Azathioprine

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

Indications[1,2]

Rheumatoid arthritis and systemic lupus erythematosus - licensed
Psoriatic arthritis, polyarteritis, giant cell arteritis and other connective tissue diseases- outside of licence (supported by national guidance[2]).

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 of proven benefit as a disease modifying agent in the treatment of rheumatological conditions. Clinical improvement may take up to 3 months.[2] NSAIDs and simple analgesics may need to be continued. 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 – prescribe generically.

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 per day.

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 Rheumatology Specialist team may advise more frequent monitoring for patients heterozygote for TPMT (increased risk of toxicity).**				

- Patient should report any rash, oral ulceration, sore throat, abnormal bruising or bleeding.
- GP to assess and manage cardiovascular risk factors – patient at higher risk of cardiovascular events due to rheumatological disease activity.
- Additional monitoring requirements are NOT required in primary care for patients receiving additional biological therapy including anti- TNF therapy.
- Routine influenza and 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	Ensure patient is taking tablets with food. If troublesome prescribe antiemetic.
Severe general malaise	This maybe part of a hypersensitivity reaction. Withhold and discuss with rheumatology specialist team.
WBC <3.5x10^9/l	Withhold until discussed with rheumatology specialist team.
Neutrophils <2x10^9/l	Withhold until discussed with rheumatology specialist team.
Platelets <150x10^9/l	Withhold until discussed with rheumatology specialist team.
AST / ALT > twice upper limit of reference range	Withhold until discussed with rheumatology specialist team.
Rash or oral ulceration	Withhold until discussed with rheumatology specialist team.
Macrocytosis (MCV > upper limit of reference range)	This does not usually signify a medical problem. Check serum folate and B12 & TSH. Treat any underlying abnormality. If results normal discuss with rheumatology specialist team.
Abnormal bruising / severe sore throat	Withhold until FBC results available and discuss with rheumatology 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 RHEUMATOLOGY SPECIALIST TEAM.

Relevant contraindications

- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- Pregnancy - Azathioprine has been safely used in pregnancy, however women wishing to become pregnant should be discussed with the specialist team.
- Breast feeding.

Relevant precautions[1,2]

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Concurrent use with allopurinol or febuxostat should be avoided.
- Renal impairment. Dose reduction may be required in moderate or severe renal impairment.[4] Please discuss with the rheumatology 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 https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book 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.
- Patients heterozygote for TPMT – use with caution due to increased risk of toxicity. The Rheumatology Specialist Team will recommend increased monitoring if necessary.

Clinically relevant medicine interactions and their management[1,2,3,5]

- Co-trimoxazole and trimethoprim should be avoided – can cause life threatening haematotoxicity.
- Concomitant use of allopurinol (haematological effects greatly increased) or febuxostat (may increase azathioprine levels) should be avoided.
- Warfarin: Azathioprine inhibits the anticoagulant effects of warfarin. Monitor closely and increase the dose of warfarin if necessary.
- Phenytoin, sodium valproate, carbamazepine absorption may be reduced by azathioprine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): 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 leucopenia.

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

Information given to patient

- 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 also be given an approved drug information leaflet from Arthritis Research UK. Further copies available at www.arthritisresearchuk.org.

Patient's roles and responsibilities

The patient will:

- Take their medication as agreed, unless otherwise instructed by an appropriate healthcare professional.
- Attend for all regular blood tests and all follow-up appointments with GP and specialist. If they are unable to attend any appointments they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.
- Inform all healthcare professionals of their current medication prior to receiving any new prescribed or over-the-counter medication.
- Report all suspected adverse reactions (as above) to medicines to their GP.
- Store their medication securely away from children.
- Read the information supplied by their GP, specialist and pharmacist and contact the relevant practitioner if they do not understand any of the information given.

References

1. Imuran Tablets 25mg & 50mg (Aspen) - Summary of Product Characteristics [Nov 2019] on Electronic Medicines Compendium: (accessed on 11/06/2020) via www.medicines.org.uk/emc
2. Ledingham J, Gillick N, Irving K. et al. (2017) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology doi:10.1093/rheumatology/kex389.
3. BNF June 2020 [online] via www.medicinescomplete.com [accessed 11/06/2020]
4..Ashley C, and Currie A [Eds]. The Renal Drug Handbook [3rd edition] Oxford: Radcliffe Publishing Ltd [2009].
5. Baxter K (ed), Stockley's Drug Interactions. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 22/06/2020)