Oxford University Hospitals NHS
NHS Foundation Trust

NHS
Oxfordshire
Clinical Commissioning Group

AZATHIOPRINE FOR USE IN ADULT RHEUMATOLOGY
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for azathioprine therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF

Shared Care Protocol – Responsibilities

Shared care assumes communication between the rheumatology specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. See Rheumatology Shared Care Responsibilities document for further information.

Rheumatology Specialist Team

At the start of treatment:

- Complete pre-treatment assessments, including baseline tests, in accordance to the specific shared care protocol
- Initiate treatment by prescribing the first 56 days
- Supply the patient with 3 blood cards (for FBC, U&E and LFTs) and inform patients to book and attend blood tests at 2, 4 and 6 weeks after starting treatment
- Ensure that patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly, as part of obtaining informed agreement to shared care
- Provide a copy of the drug-specific patient information leaflet (or direct patient to Versus Arthritis website https://www.versusarthritis.org/about-arthritis/treatments/drugs/)
- Provide a copy of OUHFT 'Rheumatology Shared Care Monitoring Card' to the patient and/or carer, which includes contact details for the rheumatology advice line
- Send a letter to the GP requesting shared care once dose is stable, confirming the above has been completed. Include any results from pre-treatment assessments if appropriate. Provide details of the dose to be continued. Outline shared care protocol criteria and/or direct them to the relevant document on the Oxfordshire CCG website

After 2-6 weeks of treatment:

- Check blood test results from week 2, week 4 and week 6 (available on EPR for Oxfordshire patients/contact GP practice for blood results if patient's GP practice is not in Oxfordshire)
- Ensure any abnormal results are acted upon promptly

After 4-6 weeks of treatment:

- Conduct a consultation with the patient and/or to check that the patient is not experiencing any issues or side effects.
- Confirm that the patient is stable (no side effects, tolerating the drug and established on monthly blood tests). Communicate this information in a shared care handover letter to the GP. Shared care can now commence.
- If the patient is not stable requiring change in the treatment regime, the patient will remain under the care of the specialist until they become stable, as above.

Unless any concerns are raised by the GP within 14 days, shared care will be assumed and the patient will collect the next prescription from the GP. [1]

Approved by APCO September 2019

During treatment:

- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient
- If the dose is increased, patient's bloods will be monitored as above
- If dose is decreased, additional monitoring may not be required at discretion of the rheumatology specialist - this will be clearly communicated in the clinic letter and the existing monitoring schedule should continue

GP

- Ensure that provision has been made for the patient to have blood monitoring as per local arrangements
- Prescribe medication once the dose is stable or shared care is agreed
- Ensure all monitoring is completed in accordance to 'Recommended monitoring schedule for patients taking disease-modifying anti-rheumatic drugs (DMARDs)'
- Check results then advise the specialist of any deteriorations or abnormal results. Results should be recorded on the monitoring card if the GP practice is outside of Oxfordshire.
- Notify the specialist to any changes in patient's condition, any adverse drug reactions or failure to attend tests
- If a patient fails to attend for monitoring:
  - Only issue a 28 day prescription and book them in for the next available appointment for a blood test
  - If they fail to attend a second blood test then contact the specialist team for advice and to discuss suitability for continuing treatment before supplying further prescriptions

Patient and/or carer

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Ensure that they are booked in for blood test monitoring as per local arrangements and attend as required
- Attend all hospital and GP appointments as scheduled
- Ensure monitoring card is kept up to date and is brought to all appointments (especially patients whose GPs are out of Oxfordshire)
- Report any side effects to the GP or a member of the specialist team

BACKGROUND FOR USE

- Azathioprine is an immunosuppressant. It is used as a disease modifying anti-rheumatic drug (DMARD) and as a steroid-sparing agent.
- Indications, dose adjustments and monitoring requirements for DMARDs (licensed and unlicensed indications) are in line with national guidance published by the British Society for Rheumatology.
- Azathioprine is indicated either alone or in combination with corticosteroids and/or other drugs, in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite high treatment with standard dose of steroids

Azathioprine is used to treat the following conditions:

- Licensed indications: Rheumatoid arthritis, Systemic lupus erythematosus (SLE), Dermatomyositis and polymyositis, polyarteritis nodosa
- Other autoimmune rheumatic diseases (ARD) including systemic vasculitis and psoriatic arthritis. Use in these conditions is unlicensed and recommended by the British Society of Rheumatology.[3]
- Juvenile idiopathic arthritis (Unlicensed)

DOSAGE

- Up to 1 mg/kg daily increasing after 4 to 6 weeks to 2 to 3 mg/kg daily, round to the nearest 25mg tablet where possible
- The maintenance dose may be 1 to 3 mg/kg daily. Usual dose range is 50 - 250mg orally daily[3]
- Azathioprine is available as 25mg and 50mg tablets
- Time to response is six weeks to three months[3]
- Take with or after meals to reduce nausea

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- FBC, LFTs, U&Es, CRP.
- Patients should have baseline TPMT (thiopurine methyl transferase) status assessed. TPMT is a key enzyme in azathioprine metabolism. Up to 0.3% of the population have reduced or very low TPMT activity and these individuals can be very sensitive to standard doses of azathioprine. Azathioprine can be initiated whilst awaiting TPMT phenotype but the dose should not be increased above 50mg daily until the result is known. The result is usually available within 10 working days and the specialist is responsible for checking the result and advising dose escalation as appropriate.

ONGOING MONITORING

More information available in separate guideline; 'Recommended Monitoring Schedule for patients taking disease-modifying anti-rheumatic drugs (DMARDs)'.

Baseline assessments should include height, weight, blood pressure, FBC, U&Es, LFTs and CRP.

Standard Monitoring Schedule as per British Society of Rheumatology Guidelines[3]:

- Following initiation or dose change: Check FBC, U+Es and LFTs **every 2 weeks** until on stable dose for **6 weeks**
- Once on stable dose, check FBC, U+Es and LFTs **monthly** for **3 months**
- Thereafter, check FBC, U+Es and LFTs **every 3 months**.
- More frequent monitoring is appropriate in patients at higher risk of toxicity (extremes of body weight, CKD3 or above, pre-existing liver disease, significant other medical co-morbidity, age over 80 years and previous DMARD toxicity)

British Society of Paediatric & Adolescent Rheumatology monitoring guidelines are currently under review and will be added in when available.

Abnormal Laboratory Results and Action to be Taken:

Please note that in addition to absolute values for haematological indices a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance.
Some patients may have abnormal baseline values; specialist will advise if so. e.g. some patients with cirrhosis will have pre-existing pancytopenia and lupus patients may have leucopenia because of lymphopenia.

Laboratory Result	Action
WBC less than 3 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
Neutrophils less than 1.6 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.

Platelets less than 140 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
MCV greater than 110 fl	Withhold and discuss with Rheumatology. May be able to continue if chronic increase. Check folate and $B_{12.}$ If level low, start appropriate supplementation.
Creatinine increase greater than 30% over 12 months and/or calculated GFR less than 60ml/min/1.73m^2	Discuss with Rheumatology as dose adjustments or further investigations may be required.
Adult liver function ALT greater than 2.5 x upper limit of normal or over 100U/l	Withhold and discuss with adult rheumatology.

CONTRAINDICATIONS AND PRECAUTIONS

Chickenpox/ shingles	Patients suffering from chickenpox or active skin lesions in shingles, withhold azathioprine and inform a specialist team. For those with exposure to chickenpox or shingles and no history of infection/vaccination, passive immunization with VZIG should be carried out.
Hepatic impairment Elderly	Use doses at the lower end of the range.
Chronic Kidney Disease 4	Use 75-100% of standard dose.
Chronic Kidney Disease 5	Use 50-100% of standard dose.
TPMT deficiency (homozygous state)	Avoid, can cause serious toxicity within 6 weeks of starting treatment. Possible increase in risk of leucopenia with aminosalicylates

SIDE EFFECTS & ACTIONS TO BE TAKEN

Side Effect	**Action**
Rash or oral ulceration	Withhold until symptoms clear. Consider re-challenging at a lower dose. If rash recurs stop azathioprine and discuss with a specialist. Treat oral ulceration.
Hypersensitivity reactions	Fever, malaise, rash, excessive nausea and vomiting, muscle/bone pain, dizziness. Stop azathioprine. Hypersensitivity to mercaptopurine should alert the prescriber to a probable hypersensitivity to azathioprine.
Abnormal bruising or sore throat	Withhold until FBC result available.
Nausea, vomiting, diarrhoea	Administer tablets after meals to reduce nausea. An anti-emetic or dose reduction may help. If symptoms persist stop azathioprine.
Photosensitivity	Limit exposure to sunlight and UV light. High SPF sunscreens and protective clothing should be used to reduce sunlight exposure.

NOTABLE DRUG INTERACTIONS

(Please note that this is not an extensive list. Refer to BNF and SPC for any specific drug interaction queries)

Drug	Action
Allopurinol/oxipurinol/thiopurinol	Reduce dose of azathioprine to one quarter of the original dose, close haematological monitoring is advisable
Febuxostat	High dose Febuxostat may increase azathioprine exposure. Use with caution with close haematological monitoring.
Warfarin	INR should be closely monitored. Inhibition of the anticoagulant effect of warfarin has been reported.
Aminosalicylate derivatives, e.g. mesalazine, mesalazine, sulfasalazine	Additional haematological monitoring is required as the combination can contribute to bone marrow toxicity
Angiotensin-converting enzyme (ACE) inhibitors	Co-prescription may cause anaemia or leucopenia. Higher incidence reported in kidney transplant and dialysis patients.

FAMILY PLANNING

Follow advice from secondary care

VACCINATIONS

Check Department of Health green book guidance and if not covered, discuss with secondary care

BACK-UP INFORMATION AND ADVICE

Contact Details	Oxford University Hospitals NHS Foundation Trust	
Rheumatology	Rheumatology Helpline (Adult and Paediatric) Monday to Friday 8am - 2pm (answerphone service) Closed on weekends and bank holidays Rheumatology Registrar/Consultant on call Monday to Friday 9am-8pm Weekends and bank holidays 9am-5pm	Tel: 01865 737656 Email: Rheumatology.NOC@nhs.net OUH switchboard number: 0300 304 7777, ask for Rheumatology on call
Medicines Information	Tel: 01865 221505 (Monday to Friday 9am - 5pm) Email: Medicines.information@ouh.nhs.uk	

REFERENCES

1. Shared Care Protocols (SCP) Best Practice Guidelines. March 2019. Available from: https://clinox.info/clinical-support/local-pathways-and-guidelines/Prescribing/Shared%20Care%20Protocol%20Best%20Practice%20Guidelines.pdf
2. NHS England. Responsibility for Prescribing Between Primary and Secondary/Tertiary Care. (2018). Available from: https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf
3. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, Gordon P, Christidis D, Galloway S, Hayes E, Jeffries A. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. (2017) Rheumatology. Jun 1;56(6):865-8
4. BNF online (Accessed via www.evidence.nhs.uk on 26/07/19)
5. Summary of Product Characteristics. Azathioprine 25mg tablets (Mylan). Last updated on eMC: 13/11/2018 (Accessed via www.medicines.org.uk on 26/07/19)