Azathioprine

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers
Part of the Shared Care Protocol: Management of Neuroinflammatory diseases in adults with the steroid sparing agent azathioprine

INDICATIONS

Neuromuscular diseases (such as Myasthenia Gravis, Lambert-Eaton Syndrome), inflammatory neuropathies (chronic inflammatory demyelinating polyneuropathy), inflammatory CNS conditions (such as Neuromyelitis optica), and autoimmune encephalitides (including antibody associated and paraneoplastic) - outside of license (supported by national guidance).

ANY PATIENT GROUP 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 disease modifying agent in the treatment of neuroinflammatory conditions which respond to steroids. Failure to control neurological symptoms with a 'safe' dose of corticosteroids is the main indication for starting immunosuppression[1]. Clinical improvement may take up to three months. Steroids and other symptomatic treatments (such as pyridostigmine in myasthenia gravis) 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 starting dose is from 1 to 3 mg/kg body weight/day, increased over a period of one month. The usual maintenance dose is in the range of 100mg-200mg per day.
- When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing Azathioprine.
- Thiopurine methyltransferase (TMPT) should be measured prior to initiation in view of the association between TMPT deficiency and myelosuppression with azathioprine. TMPT deficiency is not a contraindication to using azathioprine but may reduce the dose required. Patients with very low TMPT activity should not take azathioprine.

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 three months, with a full therapeutic effect taking up to 6-12 months. It is standard practice to continue azathioprine therapy if tolerated for at least two years. **Decisions regarding dosage modification and withdrawal shall only be taken after discussion with treating specialist.**

MONITORING REQUIREMENTS AND RESPONSIBILITIES

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

- FBC, U&Es, LFTs, and TPMT assay.

Ongoing monitoring:

- Patient should report any rash, oral ulceration, sore throat, abnormal bruising or bleeding.

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

- Routine influenza and pneumococcal vaccinations are highly recommended. Live vaccines are to be avoided.

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 <3.5x109/l	Withhold until discussed with specialist team.
Neutrophils <1.6x109/l	Withhold until discussed with specialist team.

Platelets <140x109/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 109/l	Withhold until discussed with the specialist team
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.
Worsening neurological symptoms including weakness, difficulty swallowing and breathlessness	Myasthenia gravis and other neuro-inflammatory conditions may relapse on corticosteroid withdrawal. This may be a consequence of a slow response to azathioprine or using too low a dose. Discuss urgently with neurology specialist team for advice.

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 NEUROLOGY SPECIALIST TEAM.

RELEVANT CONTRAINDICATIONS

- Known hypersensitivity to azathioprine and/or 6-mercaptopurine.
- Live vaccines should be avoided (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). N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- There is a debate as to whether taking azathioprine is a contraindication to using intrauterine contraceptive devices. This is based on a few case reports. There is probably no good reason to avoid intrauterine contraceptive devices, but specialist advice should be sought[1].
- Pregnancy: Azathioprine has been safely used in pregnancy and is considered low risk while other immunosuppressive agents carry a clearer risk to the fetus. However women wishing to become pregnant or men who wish to start a family should be discussed with the specialist team.
- The use of azathioprine during breast-feeding should be avoided.

RELEVANT PRECAUTIONS[1-3]

- 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.[4] Please discuss with the neurology 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 VZV and who have significant exposure to chickenpox or herpes zoster. See the Green Book (as above) 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; sunscreens and protective covering should be encouraged to reduce sunlight exposure.
- Patients with low TPMT activity – use with caution due to increased risk of toxicity. The Neurology Specialist Team will recommend increased monitoring if necessary.

CLINICALLY RELEVANT MEDICINE INTERACTIONS AND THEIR MANAGEMENT[1-5]

- 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 should be avoided (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk). 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 medicine 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).
- The patient will be given details of their treatment, follow up appointments, monitoring requirements and specialist contact details.
- 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; 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 VZV 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 medicine information leaflet.

PATIENT'S ROLES AND RESPONSIBILITIES

- 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. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. Practical Neurology. 2015;15(3):199-206.
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 medicines. Rheumatology doi:10.1093/rheumatology/kew149.
3. Imuran Tablets 25mg & 50mg (Aspen) - Summary of Product Characteristics [April 2017] on Electronic Medicines Compendium: (accessed on 13/12/17) via www.medicines.org.uk/emc
4. Ashley C, and Currie A [Eds]. The Renal Medicine Handbook [3rd edition] Oxford: Radcliffe Publishing Ltd [2009].
5. Baxter K (ed), Stockley's Medicine Interactions. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com