Azathioprine

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers
Part of the Shared Care Protocol: Management of Dermatological Conditions With Disease-Modifying Anti-Rheumatic Medications in Adults

Indications
Psoriasis and severe eczema (unlicensed, but supported by national guidance)

Any patient groups to be excluded from shared care
Patients receiving azathioprine for an indication classified as RED on the Nottinghamshire traffic light list, e.g. for suppression of organ transplant rejection.

Therapeutic Summary
Azathioprine is used to induce remission or partial remission in patients with inflammatory conditions including arthritis, psoriasis, connective tissue disease and vasculitis. Clinical benefit may take up to 3 months. Patient reported adverse effects usually occur early in therapy, but please see explicit criteria for review below.

Products available
Azathioprine 25mg and 50 mg tablets.

Dosage and route of administration
Azathioprine is given orally as a single daily dose. The usual maintenance dose is in the range of 100mg-200mg/day.

Azathioprine should not be taken with dairy products
(At least 1 hour before or 2 hours after any dairy containing food and drink)

Duration of treatment
All DMARDs are long term treatments. Azathioprine has a cumulative action and a clinical improvement can take up to 3 months.

Monitoring Requirements and Responsibilities
Pre-treatment assessment to be performed by the specialist and will include:

- FBC, U&Es, LFTs, and thiopurine methyltransferase (TPMT) assay.

Ongoing monitoring:

Time period in treatment	Frequency of monitoring	Tests to be done		
		FBC	**LFTs**	**U&Es**
0-6 weeks	Fortnightly	✓	✓	✓
6 weeks – 3 months	Monthly	✓	✓	✓
>3 months and stable dose for 6 weeks	3 monthly*	✓	✓	✓
Any dose increase	2 weeks post dose increase then revert to above protocol	✓	✓	✓
* The Dermatology Specialist team may advise more frequent monitoring for patients heterozygote for TPMT (increased risk of toxicity).				

- Patients should report immediately any evidence of infection, rash, oral ulceration, sore throat, abnormal bruising or bleeding or other manifestations of bone marrow depression.
- Additional monitoring requirements are NOT required in primary care for patients receiving additional biological therapy including anti-TNF therapy.
- Routine annual influenza and one-off pneumococcal vaccinations are highly recommended.

Explicit criteria for review and discontinuation of the medicine – Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by secondary care.

Adverse Event	Action
Nausea, vomiting or diarrhoea	Ensure patient is taking tablets with food. In some individual, nausea will normally resolve after a few days. If troublesome prescribe antiemetic.
Severe general malaise and flu-like symptoms	This maybe an early hypersensitivity reaction. Withhold and discuss with specialist team.
WBC <3.5x10^9/l	Withhold until discussed with specialist team.
Neutrophils <1.6x10^9/l	Withhold until discussed with specialist team.
Platelets <140x10^9/l	Withhold until discussed with specialist team.
AST, ALT > twice upper limit of reference range and/or unexplained reduction in albumin <30g/l.	Withhold until discussed with specialist team.
Rash or oral ulceration	Withhold until discussed with specialist team.
Macrocytosis (MCV > 105 fL)	This does not usually signify a medical problem. Check serum folate and B12 & TSH. Treat any underlying abnormality. If result is normal, interrupt treatment until discussed with the specialist team. (If macrocytosis is non-progressive, no action is required. If worse, contact the specialist team).
*Unexplained eosinophilia >0.5 x 10^9/l	Withhold until discussed with the specialist team *eosinophilia is commonly seen in patients with eczema and therefore not 'unexplained'
Abnormal bruising / severe sore throat/fever	Withhold until FBC results available and discuss with specialist team.
Severe abdominal pain	Withhold and consider pancreatitis, measure amylase and discuss with the specialist team.

In addition to absolute values for haematological or biochemical indices a rapid fall or rise or consistent downward or upward trend in any value should prompt caution and extra vigilance.[2]

For a full list of side effects refer to the BNF or Summary of Product Characteristics.
IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE DERMATOLOGY SPECIALIST TEAM.

Relevant contraindications

- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' - Chapter 6, page 43: Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended with a single pneumococcal booster after 5 years.
- Pregnancy. Azathioprine has been safely used in pregnancy, however women wishing to become pregnant should be discussed with the specialist team.
- Breast feeding.
- Severe hepatic impairment.

Relevant precautions

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Renal impairment. Dose reduction may be required in moderate or severe renal impairment (CrCl<20ml/min). Please discuss with the specialist team.
- Patients who have no history of exposure to varicella zoster virus (VZV) i.e. chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Varicella–zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella (including patients taking immunosuppressant medicines e.g. azathioprine, ciclosporin, methotrexate, leflunomide) and who have no antibodies to varicella–zoster virus and who have significant exposure to chickenpox or herpes zoster. See the Green Book – chapter 34, page 429

for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.
- Patients should be advised to limit exposure to sunlight and UV light and sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- Patient's heterozygote for TPMT – use with caution due to increased risk of toxicity. The Specialist Team will recommend increased monitoring if necessary.

Clinically relevant medicine interactions and their management

- Trimethoprim and co-trimoxazole should be used with caution – can cause life threatening bone marrow suppression and haematotoxicity. (Note: occasionally, some patients are on co-trimoxazole for special circumstances. E.g. PCP prophylaxis).
- Concomitant use of allopurinol (haematological effects greatly increased) or febuxostat (may increase azathioprine levels) should be avoided.
- Warfarin and acenocoumarol: Azathioprine inhibits the anticoagulant effects of coumarins. Monitor closely and increase the dose of the anticoagulant if necessary.
- Phenytoin, sodium valproate, carbamazepine absorption may be reduced by azathioprine.
- Aminosalicyclate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme and increased haematological toxicity of azathioprine, administer with caution.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book'- chapter 6, page 43): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. Inactivated polio is available although a suboptimal response may be seen.
- ACE inhibitors – increased risk of anaemia and/or leucopoenia.

For a full list of contraindications, precautions and drug interactions refer to the BNF or Summary of Product Characteristics.

Information given to patient

- Azathioprine should not be taken with dairy products (at least 1 hour before or 2 hours after milk or dairy products).
- Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection.
- Patients should be advised to limit exposure to sunlight and UV light and sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- Patients should be advised to avoid contact between themselves and individuals with chickenpox or shingles if they have no prior history of exposure. Any exposure of patients with no varicella–zoster virus antibodies to chickenpox and shingles sufferers should be reported to the GP for assessment and possible treatment.
- The patient will be given details of their treatment, follow up appointments, monitoring requirements and nurse specialist contact details.
- A patient information leaflet is available from the British Association of Dermatologists.

Patient's roles and responsibilities

- To attend for regular blood tests, routine influenza and pneumococcal vaccinations. Failure to attend for blood tests will result in medication being stopped on specialist advice.
- To report any suspected adverse reactions (as above) to the GP for assessment.
- To request supply of maintenance therapy in a timely manner, and store medication securely away from children.

References

1. Ledingham, J., Gullick, N. et al. (2017) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology **56**(6), 865-868.
2. Imuran Tablets 25mg & 50mg (Aspen) - Summary of Product Characteristics [October 2019] on Electronic Medicines Compendium: (accessed on 29/10/20) via www.medicines.org.uk/emc
3. BNF 5 October 2020 [online] via https://bnf.nice.org.uk. [Accessed 29/10/20].
4. Azathioprine (Reviewed: 30/10/2017) via The Renal Drug Database [accessed29/10/20].
5. Baxter K (ed), Stockley's Drug Interactions. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 29/10/20)

Version Control- **Azathioprine: Management of Dermatological Conditions with DMARDs in Adults**			
Version	Author(s)	Date	Changes
2.1	Shary Walker		1. Highlight that Azathioprine should not be taken with dairy products 2. Updated the explicit criteria for review and discontinuation of the medicine. 3. Routine influenza and pneumococcal vaccinations are highly recommended with a single pneumococcal booster after 5 years. 4. Updated the relevant interactions. Added a note stating "occasionally, some patients are on co-trimoxazole for special circumstances. E.g. PCP prophylaxis". 5. Clinically relevant medicine interactions and their managements updated. 6. Information given to patient added the warning about dairy products. Added more patients' roles and responsibilities.