Brighton and Sussex University Hospitals NHS Trust

IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

SUSSEX EYE HOSPITAL

Basic Guide

Abstract

Quick guide of immunosuppressive therapy in a busy uveitis clinic

Mr Edward Hughes
Dr Gabriela Ortiz Nieva
Dr Kelsey M. Jordan
S.S.Pharm Ann Marie Goacher

TABLE OF CONTENTS

SEH

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

OBJECTIVE

Corticosteroid and immunosuppressant treatments carry the risk of serious and sometimes life-threatening adverse effects.

The purpose of this booklet is to provide guidance on the safe use of immunosuppressive treatment in the uveitis clinic.

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

OVERVIEW

UVEITIS: INTERMEDIATE • POSTERIOR • PANUVEITIS

Posterior Segment Intraocular Inflammatory (PSII) conditions are sight-threatening, organ-specific autoimmune diseases; 50% are linked to systemic multisystem diseases, such as Sarcoidosis, Behcets Disease and Multiple Sclerosis. They are generally not responsive to topical treatment.

Prior to intensive treatment, over 50% of affected patients were severely visually handicapped. PSII accounts for over 10% of those registered blinds in the USA and is a leading cause of blindness in the working age population with its obvious socio-economic implications.

Vision can now be saved in the vast majority of patients with appropriate and early use of immunosuppressive and corticosteroid treatments.

CORTICOSTEROIDS (topical, intravitreal, periocular or systemic) have been the mainstay of therapy for ocular inflammation. However, in some patients' systemic corticosteroids are insufficient to control disease and adjuvant immunosuppression is required. Corticosteroids have predictable side effects in the short and long term that are well documented; consideration and monitoring for these is essential to safe and effective uveitis management.

IMMUNOSUPPRESIVE DRUGS are often required in the management of ocular inflammatory disease, alone or in combination, when corticosteroids need to be spared because of their short- and long-term side effects.

BIOLOGIC THERAPIES are increasingly used for ocular inflammation, in particular TNF inhibitors (e.g. Adalimumab) for uveitis and anti-CD20 (Rituximab) for scleritis.

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

GENERAL MONITORING

Baseline assessment of patient prior to commencement of immunosuppression:

- Weight
- Blood pressure
- Urinalysis
- Appropriate blood tests (see under individual drug sections)
- Discussion of potential risks and benefits
- Patient information sheets provided
- Drug specific investigations required e.g. CXR pre TNF-i
- Adverse effects discussed

FLOW CHARTS AND DATA SHEETS

Ocular Data sheets should be updated at each clinic visit, and it should include:

Immunosuppressive agent(s) and dose	Blood pressure, weight and urinalysis
Allergies/adverse effects	Clinical evaluation
And where relevant:	
Key blood results, incl drug levels (CyA and Tacrolimus)	Bone density (those on prednisolone)
Pregnancy planning	
Varicella history (on commencing treatment)	Other medications taken/interactions

OSTEOPOROSIS RISK ASSESSMENT

Risk of osteoporosis must be assessed prior to commencing oral steroids and following > 3 months treatment.
(FRAX questionnaire - p.9)

RISK FACTORS:

Low body weight. BMI< 19kg/m2	Fractures (prior osteoporotic fracture, maternal hip fracture)
Menopause	Falling
Alcohol	Smoking
Age >75 y/o	Medications: Corticosteroids, anticonvulsants, proton bump inhibitors, breast cancer drugs, prostate cancer drugs.

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

WATCH

- Document blood results each visit

GENERAL RISKS

- Infections. – Warn patients about infection symptoms.
- Cancer. – e.g. skin cancer.
- Avoid exposure to strong sunlight as it increases susceptibility to skin cancer and use suncream.

BLOOD TESTS

DRUG	TEST REQUIRED	
Prednisolone	Blood pressure, weight, urinalysis (glycosuria). Lipid levels. Dexa bone scan	
Azathioprine	TPMT (prior starting) FBC, U&E, LFTs	2,4,8 weeks after commencing or increasing dose, then 2 monthly. These intervals may change if results are abnormal
Ciclosporin A	FBC, U&E, LFTs Cyclosporine levels (12-14 hrs post-dose)	
Methotrexate	FBC, U&E, LFTs	
Mycophenolate	FBC, U&E, LFTs	
Tacrolimus	FBC, U&E, LFTs, Lipid profile, Tacrolimus levels. (12-14 hrs post-dose)	

VACCINATIONS

All patients on steroid and immunosuppressant drugs are advised to have the annual flu jab, and a one-off dose of the pneumococcal polysaccharide vaccine (PPV23), ideally 4-6 weeks before starting immunosuppressants. Immunosuppressed patients should not receive live vaccines.

ADVICE ABOUT CONCURRENT ILLNESS

All patients are advised to inform their doctor about any concurrent illnesses and discuss possibility about suspending treatment until recovered from it (e.g. infection). Blood tests must be checked regularly, including WBC.

SEH

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

IMPORTANT

All patient under immunosuppressive therapy should have:

- Enquiry about previous chicken pox
- Immunity to VZ checked (Ig levels) if uncertain VZV history
- Warning about risks of chickenpox and modes of transmission

VARICELLA PROPHYLAXIS IN IMMUNOSUPPRESSED PATIENTS

Varicella (chickenpox) is an acute and highly infectious disease transmitted by personal contact, droplet spread, and indirectly by fomites. The incubation period is between two and three weeks. For immunosuppressed individuals the risk is greatly increased for severe, disseminated or hemorrhagic varicella.

The department of Health recommends the use of varicella zoster Ig (VZIG) prophylaxis for "individuals who fulfil ALL of the following 3 criteria:

- A clinical condition which increases the risk of severe varicella; this includes immunosuppressed patients, neonates, and pregnant women.
- No antibodies to varicella-zoster virus
- Significant exposure to chickenpox or herpes zoster

For the purposes of the **uveitis clinic**, the threshold level of immunosuppression at which VZIG should be considered in a non-immune patient exposed to the virus is:

a) Children who within the previous 3 months have received prednisolone orally at a daily dose of 2 mg/kg for at least one week, or 1 mg/kg/day for one month.
b) Adults who have received a dose of oral prednisolone of 40 mg/day or more for more than one week in the previous 3 months.
c) Patients on lower doses of steroids, given in combination with other immunosuppressants/cytotoxic drugs.

CAUTIONS

If patients have a bleeding disorder and need VZIG, seek expert advice.

VARICELLA PROPHYLAXIS IN IMMUNOSUPPRESSED PATIENTS

Administration:

VZIG is given by intramuscular injection, no later than ten days after exposure. It must not be given intravenously.

VZIG is expensive and must be obtained from the public health laboratory after discussion with the duty microbiologist. More information can be found at "Varicella zoster immunoglobulin clinical record form "
https://www.gov.uk/government/publications/varicella-zoster-immunoglobulin
BSUH VZIG request form found here.

Dosage:

- 0-5 years: 250 mg
- 6-10 years:500 mg
- 11-14 years: 750 mg
- >15 years 1000 mg Factors in determining significant exposure

i.e. exposures with greater risks:

- Timing: 48 hrs before rash until all lesion crusted
- Type of case: chicken pox and exposed shingles lesion or any VZ in an immune-compromised individual
- Type of contact: obviously close physical contact, but also contact in same room, face to face contact (e.g. conversation)

Further reading: Department of Health "Immunisation against Infectious Disease" chapter 34. http://www.doh.gov.uk/

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- Diabetes
- Obesity
- Osteoporosis
- Concurrent infection or previous TB
- Peptic ulceration

Monitoring

- Blood pressure
- Weight
- Urinalysis (esp. glycosuria)
- Annual lipid levels
- DEXA scan

PREDNISOLONE

First-line therapy for most patients with sight – threatening or severe ocular inflammation.

Dosage

- Maximum adult oral dose 60-80 mg/day, but typically 1mg/kg initial dose. These high doses should be weaned carefully (e.g. 5-10 mg/week) to a maintenance dose.
- Maintenance dose (adult) <10 mg/day. After reaching stability with maintenance dose, the weaning dose will depend on the patient response while reducing the intake (e.g. by 1-2.5mg) which can take weeks or months.
- Abrupt discontinuation can lead to Addisonian crisis

Important side effects

- Weight gain, Cushingoid appearance
- Osteoporosis
- Hypertension, Hyperglycemia, Hyperlipidemia
- Peptic ulceration
- Sleep disturbance, behavioral disturbance and steroid psychosis
- Fluid retention
- Skin thinning and bruising, acne

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- > 7.5 mg of prednisolone per day increases the risk of fractures by 50% in the first year of treatment. All patients taking this dose for more than 3 months need bone densitometry (DEXA)

Before starting treatment:

- Weight
- Height (a drop of >4 cm, can suggest vertebral fracture)
- Assess bone profile and Vitamin D and in men SHBG and testosterone
- FBC, U&E, TSH

Monitoring

- DEXA every 2 years

GLUCOCORTICOID INDUCED OSTEOPOROSIS

Fracture Risks

- Age >70 years old
- BMI <19 kg/m2
- Postmenopausal
- Previous osteoporotic fracture(s)
- Maternal hip fracture.
- Inflammatory arthritis (inc. RA and Ank Spond)
- Alcohol 3 or more units/day
- Immobility
- Femoral Neck BMD < -1
- Glucocorticoids > 7.5 mg/day
- Smoking
- Medications: Anticonvulsants, proton bump inhibitors, breast cancer drugs, prostate cancer drugs.

Treatment outline: if patients taking ≥7.5 mg of Prednisolone and one or more of the following risk factors:

• >70 years old
• Frax tool (suggests it)
• Vertebral fracture (suspect)
• BMD T-score: -2.5

- The **FRAX** tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture.
- **Bone density**: Normal T-score: +1 to -1, Osteopenia -1 to -2.5, Osteoporosis -2.5 and bellow. Z-score (compares BD with other people same age)

GLUCOCORTICOID INDUCED OSTEOPOROSIS

Treatment outline for fracture risks

1. Bone-protection treatment should be started at the onset of glucocorticoid therapy in individuals at high risk of fracture.

2. Alendronate and risedronate orally are first line treatment options in combination with calcium and vitamin D3. Where these are contraindicated or not tolerated, IV zoledronic acid, SC denosumab or SC teriparatide are alternative options (d/w rheumatology).

3. Bone protection therapy may be appropriate in some premenopausal women and younger men, particularly in individuals with a previous history of fracture, or receiving high doses of glucocorticoids and in those who are HIV positive.

4. All patients starting steroids should be advised to take calcium and Vitamin D supplements (unless hypercalcaemic, then Vitamin D alone). Regular weight-bearing exercise and cessation of smoking,

5. Commence prophylaxis when steroid treatment is initiated if this is likely to last over 3 months.

6. Treat with Bisphosphonates if hypogonadal

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- NB reduced dose required when taken with **Allopurinol** - (Reduce Azathioprine to 25% of original dose)

Monitoring

- Blood pressure
- Weight
- Urinalysis
- FBC should be checked at 2, 4 and 8 weeks after commencement, then 2 monthly. U&E, LFTs each clinic visit.

AZATHIOPRINE

Purine analogue, that reduces lymphocyte numbers and interferes with T and B lymphocyte function.

Dosage

- 1-3 mg/kg/day. (Maximum dose 200 mg/day)
- Dependent on TPMT level – check before starting

Contra-indications

- Breast-feeding
- Recent live vaccinations
- **Mycophenolate** and Azathioprine work by similar mechanisms and should not be prescribed together

Caution

- Liver impairment

Important side effects

- Bone marrow suppression (reversible)
- Gastrointestinal symptoms (nausea, diarrhoea, vomiting, ulceration and haemorrhage)
- Hepatotoxicity
- Hypersensitivity reactions
- Increased susceptibility to infections
- **Severe pancytopenia** can be induced due to an inherited enzyme deficiency. All patients must be advised to report any evidence of infection, unexpected bruising or bleeding immediately.

SEH

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- Should **NOT** be co-prescribed with **Tacrolimus**
- Psoriasis

Monitoring

- Blood pressure
- Weight
- Urinalysis (esp. glucosuria)
- FBC, U&E, LFTs and serum trough levels should be checked at 2 and 4 weeks, then 4-8 weekly.
- Lipids every 3 to 6 months.
- Serum creatinine closely

CICLOSPORIN A

Natural product of fungi that preferentially inhibits T helper cell function. Calcineurin antagonist.

Indications

Refractory to therapy with conventional first line treatments

Dosage

- Initially 2.5 mg/kg/day given in two divided doses, increase dose dependent on clinical need and trough levels (12-14 hours post-dose)
- Aim for trough levels of 50-100µg/L

Contra-indications

- Renal impairment
- Uncontrolled hypertension
- Pregnancy (appropriate contraception)
- Breastfeeding
- Recent life vaccinations
- Malignancy
- Do not prescribe along with Tacrolimus
- Do not use with St Jhon's Wort

Important side effects

- Nephrotoxic (dose-related)
- Gingival hyperplasia
- Hypertension
- Infections
- Nausea, vomiting
- Hirsutism
- Tremor, paresthesia
- Muscle cramps
- Hyperlipidemia
- Hypomagnesaemia
- Cancer (esp. lymphoma, skin Ca)
- Headaches
- Leucopenia
- Liver disfunction

SEH

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- Avoid in severe blood disorders.
- Peptic ulceration.
- Pulmonary fibrosis
- Contraception required in men and women.
- Interaction with Trimethoprim and co-trimoxazole.
- In hepatic and renal impairment, dose would need to be adjusted down.

MONITORING

- FBC, U&E, LFTs every 2 weeks for 6 weeks or until therapy stabilized, and then every 2-3 months.

METHOTREXATE

Inhibits the enzyme dihydrofolate reductase, essential in the synthesis of purines and pyrimidines.

Dosage

- Adult starting dose 15-20 mg/week. Maximum dose 25-30mg/week. In children dose according to body surface area
- **NB methotrexate is taken weekly.**

Folic acid, helps to prevent mucositis and myelosuppression.

- 5mg once to 6 times a week (Not on the same day as the methrotexate)

Contra-indications

- Pregnancy (teratogenic). Discontinue 3 months before conception planned, in men and women.
- Breast feeding
- Active infections
- Pre-existing blood dyscrasias

IMPORTANT SIDE EFFECTS

- Gastrointestinal disturbance including ulceration
- Diarrhoea
- Hepatotoxicity
- Hypotension
- Pericarditis
- Pulmonary fibrosis, interstitial pneumonitis
- Anaphylactic reaction
- Steven -Johnson syndrome
- Bone marrow suppression

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- Bone marrow suppression
- Active GI disease
- Childbearing age

Monitoring

- Blood pressure
- Weight
- Urinalysis (esp.glycosuria)
- FBC should be checked at 1,2,4 weeks after commencement, then monthly.
- U&E, LFTs each clinic visit.

MYCOPHENOLATE MOFETIL (CELLCEPT)

Inhibits the Inosine monophosphate dehydrogenase (IMPDH) and DNA replication of the T and B lymphocyte cells, by interfering with guanosine nucleotide synthesis

Indications

- Refractory to therapy with conventional first line treatments
- Intolerance/contraindication to other immunosuppressive therapy

Dosage

- Start 1-2 g/day (depending on the weight) in divided doses; increase to 3g/day maximum dependent on clinical effect and tolerance
- Aim to titrate prednisolone down after stabilization of dose at ~3 months

Contra-indications

- Pregnancy planning (**advice 2 methods of contraception**)
- Breast-feeding.
- Malignancy
- Liver impairment
- **Mycophenolate** and **Azathioprine** work by similar mechanisms and should not be co-prescribed

Important side effects

- Gastrointestinal symptoms
- Abnormal LFT's
- Leukopenia
- Thrombocytopenia
- Infections
- Renal impairment
- Hyperglycemia
- Bone marrow suppression

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- Should **NOT** be co-prescribed with **Ciclosporin A**
- Interactions with antifungals
- If used with macrolides - reduce the dose of Tacrolimus

Monitoring

- Blood pressure
- Weight
- Urinalysis
- FBC, U&E, LFTs and serum trough levels should be checked at 2,4 weeks, then 4-8 weekly. And 12 weeks post dose.
- Lipids and serum magnesium every 3 to 6 months.

TACROLIMUS

Calcineurin antagonist that inhibits the action of T helper cells with a mechanism similar to ciclosporin.

Dosage

- 1-2 mg BD increasing to 4 mg BD depending on clinical response and trough levels (12-14 hours post-dose)
- Aim for trough levels of 5-10µg/L
- Prescribe as brand specific (e.g. Prograf)

Cautions

- Renal impairment
- Uncontrolled hypertension
- Pregnancy (Barrier contraception, as the drug interferes with OCP)
- Breastfeeding
- Recent live vaccinations
- Diabetes mellitus
- Malignancy
- Do not co-prescribe with ciclosporin A

Important side effects

- Nephrotoxic
- Hyperglycemia
- Hypertension
- Infections
- Nausea, vomiting
- Headache
- Tremor, paresthesia
- Cramps
- Hyperlipidemia
- Hypomagnesaemia
- Cancer (esp. lymphoma, skin Ca)
- Hyperkalemia / Hypokalemia
- Diarrhoea
- QT interval prolongation

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY IN THE OCULAR INFLAMMATORY CLINIC

CAUTIONS

- In patients with predisposition to infections (TB, Varicella zoster)
- Demyelinating disorders (exacerbation)
- Pregnancy, stop, specially in 3rd trimester.

Screening prior to starting treatment:

- T spot
- CXR
- HIV
- Hep B Ag, Anti Hep B core, Anti Hep B s, Anti Hep virus.
- FBC, U&E, LFTs.
- ANA
- (TNF- i can cause lupus like illness)

Monitoring

- FBC, U&E, LFTs every 3 months for 1st year and then 6 monthly.

BIOLOGICS

Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab are cytokine modulators, that inhibit the activity of tumor necrosis factor alpha (TNF-α). *Etanercept has been causally linked with uveitis so is not used for ocular inflammation*.

ADALIMUMAB (prescribe using trade name e.g Humira, Amgevita)

Indications

Refractory to therapy with conventional first line of treatments

Dosage

Drug	Dosage
Adalimumab	Induction: subcutaneous 80 mg/week; 40 mg/week. Maintenance: subcutaneous 40 mg/fortnight (reduced dose if under 40kg)

General contra-indications

- Active/Severe infection
- Multiple Sclerosis - Screen with MRI scan if intermediate uveitis
- Recent live vaccinations
- Malignancy
- Heart failure
- Breastfeeding (avoid for 5 months after last dose)
- Hypersensitivity reaction

Important general side effects

- Infections (TB reactivation, septicemia, hepatitis B reactivation)
- Fever
- Antibody formation (LES)
- Blood disorders
- Nausea, abdominal pain
- Risk of malignancy (e.g. Lymphoma)
- Headache
- Worsening heart failure
- Hypersensitivity reactions
- Depression

Infliximab dose: IV 5mg/kg. With initial treatment at 0 weeks, 5mg/kg at 2 and 4 weeks, then every 8 weeks.

LITERATURE

United Kingdom

National Institute for Care and Excellence (NICE): Technology appraisal guidance on adalimumab and dexamethasone for treating non-infectious uveitis (2017)

Scottish National Managed Clinical Network (NMCN): Uveitis treatment guidelines (2010)

British Society for Paediatric and Adolescent Rheumatology (BSPAR) and Arthritis and Musculoskeletal Alliance (ARMA): Standards of care for children with juvenile idiopathic arthritis (2010)

BSPAR and The Royal College of Ophthalmologists (RCOphth): Guidelines for screening for uveitis in juvenile idiopathic arthritis (JIA)(2006)

NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis

The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporosis Int. 2002;13(10):777.

National Osteoporosis Society. https://nos.org.uk/about-osteoporosis/your-bone-strength/factsheets/glucocorticoids/

Europe

Single Hub and Access point for pediatric Rheumatology in Europe (SHARE): Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis (2018)

International

Fundamentals of Care for Uveitis (FOCUS): Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis(2017)

Canada

Canadian Rheumatology Association (CRA): A position statement for the management of juvenile idiopathic arthritis, 2015 (published 2016)

United States

American Academy of Ophthalmology (AAO): Uveitis guidelines – Immunomodulator therapy (2018)

American Academy of Pediatrics (AAP): Clinical report on ophthalmologic examinations in children with juvenile rheumatoid arthritis (2006, reaffirmed 2018)

Expert panel recommendations for the use of anti–tumor necrosis factor biologic agents in patients with ocular inflammatory disorders(2014)

American Optometric Association (AOA): Optometric clinical practice guideline on the care of the patient with anterior uveitis (2004)