Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

AZATHIOPRINE FOR USE IN DERMATOLOGY, GASTROENTEROLOGY LIVER, NEUROLOGY, RESPIRATORY AND RENAL
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for azathioprine therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc , the BNF and the Shared Care Protocol Responsibilities.

BACKGROUND FOR USE

- Azathioprine is an immunosuppressant. It is for use alone or with other agents to enhance the survival of organ transplant patients.
- It is used as a disease modifying anti-rheumatic drug (DMARD) and as a steroid-sparing agent.
- Indications, dose adjustments and monitoring requirements for DMARDs (licensed and unlicensed indications) are in line with national guidance published by the British Society for Rheumatology, the British Association of Dermatologists, the British Society of Gastroenterology, the European Crohns and Colitis organization, British Thoracic Society and NICE.
- Azathioprine uses in this protocol are limited to:

Dermatology

- Pemphigus vulgaris (licensed).
- Atopic eczema, bullous pemphigoid, pyoderma gangrenosum, chronic actinic dermatitis and cutaneous vasculitis. Use in these conditions is unlicensed and recommended by the British Association of Dermatologists.[1]

Gastroenterology

- Inflammatory bowel disease (unlicensed) and recommended by the British Society of Gastroenterology, NICE, European Crohns and Colitis Organisation.

Neurology

- Unlicensed indications as second-line therapy for a range of neurological disorders including myasthenia gravis, inflammatory myopathies and neuropathies, vasculitis and other immune-mediated central and peripheral nervous system diseases

Respiratory Medicine

- Sarcoidosis
- Interstitial lung disease (unlicensed). Its use in this condition is recommended by the British Thoracic Society.[3]

Liver Disease

- auto immune liver disease
- Post liver transplant

Renal

- Used for systemic lupus erythematosus and systemic vasculitis, used occasionally for patients with nephritis
- Use is unlicensed in these conditions.
- Use in kidney and pancreas transplant patients is not covered by this protocol as supply and monitoring is undertaken by Oxford Transplant Centre.

Rheumatology – see separate protocol

Approved by APCO March 2016. Minor amendment November 2019

SUPPORTING INFORMATION

- Azathioprine is an established drug with a known side effect profile.

Contraindications and Precautions

Immunisation with LIVE vaccines	Patients receiving azathioprine must NOT receive immunisation with LIVE vaccines (that BCG, oral typhoid, oral cholera, measles, mumps, rubella, yellow fever, Sabin polio, Varicella/ Chickenpox, Rotavirus and Japanese Encephalitis). Inactivated polio is available although sub-optimal response may be seen.
Chickenpox/ shingles	Patients suffering from chickenpox or active skin lesions in shingles, withhold azathioprine and inform a specialist team. For those with exposure to chickenpox or shingles and no history of infection/vaccination, passive immunisation with VZIG should be carried out.
Pregnancy and breastfeeding	Patients planning on becoming pregnant must be seen by a specialist. Those patients who become pregnant while on treatment should not have their dose altered but should be reviewed more frequently. It is important that the mother's disease is under control while pregnant. Present in milk in low concentration. No evidence of harm in small studies-continue if benefit outweighs risk. Daily dose should be taken immediately after a feed.
Renal impairment Hepatic impairment	Dose reduction necessary.
TPMT deficiency (homozygous state)	Avoid, can cause serious toxicity within 6 weeks of starting treatment. Possible increase in risk of leucopenia with aminosalicylates

Nb: Treatment for patients with renal transplant should be provided by secondary care and is funded by NHSE. Liver transplant patients are currently managed as shared care in Oxfordshire although it is a service commissioned by NHSE and repatriation.

DOSAGE

Indication	Dose	Ref
Dermatological conditions	Usual maintenance dose of 1 mg to 2.5 mg/kg daily. Usual dose range 50 - 250 mg daily.	1
Inflammatory bowel disease	Usual maintenance dose of 2 to 2.5 mg/kg daily. Some patients respond to lower doses. Usual dose range 100 – 250 mg daily.	2
Interstitial lung disease	Usual maintenance dose 2 mg/kg daily. Initially 50 mg daily. Increase dose by 50 mg each month up to a maximum of 150 mg daily. Usual dose range 50 – 150 mg daily.	3
Autoimmune liver disease/post liver transplant	1-2mg/kg. maximum dose rarely exceeds 150mg	
Neurological conditions	Usual maintenance dose 2-3mg/kg per day	
Renal	Usual maintenance dose 1 to 3 mg/kg daily. Usual dose range 50 – 250 mg daily.	

TIME TO RESPONSE

Six weeks to three months.[1]

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- FBC, U&E, creatinine, LFT and CRP.
- TPMT (thiopurine methyl transferase) genotype should always be checked unless advised otherwise by consultant. TPMT is a key enzyme in azathioprine metabolism which is inherited in an autosomal dominant pattern. Up to 12% of the population has reduced or very low TPMT activity and these individuals can be very sensitive to standard doses of azathioprine.

ONGOING MONITORING SCHEDULE

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- **FBC and LFTs:** Weekly for the first 4 weeks
- Then every 2 weeks until dose stable for 4 weeks
- Thereafter, monthly for Rheumatology or 3 monthly other specialties or as advised by specialist.
- Repeat FBC and LFTs 2 weeks after dose change.
- **U&Es and creatinine:** 6 monthly.
- **CRP:** 1 to 3 monthly (Rheumatology).

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In addition to absolute values for haematological indices, a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance. In order to monitor trends it is recommended that all blood test results are entered in the patient held monitoring booklet.

ACTIONS TO BE TAKEN

Side Effects	Action
WBC <3.5 x 10^9/l Neutrophils <2.0 x 10^9/l In liver WBC <3.0 x 10^9/l Neutrophils <1.0 x 10^9/l	Withhold and discuss with a specialist.
Platelets <150 x 10^9/l In liver <50.0 x 10^9/l	Withhold and repeat. If low discuss with a specialist.
AST/ALT >2 upper limit of normal reference range	Withhold. Look for alternative cause. Repeat LFTs, if abnormal discuss with a specialist.
MCV >105 fl	Check B12, folate and TFT. If low, start appropriate supplementation. Check alcohol status. If no cause found discuss with a specialist.
Rash or oral ulceration	Withhold until symptoms clear. Consider re-challenging at a lower dose. If rash recurs stop azathioprine and discuss with a specialist. Treat oral ulceration.
Hypersensitivity reactions	Fever, malaise, rash, vomiting, muscle/bone pain, dizziness. Stop azathioprine. Hypersensitivity to mercaptopurine should alert the prescriber to a probable hypersensitivity to azathioprine.
Abnormal bruising or sore throat	Withhold until FBC result available.
Nausea, vomiting, diarrhoea	Administer tablets after meals to reduce nausea. An anti-emetic or dose reduction may help. If symptoms persist stop azathioprine.

- Azathioprine can usually be withheld for several days without causing a flare,
- **DO NOT with-hold in liver disease unless on advice of hepatologist**.
- Annual 'flu' vaccination is recommended and Pneumovax may be considered.
- Sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- HPV and hepatitis B according to national guidance for selected patients.

NOTABLE DRUG INTERACTIONS (REFER TO BNF AND SPC)

- **NSAIDs:** May be continued, not recommended in cirrhosis or IBD.
- **Allopurinol/oxipurinol/thiopurinol:** The dose of azathioprine should be reduced to one quarter of the original dose.
- **Warfarin:** Inhibition of the anticoagulant effect of warfarin has been reported.
- **Drugs which may have a myelosuppressive effect, e.g. penicillamine:** Where possible, avoid co-prescribing.
- **Aminosalicylate derivatives, e.g. mesalazine, sulfasalazine:** Should be administered with caution as can contribute to bone marrow toxicity.
- **Vaccines:** Atypical reactions to live vaccines could occur and a diminished response to killed vaccines can be expected.
- **Phenytoin, sodium valproate, carbamazepine:** When co-prescribed with azathioprine, the absorption of these anti-epileptic drugs is reduced.
- **Angiotensin-converting enzyme (ACE) inhibitors:** Co-prescription may cause anaemia.
- **Co-trimoxazole and trimethoprim:** Can cause life threatening haematotoxicity.

BACK-UP INFORMATION/ADVICE

Contact Details	Oxford University Hospitals NHS Trust	
Dermatology	Dermatologist	01865 741155 ask for SR
Respiratory Medicine	Dr Rachel Hoyles, Lead Consultant for the ILD service Dr Ling-Pei Ho,Lead Consultant for Sarcoidosis Linda Brown, Medical Secretary Interstitial Lung Disease Sarah Poole, Lead Respiratory Pharmacist	 01865 225223 01865 741841 (bleep 4500)
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Neurology	Dr David Hilton –Jones Neurology Consultant Or Neurology Registrar	01865 231893 Or 01865 741166 bleep registrar on call
Renal	Dr Phil Mason Dr Paul Harden Dr Chris Winearls Dr Ed Sharples Dr Richard Haynes Dr Tom Connor	01865 228680 01865 228681 01865 228688 01865 228688 01865 228688 01865 228681

	Dr Paul Altmann Renal Reg on call: Renal Pharmacist: Paul Clarke Wen Yuen Lim	01865 228681 01865 741 841, #5924 (9am-9pm) 01865 226105 01865 226105

REFERENCES

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2. Carter MJ, Lobo AJ and Travis SPL on behalf of the IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011
3. British Thoracic Society Interstitial Lung Disease Guidelines http://www.brit-thoracic.org.uk/Portals/0/Guidelines/DPLDGuidelines/Thorax%20Sept%2008.pdf
4. BNF 68, Sept 2014
5. The management of Crohn's disease in adults, children and young people. NICE CG152. Jan 2013
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7. European Cohn's and Colitis Organisation. https://www.ecco-ibd.eu/

Acknowledge:
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