA, and overlaps between groups do occur. For this reason an initial screening examination may be indicated.

*Some important facts about uveitis in JIA*

Boys do get severe uveitis

ANA negative patients get significant uveitis

Uveitis does occur in young patients with psoriatic arthritis

Patients with polyarticular JIA do get uveitis.
Patients with enthesitis related arthritis may get chronic as well as acute iritis.

Scottish modification Nov 2009
Appendix 8: Membership of NMCN treatment guideline development group and stakeholders group

Uveitis national managed clinical network treatment guideline development group

Dr Graeme Williams Consultant Ophthalmic Physician, Gartnavel General Hospital, Glasgow
(Chair)

Dr John Olson Consultant Ophthalmic Physician, Aberdeen Royal Infirmary
(NMCN Lead Clinician)

Ms Frances Philip, MCN Support Manager, Woolmanhill Hospital, Aberdeen
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Dr Nicholas Fluck Consultant Nephrologist, Aberdeen Royal Infirmary

Dr Janet Gardner-Medwin Senior Lecturer in Paediatric Rheumatology, Royal Hospital for Sick Children, Glasgow

Dr Catherine Guly Medical Ophthalmology Specialty Registrar, Aberdeen Royal Infirmary

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Uveitis national managed clinical network stakeholders group

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Dr John Olson Consultant Ophthalmic Physician, Aberdeen Royal Infirmary
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Mrs Lorraine Urquhart, Managed Clinical Network Manager, Woolmanhill Hospital, Aberdeen
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Dr Neil Basu Honorary Consultant Rheumatologist, Aberdeen Royal Infirmary

Mr Donald Cameron Independent Optometrist, Optometry Scotland

Professor Bal Dhillon Consultant Ophthalmologist, Princess Alexandra Eye Pavilion, Edinburgh

Dr Suzanne Brannan Consultant Ophthalmologist, Queen Margaret Hospital, Dunfermline

Dr Brian Fleck Consultant Ophthalmologist, Princess Alexandra Eye Pavilion, Edinburgh

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Mr Allan Jones Edinburgh & The Lothians Operations Manager, RNIB Scotland

Dr Lucia Kuffova Senior Lecturer in Ophthalmology, University of Aberdeen

Mr John Legg Director of RNIB Scotland

Mrs Ali McAllister Project Office Standards Development Team, NHS Quality Improvement Scotland

Mrs Gill Ogden Uveitis Nurse Specialist, Queen Margaret Hospital, Dunfermline
Dr Sheila Paterson-Brown Associate Specialist in Ophthalmology, Princess Alexandra Eye Pavilion, Edinburgh

Miss Vanessa Sandison Clinic Nurse Manager, Aberdeen Royal Infirmary

Dr Angus Scott Consultant Ophthalmologist, Stirling Royal Infirmary

Miss Caroline Smith Patient Representative

Mrs Fiona Smith Patient Representative

Mr James Stephen Programme Manager, National Services Division, NHS National Services Scotland

Dr Mohan Varikkara Consultant Ophthalmologist, Ayr Hospital

Dr Meena Virdi Consultant Ophthalmologist, Hairmyres Hospital, East Kilbride

Mrs Carri-Anne Walker Director of Fundraising, Uveitis Information Group

Dr Graeme Williams Consultant Ophthalmic Physician, Gartnavel General Hospital, Glasgow

Dr Imran Zaheer Consultant Ophthalmologist, Dumfries Infirmary
Appendix 9: Evidence Base


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293. BSPAR Clinical Guidelines for DMARDs and Biologics

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