Azathioprine

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers
Part of the Shared Care Protocol: Management of Auto-Immune Hepatitis in Adults

Indications:[1, 2]
Auto-immune Hepatitis

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.
Children (under 18 years of age).

Therapeutic summary:
Azathioprine is of proven benefit as a steroid sparing agent in the treatment of auto-immune hepatitis. Clinical efficacy may take up to 3 months. Therefore, majority of the patients start azathioprine while still on steroid therapy. Patient reported adverse effects usually occur early in therapy, but please see explicit criteria for review below.

Any modifications of the therapy including changes in the dose of immunosuppressive therapy shall be determined by the treating specialist.

Products available:[1]
Azathioprine 25mg and 50 mg tablets.

Dosage and route of administration:
Azathioprine is given orally as a single daily dose; but, this can be individualised in those who tolerate divided daily doses. The usual maintenance dose is 1 to 2 mg/ kg/ day (50-150mg/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:
Azathioprine has a cumulative action and a clinical improvement can take up to 3 months. It is standard practice to continue azathioprine therapy if tolerated for at least 2 years.

Decision regarding dosage modification and withdrawal shall be taken with discussion between patient and the treating specialist.

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	Liver tests	U&Es[8] (CrCl)
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	✓	✓	✓

Routine influenza and pneumococcal vaccinations are highly recommended.

Monitoring for patients associated with long term corticosteroid use:
For more detail (including monitoring for adrenal suppression) please see NICE CKS Corticosteroids – oral.

Explicit criteria for review and/or 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 the patient is taking the tablets with food. In some individual, nausea will normally resolve after a few days. If not, consider a low dose. If troublesome prescribe antiemetic.
Severe general malaise	This may be part of a hypersensitivity reaction. Withhold and discuss with specialist team.
WBC <3.5x10^9/l (patients with normal baseline values)	For patients with normal baseline values, withhold until discussed with specialist team For some cirrhosis patients with pancytopenia, **these ranges are not appropriate and an individualised range will be provided by the specialist.**
Neutrophils <2x10^9/l (patients with normal baseline values)	
Platelets <150x10^9/l (patients with normal baseline values)	
Rash or oral ulceration	Withhold until discussed with specialist team.
Macrocytosis (MCV > upper limit of reference range)	This does not usually signify a medical problem. Check serum folate, B12 and TSH. Treat any underlying abnormality. (If macrocytosis is non-progressive, no action is required. If worsen, contact the specialist team).
Abnormal bruising / fever / severe sore throat	Withhold until FBC results are available 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.

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 SPECIALIST TEAM.

Relevant contraindications:[1]

- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at https://www.gov.uk/government/collections/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.
- 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]

- 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 (CrCl<20ml/min) [4]. 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. Contact the on-call microbiologist via the hospital switchboard for advice if required.
  See https://www.gov.uk/government/collections/immunisation-against-infectious-disease-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.
- Patients' 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: [1, 3, 5]

- Co-trimoxazole and trimethoprim should be avoided – can cause life threatening bone marrow suppression.
- 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. Consider increasing the dose of the anticoagulant and monitor closely.
- Phenytoin, sodium valproate, carbamazepine absorption may be reduced by azathioprine.
- Aminosalicyclate derivatives (eg. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, administer with caution.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at https://www.gov.uk/government/collections/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 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 be given details of their treatment, follow up appointments, monitoring requirements and nurse specialist contact details.

Patient's roles and responsibilities:

- To attend for regular blood tests.
- The patient will report any suspected adverse reactions (as above) to the GP for assessment.

References:

1. Imuran Tablets 25mg & 50mg (Aspen) - Summary of Product Characteristics [October 2019] on Electronic Medicines Compendium: (accessed on 13/08/2020) via www.medicines.org.uk/emc
2. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2011; 60: 1611-29.
3. BNF August 2017 [online] via www.medicinescomplete.com [accessed 13/08/2020]
4. The Renal Drug Database. Accessed 13/08/2020.
5. Baxter K (ed), Stockley's Drug Interactions. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 13/08/2020)
6. NICE. Corticosteroids-oral: Monitoring. CKS (last revised June 2020) accessed via: https://cks.nice.org.uk/corticosteroids-oral#!scenariorecommendation:5
7. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, Asthma & Clinical Immunology 2013, 9:30. accessed via http://www.aacijournal.com/content/pdf/1710-1492-9-30.pdf
8. 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.

Appendix I. Monitoring associated with long term corticosteroid use:

Most patients with AIH are treated with long term corticosteroids and should be monitored accordingly.

Baseline:
Blood pressure, body weight, ophthalmic examination (can be done by optician), HbA_{1c}, triglycerides and potassium.[6]

Regular monitoring:
Blood pressure (every visit), body weight, triglycerides & potassium (1 month post initiation, then 6-12 monthly), HbA_{1c} (1 month post initiation then 3 monthly). Monitor people with confirmed diabetes mellitus regularly, depending on clinical judgement.[6]

Osteoporosis risk management:
Patients should receive calcium and vitamin D supplementation. Bone DEXA scanning should be performed at commencement of prednisolone treatment and at 1-2 yearly intervals while on steroids, with osteopenia/ osteoporosis actively treated.[2]

Glaucoma & cataract monitoring:
Annual examination by an ophthalmologist is recommended. An earlier examination is required in patients with symptoms of cataracts (namely blurred vision).[7]
Early referral for monitoring of intra-ocular pressure (glaucoma) is recommended in patients at higher risk of developing steroid-induced glaucoma, such as those with a personal or family history of open angle glaucoma, diabetes mellitus, high myopia, or connective tissue disease (especially rheumatoid arthritis).[7]

For more detail (including monitoring for adrenal suppression) please see NICE CKS Corticosteroids – oral.

Version Control- **Azathioprine: Auto-immune Hepatitis in Adults**			
Version	Author(s)	Date	Changes
2.1	Lynne Kennel	21/09/2017	
3.1	Shary Walker	17/09/2020	- Dairy products warning - Monitoring associated to corticosteroid used moved as appendix I and linked - CrCl specified for U&E's and CrCl calculator link added - Some changes under explicit criteria for review - Additional medicine interactions