NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Shared Care Guideline

Azathioprine- for inflammatory conditions

Executive Summary

- Used for several inflammatory conditions.
- Dosing: 25-50mg daily for two weeks. Gradually increase in 50mg increments to 2-2.5mg/kg/day if tolerated
- Clinical response can usually be expected within 6-12 weeks.
- GP to monitor FBC & LFTs as set out within this document.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

Prescribing and monitoring by general practitioners (GPs).

2. Aim

To provide advice on safe prescribing and monitoring of azathioprine for use in the management of inflammatory bowel disease, myasthenia gravis, connective tissue diseases, dermatological diseases and respiratory indications for adult patients.

3. Introduction

Azathioprine is used as a disease-modifying agent for the management of inflammatory bowel disease, myasthenia gravis, connective tissue diseases, autoimmune liver disease and respiratory indications.

Clinical response to treatment can usually be expected in 6-12 weeks.

4. Abbreviations

- GP General Practitioner
- IBD Inflammatory bowel disease
- mg Miligrams
- kg Kilograms
- VZV Varicella zoster virus

- TPMT Thiopurine methyltransferase
- MMR Measles mumps and rubella
- BCG Bacillus Calmette-Guérin
- FBC Full blood count
- LFTs Liver function tests
- U&Es Urea and electrolytes
- CRP C-Reactive protein
- L Litre
- TSH Thyroid stimulating hormone
- AST Aspartate transaminase
- ALT Alanine transaminase

5. Dose and Administration

All doses are to be administered after meals to minimise risk of nausea.

Indication	Initial Dosing
Inflammatory bowel disease (IBD) *Crohn's disease or ulcerative colitis* ***Rheumatic diseases*** *Dermatomyositis; polymyositis; rheumatoid arthritis; polymyalgia rheumatica; giant cell arteritis)* ***Neurological diseases*** *Myasthenia gravis* ***Respiratory diseases*** *Interstitial lung disease; pulmonary vasculitis; granulomatosis with polyangiitis; wegener's granulomatosis; churg-strauss syndrome; microscopic polyangiitis; sarcoidosis; severe asthma* ***Dermatological diseases*** *Systemic lupus erythematous, systemic vasculitis and related disorders; autoimmune blistering disorders; eczema* ***Haematological conditions*** Immune thrombocytopenia ***Liver conditions*** *(Autoimmune hepatitis (AIH); primary biliary cholangitis with autoimmune features*	25-50mg daily for two weeks Gradually increase in 50mg increments to 2-2.5mg/kg/day if tolerated. Clinical response can usually be expected in 6-12 weeks. Note: Some clinicians (e.g. Gastroenterology) may go straight to target dose i.e. 2-2.5mg/kg/day. For the listed liver conditions, 25-50mg daily for two weeks. Gradually increase in 25mg increments to 1 – 1.5mg/kg/day.

(PBC/AIH overlap); primary scelerosing cholangitis with autoimmune features (PSC/AIH) overlap; autoimmune scelerosing cholangitis (ASC)).	

Further information can be found in the Summary of Product Characteristics:
http://www.medicines.org.uk/emc/medicine/2882

6. Adverse Effects

Common (≥ 1 in 100 and < 1 in 10)

- Nausea
- Diarrhoea
- Vomiting
- Anorexia
- Abdominal discomfort
- Headaches

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Rash
- Skin photosensitivity
- Signs of bone marrow suppression (leukopenia, thrombocytopenia) and therefore increased risk of infection i.e. fever, sore throat, oral ulceration, abnormal bruising or bleeding.
- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness)
- Hepatotoxicity (hepatic necrosis, biliary stasis, cholestatic jaundice)
- Alopecia
- Severe diarrhoea in inflammatory bowel disease population.

Rare (≥ 1 in 10000 and < 1 in 1000)

- Skin cancer and other malignancies
- Pneumonitis (reversible)
- Pancreatitis
- Non-Hodgkin lymphoma (more significant in older patients >60yrs)

Further information can be found in the Summary of Product Characteristics:
http://www.medicines.org.uk/emc/medicine/2882

7. Cautions

- Careful assessment of risk versus benefit should be carried out before use during pregnancy, in patients likely to become pregnant and breastfeeding.
- The patient should be advised to report any signs of bone marrow suppression or hypersensitivity (i.e. infection, fever, chills, cough, unexplained bruising or bleeding, fatigue, hypotension, myalgia, dizziness) to the GP; this should then be reported to the hospital specialist clinician or specialist nurse.
- Patients should be advised to limit exposure to ultraviolet light and sunlight and to wear high factor sun creams and/or protective clothing to limit risk of photosensitivity and skin cancer.
- Patients with no history of exposure to varicella zoster virus (VZV) or who are serology negative should be advised to avoid contact with people who have active chickenpox or shingles and should report any such contact to their GP or hospital specialist.
- Renal or hepatic impairment.
- Thiopurine methyltransferase (TPMT) homozygous deficiency

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8. Contraindications

- Allergy/hypersensitivity to azathioprine or 6-mercaptopurine.
- Moderate/ severe renal or liver impairment
- Significant haematological impairment
- Avoid prescribing allopurinol in patients on azathioprine due to a clinically significant interaction that can lead to increased azathioprine toxicity, unless advised by specialist gastroenterologist.
- Avoid prescribing azathioprine with co-trimoxazole or trimethoprim due to increased haematological toxicity.
- Avoid prescribing azathioprine with febuxostat
- Avoid prescribing azathioprine with clozapine due to increased risk of agranulocytosis

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9. Interactions

- Allopurinol (see above)
- Febuxostat (see above)
- Co-trimoxazole or trimethoprim (see above)
- Warfarin (enhanced anticoagulant effect)
- Increased risk of leucopenia or anaemia when azathioprine given with captopril or enalapril especially in renal impairment.

- Possible increased risk of leucopenia when Azathioprine prescribed with aminosalicylates.
- Patients taking Azathioprine along with other immunosuppressive therapy, including steroids are at increased risk of secondary infections.

- Patients should avoid 'live' vaccines such as Oral Polio, Oral Typhoid, measles, mumps and rubella (vaccine) (MMR), bacillus Calmette-Guérin (BCG) and yellow fever, whilst on immunosuppressive therapy. If a pre-treatment check of varicella zoster serology reveals no previous exposure then Varilix® is considered safe to administer provided the last dose of vaccine is at least 4 weeks before the start of azathioprine therapy.

- Contact hospital specialist for advice on any vaccinations if required.
- Yearly influenza vaccine is recommended in patients on Azathioprine therapy.

Further information can be found in the Summary of Product Characteristics:
http://www.medicines.org.uk/emc/medicine/2882

10. Monitoring standards & actions to take in the event of abnormal test results/symptoms

Pre-treatment monitoring	
FBC, U&Es, LFTs, TPMT phenotype, varicella status	• Consider performing TPMT testing • Hospital to perform FBC, LFTs, assessment of renal function and U&Es. • Check varicella zoster serology in patients where there is an unclear history of chicken pox or shingles.
On-going monitoring	
FBC	• Every 2 weeks for two months then monthly for four months, then if stable three monthly thereafter.
LFTs	• Every 2 weeks for two months then monthly for four months, then if stable three monthly thereafter.
CRP	• Every three months to assess response to treatment.
Renal function; U&Es	• 6 monthly

Note: Exact frequency of monitoring of above parameters may differ according to clinical discretion or specialist advice".

Note: If a pre-treatment check of varicella zoster serology reveals no previous exposure then

the hospital specialist will write to the GP practice asking that the patient be given varicella zoster vaccine (2 doses of Varilrix® with an interval of 6 weeks between doses). After confirmation that these doses have been administered then the hospital specialist will consider initiation of azathioprine at least 4 weeks after the last dose of vaccine.

Abnormal Full Blood Count Results	
Test	**Action**
White Cell Count <2.5 x 10^9/L	**Stop Azathioprine** and discuss with hospital consultant or specialist nurse immediately.
Neutrophils > 1.5 but < 2.0 x 10^9/L	Discuss with hospital consultant or specialist nurse.
Neutrophils < 1.5 x 10^9/L	**Stop Azathioprine** and discuss with hospital consultant or specialist nurse immediately.
Platelet count <150 x 10^9/L	Discuss with hospital consultant or specialist nurse.
MCV >105 fl	Check B12, folic acid and thyroid stimulating hormone (TSH). Supplement as appropriate or discuss with hospital consultant or specialist nurse
Lymphocytes <0.5 x 10^9/L	Discuss with hospital consultant or specialist nurse.
Abnormal LFT Results	
>2 fold rise in aspartate transaminase (AST), alanine transaminase (ALT) (from upper limit of reference range)	Discuss with hospital consultant or specialist nurse.
> 4 fold rise in AST, ALT(from upper limit of reference range)	**Stop Azathioprine** and discuss with hospital consultant or specialist nurse immediately.
Abnormal symptoms	
Rash (significant new)	**Stop Azathioprine and check FBC**. If FBC abnormal contact hospital consultant or specialist nurse. Wait until rash resolved and consider restarting at reduced dose, providing no blood dyscrasias.
Severe or persistent infections, fever, chills and/ or persistent sore throat	**Stop Azathioprine**, **check FBC** and contact hospital consultant or specialist nurse. Do not restart until results of FBC known. For sore throat throats, take FBC, and contact hospital consultant or specialist nurse.
Abnormal bruising or bleeding	**Stop Azathioprine until recovery** and check FBC. Do not restart if blood test abnormal, contact hospital consultant or specialist nurse.

Varicella	If in contact with the virus and no history of chickenpox or shingles contact hospital consultant or specialist nurse.
Nausea	Advise patient to divide dosage and take with food. If no improvement, reduce dosage or stop and contact hospital consultant or specialist nurse if reducing dose ineffective.

Note: Where the advice for abnormal tests or symptoms above is “stop” and then consult hospital specialist and the situation arises out of hours, the GP should refer the patient to the Emergency Department if cause for concern.

11. Shared Care Responsibilities

a. Hospital specialist:

- Send a letter to the GP requesting shared care for the patient. Agreement to shared care will be assumed unless GP advises otherwise.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer when requested.
- Initiate treatment and prescribe the first month of treatment.
- Routine clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Ensure that backup advice is available at all times.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- Monitor patient's overall health and well-being.
- Prescribe the drug treatment as described.
- Monitor blood results (FBC, U+Es and LFTs, CRP) in line with recommendations from hospital specialist.
- Help in monitoring the progression of disease.
- Complete blood monitoring details in Patient Held Record Book/provide updated electronic record.
- Provide vaccinations where appropriate (e.g. if serology negative for varicella)

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant) to assist health professionals to provide effective, safe, appropriate treatment.
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.
- Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
- Check that where possible the specialists have provided a patient-held record or information sheet for monitoring and/ or to alert other clinical staff to the treatment they are receiving.
- Share any concerns they have in relation to treatment with Azathioprine.

- Report any adverse effects to their specialist or GP whilst taking Azathioprine.

12. Contact numbers for advice and support

Cambridge University Hospitals NHS Foundation Trust		
Medicines Information Department		**01223 217502**
Dermatology Department		
Specialist	**Post**	**Telephone**
Jane Day; Diane Joseph	Specialist sisters - Dermatology	01223 217391
Dr N Burrows	Consultant Dermatologist	01223 216459
Dr Shiu Kwan Chan	Consultant Dermatologist	01223 216501
Dr Niamh Flanagan	Consultant Dermatologist	01223 586678
Dr Julia Gass	Consultant Dermatologist	01223 216501
Dr Thomas Ha	Consultant Dermatologist	01223 216459
Dr Shaheen Haque	Consultant Dermatologist	01223 216501
Dr Paul Norris	Consultant Dermatologist	01223 216459
Dr Jane Sterling	Consultant Dermatologist	01223 216501
Dr Justyn Thomas	Consultant Dermatologist	01223 216459
Dr Pamela Todd	Consultant Dermatologist	01223 216459
Dr Marc Wallace	Consultant Dermatologist	01223 216459
Rheumatology Department Decisions to alter or discontinue treatment are usually discussed via the Rheumatology Helpline on 01223 217398. The on-call rheumatology specialist registrar (SpR) may also be contacted via the Addenbrooke's Contact Centre.		
Specialist	**Post**	**Telephone**
Jill Bloxham; Julie Isaacson; Tracey Nash Teresa Del Sordo	Rheumatology Practitioners CTD Nurse	01223 254933 01223 274544
Dr Gavin Clunie	Consultant Rheumatologist	01223 216774
Dr Frances Hall	Consultant Rheumatologist	01223 256883
Dr Deepak Jadon	Consultant Rheumatologist	01223 217716
Dr Natasha Jordan	Consultant Rheumatologist	01223 256883
Dr Mark Lillicrap	Consultant Rheumatologist	01223 217716
Dr Anshuman Malaviya	Consultant Rheumatologist	01223 217716
Dr Andra Negoescu	Consultant Rheumatologist	01223 216774
Dr Kenneth Poole	Consultant Rheumatologist	01223 216774
Dr Nick Shenker	Consultant Rheumatologist	01223 256883
Gastroenterology Department		
Specialist	**Post**	**Telephone**

Inflammatory Bowel Disease Helpline for Patients		01223 257212 (voice mail)
Dr Miles Parkes	Consultant Gastroenterologist	01223 216389
Dr Jeremy Woodward	Consultant Gastroenterologist	01223 596231
Dr Stephen Middleton	Consultant Gastroenterologist	01223 216226
Dr Timothy Raine	Consultant Gastroenterologist	01223 348456
Dr Ewen Cameron	Consultant Gastroenterologist	01223 348718
Dr Gareth Corbett	Consultant Gastroenterologist	01223 348716
Prof Arthur Kaser	Consultant Gastroenterologist	Ext 768308
Sr Allison Nightingale	Inflammatory Bowel Disease Nurse Specialist	01223 217990 **(for GPs to contact for advice)**
Hepatology Department		
Dr George Mells	Consultant Hepatologist	01223 216110
Vasculitis/Lupus		
Specialist	**Post**	**Telephone**
Dr D. Jayne	Consultant in Nephrology & Vasculitis	01223 217259
Dr Frances Hall	Consultant Rheumatologist	01223 256883
Dr Lisa Willcocks	Consultant in Nephrology	
Stella Burns	Specialist Vasculitis Sister	01223 586796
Jane Hollis	Lupus Nurse Specialist	01223 217050
Neurology Department		
Specialist	**Post**	**Telephone**
Dr Alasdair Coles	Consultant Neurologist	01223 216073
Respiratory Department		
Specialist	**Post**	**Telephone**
Professor Edwin Chilvers	Consultant Respiratory Physician	01223 217079
	ILD Specialist Nurse	07872 048641

Papworth Hospital NHS Foundation Trust		
Medicines Information department		**01480 364179**
Respiratory Medicine ILD Department		
Specialist	**Post**	**Telephone**

Dr Muhunthan Thillai	Consultant Respiratory Physician	01480 364530
Dr Helen Parfrey	Consultant Respiratory Physician	01480 364530
Dr Nicola Simler	Consultant Respiratory Physician	01480 364521
Duncan Grady	Thoracic directorate pharmacist	01480 830541 bleep 845
Emma Harris Luis Matos	ILD Specialist Nurses	01480 364184 bleep 109 or 01480 364184

13. Monitoring compliance with and the effectiveness of this document

Specialties will regularly review their incidents and feedback from GPs with regard to the use of this drug and update the guideline accordingly.

14. Equality and Diversity Statement

This document complies with the Cambridge University Hospital NHS Foundation Trust service Equality and Diversity statement.

15. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

16. Document Management

Document ratification and history	
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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/2882

This pathway is approved across the Cambridgeshire and Peterborough NHS system.
Ratified at February 2018 Cambridgeshire and Peterborough CCG Joint Prescribing Group