SHARED CARE GUIDELINE

Homerton University Hospital NHS
NHS Foundation Trust

NHS
City and Hackney

AZATHIOPRINE

INTRODUCTION

Azathioprine is an immunosuppressant antimetabolite used either alone or in combination with other agents (usually corticosteroids). It is used in many conditions, some of which are not mentioned in the product literature. This guideline covers its use in the following areas:

• Organ transplantation • Severe rheumatoid arthritis • Systemic lupus erythematosus • Dermatomyositis and polymyositis • Auto-immune chronic active hepatitis • Pemphigus vulgaris	• Polyarteritis nodosa • Auto-immune haemolytic anaemia • Chronic refractory idiopathic thrombocytopenic purpura • Ulcerative colitis and Crohns disease (unlicensed) • Inflammatory bowel disease

Azathioprine is converted in the body to mercaptopurine. This is an anti-metabolite interfering with nucleic acid synthesis.

DOSE AND ADMINISTRATION

Starting dose usually **0.5 to 1.5 mg/kg/day** increased (after 4 to 6 weeks) to **2 to 3mg/kg.**
Maximum dosage depends on response and side effects.
(Lower doses if there is significant renal or hepatic impairment or if there is known low thiopurine methyltransferase (TMPT)

Azathioprine is available as 25mg and 50mg tablets.
Azathioprine should be taken with or after food and the dose can be divided if preferred.

Indication

- Organ Transplant: starting and maintenance dosage in adult renal transplant recipients: 1.5 mg/kg daily taken orally and rounded to nearest 25 mg.
- Inflammatory bowel disease: The usual dose is between 2 to 2.5 mg/kg/day. The maximum dose differs between individuals
- Inflammatory arthritis, connective tissue disease and vasculitis: 1.5 to 2.5 mg/ kg daily in divided doses

CAUTION

- **Breastfeeding and Pregnancy**: Careful assessment of risk versus benefit should be carried out before use during pregnancy and breast-feeding as there is clinical experience of safe use in “lupus” pregnancy. There is good evidence that azathioprine is safe in pregnancy with IBD, and it should generally be continued in stable patients with IBD who become pregnant.
- Malignancies: patients receiving immunosuppressive regimens involving combination of drugs, including azathioprine, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Patients should be advised to wear protective clothing and use sunscreen with a high protection factor.
- Patients with renal/hepatic dysfunction and cardiac failure.
- Extreme caution in blood disorders.

SHARED CARE GUIDELINE

- **Vaccinations**: live vaccines should be AVOIDED (ie oral polio, MMR, BCG and yellow fever and oral typhoid). Passive immunization should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immune patients exposed to active chickenpox or shingles. Annual flu and pneumococcal vaccination is recommended.

CONTRA-INDICATIONS

- Moderate/severe renal or hepatic impairment.
- Hypersensitivity to azathioprine or 6-mercaptopurine.
- Inherited thiomethyltransferase deficiency (TMPT)- these patients are at an increased risk of bone marrow toxicity.
- Lesch-Nyhan syndrome.
- Severe haematological impairment.

DRUG INTERACTIONS

- **Allopurinol**: ***Reduce azathioprine dose to one-quarter (25%) of original dose.***
- **Co-trimoxazole/trimethoprim**: increased risk of haematological toxicity.
- **Warfarin:** anticoagulant effect possibly reduced.
- **Clozapine**: increased risk of agranulocytosis.
- **Ciclosporin**: decreased ciclosporin plasma levels (monitor levels).
- **Phenytoin, sodium valproate, carbamazepine**: azathioprine reduces the absorption of these drugs
- **ACE inhibtors**: co-prescription of azathioprine may cause anaemia. If significant, consider alternative to ACE inhibitor or different DMARD.
- **Aminosalicylates** i.e mesalazine, olsalazine, balsalazide or sulfasalazine: may contribute to bone marrow toxicity,
- Note: **Simvastatin should not be prescribed for hyperlipidaemia** in renal transplant as there is an increased risk of rhabdomyolysis with some immunosupressnats. To avoid any complications, all patients should be prescribed atorvastatin instead.

SIDE- EFFECTS

- Bone marrow suppression (leucopenia, thrombocytopenia)
- Hepatotoxicity (hepatic necrosis, billiary stasis)
- Anorexia, nausea, vomiting
- Oral ulceration, rarely gastrointestinal ulceration
- Hypersensitivity reactions (fever, rigors, rash)
- Pancreatitis (rare)
- CNS disturbances (headache, drowsiness, blurred vision)
- Alopecia

** **Patients should be advised to report any mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding and any unexpected illness or infection and should be seen URGENTLY for a full blood count, liver function tests, urea and electrolytes.**

See BNF for comprehensive list

SHARED CARE GUIDELINE

MONITORING STANDARDS FOR AZATHIOPRINE

The following standards have been agreed for the monitoring of azathioprine:

Pre-treatment: FBC, LFTs, U&Es & TPMT* (ESR in rheumatology patients)
* = optional

Minimum monitoring: FBC, LFT and U&Es every 2 weeks for 6 weeks or until dose stabilised then at least every 3 months if stable.

Note: there is no evidence that regular monitoring of FBC prevents myelotoxicity. It is important that patients are counselled to report symptoms of infection promptly, which should be reinforced in writing. However, FBC should be monitored at least every 3 months in stable patients.

EVENTS AND ACTION

Laboratory Events	Values	Action
• MCV	> 110 fl	**Seek specialist advice**. Check TFT, B12 and folate, Monitor LFTs as could be dose-related.
• WBC	< 3.0 x 10^9/L	**Seek specialist advice**, repeat FBC in 1 or 2 weeks.
• Neutrophils	< 1.5 x 10^9/L	
• Platelets	< 100 - 150 x 10^9/L	
• Significant deterioration in renal function		**Seek specialist advice**.
• Elevation in liver enzymes (AST, ALT) • or falling albumin	>2x Normal on 2 occasions	
• Serial decrease in WBC and or platelets within normal range	Eg.6.0→5.0→4.5 over 3 occasions	

Symptoms	Management
• Rash	**Stop** and discuss with specialist.
• Oral ulceration, stomatitis	
• Cough, dyspnoea or fever	**Stop** and discuss with specialist.
• Abnormal bruising or bleeding or severe sore throat.	**Stop,** repeat FBC immediately.
• Nausea, vomiting and diarrhoea	Withdrawal of drug may be necessary if persistent.
• Hair loss, pancreatitis, pneumonitis	Rare but **stop** and discuss with specialist.

REMEMBER if unsure at any point: Contact the various Specialists and or Specialist Nurse/ Nurse Practitioner via the Homerton Hospital switchboard on 020 8510 5555.

Share care guideline: is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibility for each party. The intention to shared care should be explained to the patient and accepted by them. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

SHARED CARE GUIDELINE

Responsibility of Consultant prescribing Azathioprine in shared care agreement

1. Ensure that the patient/carer is an informed recipient in therapy
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate)
3. Ensure baseline investigations are appropriate before commencing treatment
4. Initiate azathioprine and stabilise patient on a therapeutic dose of azathioprine before referral to the GP.
5. Send a letter to the GP requesting shared care for this patient
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis
7. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring
8. Evaluation of any reported adverse effects reported by GP or patient
9. Advise GP on review, duration or discontinuation of treatment where necessary
10. Inform GP of patients who do not attend clinic appointments
11. Ensure that back up advice is available at all times

Responsibility of General Practitioner prescribing in shared care agreement

1. Check and reinforce patient understanding of the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate
2. Monitor patient's overall health and well-being
3. Prescribe azathioprine after communication with specialist regarding the need for treatment
4. Monitor treatment as outlines by shared care guideline
5. Promptly refer to the specialist if there is a change in the patient's condition
6. Report any adverse events to the consultant where appropriate
7. Report ant adverse events to the CHM where appropriate
8. Help in monitoring the progression of disease

Responsibility of PCT

1. To provide feedback to trusts via Trust Medicines Committee
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing
3. To develop and revise shared care guidelines
4. To support trusts in resolving issues that may arise as a result of shared care

Patient responsibility

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment
3. Report any changes in disease symptoms to GP and/ or specialist
4. Alert GP and/or specialist of any changes of circumstances which could affect management of disease e.g. becoming pregnant of plans for starting a family.

References

Shared Care Guidelines; NHS Tower Hamlets and Barts and The London. Azathioprine in Renal Transplant. Approved March 2007. Review date 2008.

Mid Essex Hospital Services NHS. Shared Care Guidelines. Azathioprine and Mercaptopurine for the treatment of inflammatory bowl disease in adults

NHS Brighton and Hove and Brighton and Sussex University Hospitals. Shared Care Guidelines. Azathioprine tablets for the treatment of inflammatory arthritis, connective tissue disease and vasculitis in adults. Approved January 2009. Review date January 2010.