Torbay and South Devon NHS
NHS Foundation Trust

Azathioprine Shared Care Guideline for GPs

Indication:

Active rheumatoid arthritis and other types of inflammatory arthritis, systemic lupus erythematosus, dermatomyositis and polymyositis, vasculitis

Specialist Responsibility:

- Assess patient for co-morbidities
- Request baseline tests including FBC, U+Es and eGFR, LFTs
- Confirm **TPMT level** within normal range before initiating treatment
- Counsel patient on benefits, side effects, frequency of dosing and monitoring requirements and provide written information
- **Treatment with these drugs will be initiated by the specialist, who is responsible for prescribing until shared care is agreed. Any GP who does not feel confident to undertake the clinical and legal responsibility for a shared care drug is not obliged to undertake the prescribing and should discuss this with the specialist.**
- Specify target doses, monitoring and review dates at clinically relevant time intervals for both the GP and specialist team and any other patient specific information.
- **Initiate therapy and provide at least the first 4 weeks of Azathioprine and until the GP has confirmed willingness to share care.**
- Provide advice as required by the GP and review patient as necessary

GP responsibility

- On-going prescription of Azathioprine
- Monitoring as per instructions below
- Report adverse events to specialist team and to the MHRA via the yellow card scheme
- Report and seek advice from the specialist team on any aspect of patient care which is of concern and may affect treatment
- Inform specialist team if treatment is stopped for any reason

Dosage:

- Azathioprine can be prescribed in 25mg and 50mg tablets.
- The dose is typically 150mg daily but ranges from 1mg/kg/day – 3mg/kg/day.
- Dose should be increased as set out in the dosing letter. This is usually an increase of 50mg (1 tablet) every 2 weeks to target dose.
- In common with other 2nd line agents, Azathioprine will take 10-12 weeks to have any effect.

Monitoring:

- **Blood tests:**
    - **FBC, U+Es, LFTs and albumin**
- **Frequency:**
    - **every 2 weeks for 6 weeks**
    - **then monthly for 3 months**
    - **Then 12 weekly there after unless there are exceptions as detailed below**
- **For dose increases monitor blood tests every 2 weeks until stable dose for 6 weeks**
- **Exceptions to monitoring rules**
    - Frequency of blood tests may be increased to monthly
        - Azathioprine taken in combination with Leflunomide, methotrexate or mycophenolate
        - High risk or significant co-morbidities that would affect monitoring results i.e. co-existing liver or renal disease, highly fluctuant blood results.
    - The specialist will inform the GP if this is required
- Consider stopping Azathioprine and seek advice (e-mail tsdft.rheumatologydmards@nhs.net or **01803-654939**) if any of the following occur:
    - WCC or platelet count falls on 3 successive occasions
    - Total WCC <3.5 or
    - Neutrophils < 1.6
    - Isolated lymphopenia is not usually an indication for cessation of Azathioprine therapy
    - Platelet count < 140
    - MCV >105
    - Unexplained eosinophilia >0.5
    - ALT or AST >100 U/l
    - Unexplained drop in albumin <30g/l
    - Creatinine >30% above baseline +/- eGFR <60
- The MCV may rise on Azathioprine – if >105, consider checking B12 / folate if patient is anaemic.
- The patient should be advised to report signs of infection (e.g. persistent sore throat, fever) or easy bruising.

Side effects:

- This list is not exhaustive, for additional information please consult the BNF and product SPCs

- Patients must report rash, oropharyngeal ulceration, abnormal bruising, severe sore throat or any unexplained illness/infection. Azathioprine should be withheld and urgent FBC and LFTs arranged. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday

Common	• **Nausea, vomiting, GI upset** – Usually mild and settles with continuation of treatment. Advise patient to take tablets with or after meals.
Less common	• **Hypersensitivity reactions** • **Bone marrow depression –** more likely in patients with TPMT deficiency, hepatic or renal failure or concurrent allopurinol therapy • **Pancreatitis**
Uncommon	• **Hair loss**

Drug interactions:

- This list is not exhaustive, for additional information please consult the BNF and product SPCs

ACE inhibitors	**Caution**	Increased risk of haematological toxicity. Consider alternative to ACEi.
Allopurinol	**Avoid**	Increased risk of myelosuppression. Reduce dose of Azathioprine to 25% original dose if concomitant use cannot be avoided.
Aminosalicylates i.e. Sulfasalazine	**Caution**	Increased risk of haematological toxicity
Anticonvulsants	**Caution**	Possible reduced absorption of these anticonvulsants
Co-Trimoxazole	**Avoid**	Increased risk of haematological toxicity
Febuxostat	**Avoid**	Increased risk of haematological toxicity
Trimethoprim	**Avoid**	Increased risk of haematological toxicity
Warfarin	**Caution**	Possible reduced anticoagulant effect. May need to reduce azathioprine dose or increase warfarin dose.

Cautions and Contraindications

Contraindication:

- **Hypersensitivity to Azathioprine/Mercaptopurine**

Caution:

- Hepatic impairment – use doses at lower end of normal range
- Renal impairment – consider doses adjustment in chronic kidney disease
- Increased risk of skin cancer. Patients should be aware of need to limit exposure to sunlight and use adequate sun protection measures. Risk is increased in patients with history of PUVA.

Alcohol:

- Alcohol should be limited to less than 14 units of alcohol per week.

Vaccines:

- **Pneumococcal vaccination** (Pneumovax® II) every 10 years and **annual influenza vaccinations** are strongly recommended for patients with inflammatory arthritis
- Live vaccinations are contraindicated until 3 months after cessation of Azathioprine
- Although the shingles (Zostavax) vaccine is a live attenuated vaccine, treatment with <3mg/kg/day is not considered sufficiently immunosuppressive and is not a contraindication to administering the vaccine.
- Passive immunisation may be given with varicella zoster immunoglobulin (VZIg) in non-immune patients exposed to chicken pox or shingles. Contact specialist for advice.

Pregnancy, breastfeeding and fertility:

Important safety information

MHRA Drug Safety Update (May 2025): Thiopurines and intrahepatic cholestasis of pregnancy (ICP)

- Cholestasis of pregnancy has rarely been reported in association with azathioprine therapy
- This risk is believed to also apply to the other thiopurine drugs, mercaptopurine and tioguanine
- It may occur earlier in pregnancy than non drug-induced cholestasis of pregnancy, and it may not respond to ursodeoxycholic acid
- Withdrawal or dose reduction of the thiopurine drug may improve liver function tests
- Remain vigilant to signs and symptoms of ICP in pregnant patients taking thiopurines (intense itching without a rash, nausea, and loss of appetite) and discuss any concerns with clinicians managing the patient's immunosuppressant therapy and a hepatologist, as necessary
- If cholestasis of pregnancy occurs, a case-by-case assessment is required to determine the appropriate course of action. Consider the risks and benefits of remaining on the product against the risks and benefits of stopping.
- In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM)

- Azathioprine at <2mg/kg/day is considered safe in pregnancy and in breastfeeding women, but patients are advised to contact their specialist if they wish to become pregnant.
- Azathioprine is considered safe in paternal exposure.

Elective surgery

- Continue azathioprine but consider infection risk and drug interactions

Infection

- Azathioprine can be continued while patient receiving oral antibiotics
- Azathioprine should be stopped in the acutely unwell older person or while receiving IV antibiotics.
- Please seek advice if there are recurrent infections

Advice and Support

- Rheumatology.sdht@nhs.net
- Nurses helpline: 01803 654939
- Rheumatology secretaries: 01803 655897/54832/55759

References

1. BNF 74. September 2017-March 2018
2. SPC Azathioprine 50mg tablets. Accessed via www.medicines.org.uk June 2018
3. Ledingham J et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology*, Volume 56, Issue 6, 1 June 2017, Pages 865–868
4. Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology*, Volume 55, Issue 9, 1 September 2016, Pages 1693–1697

Appendix 1 Shared Care Agreement Letter

Consultant Request

To Dr ……..

Practice Address:

Patient Name
Hospital number
Date of birth
Address

Diagnosed condition:…….

I recommend treatment with the following drug:……Azathioprine…….

I am requesting your agreement to sharing the care of this patient according to the South Devon Shared Care Guideline for this drug. If you agree, I will send you, in writing, any additional information required for you to undertake prescribing responsibility, as laid down in the Shared Care Guideline.

Signed:…….. Date……

Consultant name:……..

Department:……..……

Contact telephone number: …….

GP Response

I agree / do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed:…….. Date……

GP name:……...
*Delete as appropriate