THE SHEFFIELD AREA PRESCRIBING GROUP

Shared Care Protocol

For
Azathioprine and Mercaptopurine
in adults and young people over 16 years

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Shared Care Protocol for Azathioprine / Mercaptopurine

Statement of Purpose

This shared care protocol has been written to enable the continuation of care by primary care clinicians of patients initiated and stabilised on azathioprine / mercaptopurine by the rheumatology, gastroenterology, oral medicine, neurology and dermatology departments within Sheffield Teaching Hospitals. The patient will remain under the care of the consultant and primary care will only be requested to take over prescribing of azathioprine / mercaptopurine within its licensed indication unless specifically detailed otherwise below.

The use of azathioprine in transplant patients is not covered by this shared care protocol

The use of mercaptopurine in acute leukaemias and chronic myeloid leukaemia is not covered by this shared care protocol.

Responsibilities of consultant clinician / secondary care clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent. This is particularly important for unlicensed indications.
- Carry out pre-treatment tests
- To initiate azathioprine / mercaptopurine in appropriate patients, issue patient with patient information leaflet and counsel on contraceptive advice, if applicable
- To prescribe and monitor for at least the first three months or until patient stable
- To refer patients to their GP for shared care once stabilised on treatment and on three monthly monitoring
- To contact patient's GP to request prescribing under shared care using Shared Care Transfer form. Send a link to or copy of the shared care protocol to the patient's GP
- To advise the GP regarding continuation of treatment, including the length of treatment
- To include a statement of their opinion on the patient's suitability for Zostavax® in their correspondence with primary care for patients in the vaccine eligible age cohorts
- To provide the GP/primary care team with advice regarding abnormal blood results, or any queries relating to this treatment
- To monitor disease appropriately whilst the patient is under shared care
- Whilst on azathioprine / mercaptopurine, the patient must not be discharged from the consultant's care
- To issue the patient with a blue blood monitoring booklet once shared care is agreed

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- To agree to prescribe azathioprine / mercaptopurine for patients in line with the shared care agreement and return completed Shared Care Transfer form to relevant department.
- To report any adverse reaction to the MHRA and the referring consultant
- To continue to prescribe for the patient as advised by the consultant
- To oversee that the patient is adhering to shared care monitoring protocol, see below
- To inform the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant if any concerns with the patient's therapy

- To conduct an annual face to face medication review or more frequent if required
- In the event that the GP is not able to prescribe, or where the shared care protocol is agreed but the consultant is still prescribing certain items e.g. hospital only product; the GP will provide the consultant with full details of existing therapy promptly by fax on request
- For medication supplied from another provider, GPs are advised to follow recommendations for Recording Specialist Issued Drugs on Clinical Practice Systems

Responsibilities of patients/carers

- To attend hospital and GP clinic appointments and to bring monitoring booklet. Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the GP or specialist should their clinical condition significantly worsen
- Report any suspected adverse effects to their specialist or GP whilst taking azathioprine / mercaptopurine, including any abnormal bruising, dyspnoea, cough, fever, and presence of oral ulceration or sore throat
- To read the drug information given to them
- To take azathioprine / mercaptopurine as prescribed
- To inform the specialist, GP or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication
- To take responsibility for appropriate contraceptive precautions, where applicable
- To restrict alcohol intake to no more than government recommended safe limits as advised in the patient information literature

Indication

Azathioprine

Azathioprine is licensed for use in auto-immune conditions to influence the immune response. Licensed conditions where azathioprine may have a benefit on disease or reduce need for steroids include:

- severe rheumatoid arthritis;
- severe acute Crohn's disease, maintenance of remission of Crohn's disease or ulcerative colitis*;
- systemic lupus erythematosus (SLE);
- dermatomyositis and polymyositis;
- auto-immune chronic active hepatitis;
- pemphigus vulgaris;
- polyarteritis nodosa;
- auto-immune haemolytic anaemia;
- chronic refractory idiopathic thrombocytopenic purpura.
  *different brands may have different licensed indications

Not licensed for, but may be used in the treatment of other oral, dermatological, gastroenterological, neurological or rheumatological diseases, examples of which are listed below. Some of these indications are sufficiently rare that their prevalence does not allow sufficient randomized controlled trials to be conducted to prove efficacy. The use of azathioprine may be based on case series and expert opinion; see reference section.

- Neurology – myasthenia gravis, neuromyelitis optica, multiple sclerosis (rarely), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multi-focal motor neuropathy, Lambert-Eaton myasthenic syndrome (LEMS).

- mucous membrane pemphigoid
- recurrent aphthous ulcers
- orofacial granulomatosis
- erosive oral lichen planus
- pemphigoid
- vasculitis
- severe recurrent erythema multiforme

Mercaptopurine

Mercaptopurine is used to influence the immune response in treatment of severe acute Crohn's disease, maintenance of remission of Crohn's disease and ulcerative colitis (unlicensed indications). The main role of mercaptopurine is steroid sparing.

Selection of patients

All patients should be assessed for thiopurine methyltransferase (TPMT) activity before offering azathioprine / mercaptopurine. Patients will not be offered azathioprine / mercaptopurine if TPMT activity is deficient (very low or absent). Azathioprine / mercaptopurine may be considered at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).

All patients will be treated and stabilised on azathioprine / mercaptopurine by a secondary care specialist. Patients initiated on therapy are suitable for referral to a primary care service once stabilised on treatment.

Patients with the following conditions are excluded from this Shared Care Protocol:

- Severe hepatic impairment;
- Severe pleural effusion or ascites;
- On more than the maximum recommended dose (see dosage section below);
- Children under 16 years;
- Those being treated with azathioprine for any form of cancer or for transplant;
- Those being treated with mercaptopurine for any form of leukaemia;
- Patients who prefer to attend the hospital;
- Interstitial lung disease.

NB. Caution needed in patients with severe renal impairment – lower doses advised-see dosage section.

Dosage

Azathioprine

Azathioprine is available as 25 and 50 mg tablets.

Refer to individual product patient information leaflet for information on administration.

In general, the starting dosage is 1-3 mg/kg bodyweight/day, and is adjusted according to the clinical response and haematological tolerance. When the therapeutic response is evident, consideration may be

given to reducing the maintenance dosage to the lowest level compatible with maintenance of the response. If no improvement occurs in the patient's condition within three to six months, consideration should be given to withdrawing the medicinal product. The maintenance dosage required may range from less than 1 mg/kg bodyweight/day to 3 mg/kg bodyweight/day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.

Typically doses used in the different directorates are;

Dermatology – 0.5-2.5mg/kg/day dependent on TPMT activity

Rheumatology – 50mg daily, increasing to 150mg daily if able to tolerate. (1-3mg/kg/day)

Gastroenterology – 2-2.5mg/kg/day (dose may be adjusted following 6-thioguanine nucleotides measurement)

Oral Medicine – 50mg daily, increasing to 150mg daily if able to tolerate. (1-3mg/kg/day -dependent on TPMT activity)

Neurology – typically 50mg daily, increasing to 1-3mg/kg/day. Higher starting doses may be used if TPMT activity known.

In patients with renal impairment (creatinine >150 micromoles/L or eGFR <60 ml/min/1.73m^2) and/or mild to moderate hepatic dysfunction, dosages should be given at the lower end of the normal range. There is no specific information available on how elderly patients tolerate azathioprine. It is recommended that the dosages used should be at the lower end of the normal range.

For rheumatology patients, continue NSAIDs or analgesics at least until response to treatment. Patients should be carefully monitored according to the monitoring section below.

<u>Mercaptopurine</u>

Mercaptopurine is available as 50mg scored tablets and 20mg/ml oral suspension

Usual dose 1-1.5mg/kg/day

The maximum dose will differ between individuals. Some patients may respond to lower doses.

NB. Caution needed in patients with renal and hepatic impairment, consider using lower doses.

Contra-indications

- TPMT deficiency homozygous state
- Malignant disease
- Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients
- Severe infections
- Severely impaired hepatic or bone-marrow function
- Pancreatitis

- Lactation (refer to secondary care if patient breast feeding).
- Pregnancy - unless the benefits outweigh the risks. See also pregnancy section below.
- Live vaccines are contra-indicated during treatment with azathioprine / mercaptopurine, see also Additional Information section below.

Side –effects

The details below are not a complete list and the BNF and the SPCs remain authoritative.

Very common / common; depression of bone marrow function; leucopenia, thrombocytopenia, nausea, vomiting, anorexia, pancreatitis, anaemia, infections, hepatotoxicity

Patients must be advised to inform their doctor immediately about sore throat with mouth or throat ulcers, fever, infections, unexplained bruising / bleeding or other signs of myelosuppression.

Monitoring

Secondary care:

All patients should have their TPMT level checked prior to starting azathioprine / mercaptopurine.

Baseline FBC, extended LFTs (including GGT), U&E/creatinine and CRP in rheumatology and inflammatory bowel disease (IBD) patients.

Monitoring frequency varies slightly on initiation of azathioprine / mercaptopurine depending upon directorate / indication for which it is being used. Typically patients have FBC, extended LFTs, U&E/creatinine (rheumatology - CRP) weekly /two weekly for 1-2 months, then monthly until stable.

Secondary care assumes responsibility for the monitoring and prescribing of azathioprine / mercaptopurine until stable dosage has been successfully achieved.

When patients are stable and suitable for 3 monthly monitoring they can be transferred to shared care arrangements.

Primary care:

FBC, extended LFTs, U&E/creatinine 3 monthly, once care shared. Also measure CRP in rheumatology patients prescribed azathioprine.

NB. More frequent monitoring may be needed if pre-existing liver disease or receiving other potentially hepatotoxic therapy, as advised by secondary care clinician.

Remind patients at each visit to report any abnormal rash, bleeding, bruising, infections, fever, and presence of oral ulceration or sore throat immediately if they occur while on azathioprine / mercaptopurine

Specialist will advise GPs regarding any changes in monitoring if doses are increased.

Caution needed:

If CRP is significantly and persistently raised above what is normal for that patient, consider infection, and ask the patient about a flare in symptoms of their disease. If infection is present, this should be treated and blood tests then repeated (see infection section below). If there is no apparent explanation for the elevated

CRP, this should be repeated a few weeks later, and if remains unchanged or higher, the secondary care team should be contacted.

Stop azathioprine / mercaptopurine and contact help line (see below) if:

WBC <3.5 x 10^9/L

Neutrophils <1.6 x 10^9/L *Please note for rheumatology patients with SLE low WBC, lymphocyte, neutrophil and platelet counts may be a manifestation of the SLE. If low counts are new, please contact rheumatology department within 48 hours for advice. If previously known, please follow advice in clinic* letters

AST/ALT >100U/L

Platelets <100 x 10^9/L

eGFR <40 ml/min/1.73m^2

Overdose – refer directly to secondary care

Non-compliance with monitoring.

In the event of the following abnormalities, azathioprine / mercaptopurine can be continued, but tests repeated within 2-3 weeks and then seek advice from department initiating azathioprine / mercaptopurine if the abnormality is persistent:

eGFR <50 (but above 40) ml/min/1.73m^2

Unexplained eosinophilia >0.5x10^9/L

Lymphocytes < 0.5 10^9/L

MCV>105fL: check B12, folate and thyroid function - if abnormal prescribe as appropriate.

Platelet count <130 (but >100) x 10^9/L

Unexplained reduction in albumin <30g/L

ALT and or AST 70-100 U/L (consider recent flu vaccination i.e. within the last 2-3 weeks, as possible cause)

Unexplained new rash, bruising/bleeding, fever, dizziness, sore throat with oral or pharyngeal ulceration

Nausea, vomiting or diarrhoea

Pregnancy

If a patient becomes pregnant or wishes to conceive contact the initiating consultant to discuss management of condition and ongoing treatment options.

Please note, azathioprine is the preferred immunosuppressive drug in pregnant rheumatology patients.

For rheumatology patients taking azathioprine, the drug may be continued, but please contact the rheumatology department for advice, unless recent clinic letters indicate intention to continue azathioprine during planned pregnancy.

Azathioprine and mercaptopurine usually continued in pregnancy in IBD patients - contact IBD team for advice and review.

Dermatology advises to stop treatment in pregnancy and to contact the initiating consultant.

Infections

In the event of a patient developing a severe infection or requiring antibiotic treatment whilst on azathioprine / mercaptopurine, check FBC and CRP and withhold azathioprine / mercaptopurine for the duration of antibiotic treatment or until the infection has resolved.

Interactions

The details below are not a complete list and the current BNF and the SPC remain authoritative.

Allopurinol - highly significant (decreases the rate of metabolism of azathioprine / mercaptopurine. Reduce dose of azathioprine / mercaptopurine to one quarter of usual dose. This should not be initiated without discussion with the specialist team for dose adjustment of azathioprine / mercaptopurine and appropriate monitoring).
Please note *allopurinol may be used in IBD patients who cannot tolerate higher doses of azathioprine / mercaptopurine to potentiate the effect of azathioprine / mercaptopurine; dose reduction of azathioprine / mercaptopurine would be the same as if they were on allopurinol for gout.*

Additional interactions for both azathioprine and mercaptopurine are noted with febuxostat, trimethoprim, co-trimoxazole, aminosalicylates, ribavirin and, warfarin.
Azathioprine may also interact with ACE inhibitors, cimetidine and indometacin
Mercaptopurine may also interact with clozapine.

Dairy products possibly reduce plasma concentration of mercaptopurine— manufacturer of mercaptopurine advises to take at least 1 hour before or 2 hours after dairy products.

Additional information

Live vaccines, e.g. MMR, BCG, small pox, yellow fever, etc, should not be given to patients taking azathioprine / mercaptopurine (refer to Green book for further advice on vaccines).

Patients on azathioprine for the management of inflammatory conditions may not be sufficiently immunosuppressed to contraindicate administration of Zostavax® (shingles vaccine). The degree of immunosuppression should be assessed on a case by case basis. Practitioners should refer to the latest edition of the Green-book-chapter-28a for advice. If clinicians administering the vaccine have concerns about the degree of immunosuppression they should first contact the relevant specialist.

Women taking azathioprine and mercaptopurine should be advised to attend for routine cervical smear testing

NB. Pneumococcal polysaccharide vaccine & annual inactivated flu vaccine should be given.

Re-Referral guidelines

See under monitoring section above
Pregnancy and / or preconception advice /management
Deterioration of disease

Financial implications

If azathioprine / mercaptopurine issued under the shared care arrangements then drug costs will move from secondary to primary care. In primary care azathioprine / mercaptopurine will be issued on FP10 prescriptions. Outpatient appointments at STH will be reduced, but there will be an increase in payments to GPs under the DMARD Locally Commissioned Services.

Support, education and information

A drug information sheet and shared care booklet has been issued to your patient.

If any problems occur or you have any concerns please contact relevant specialist:

Rheumatology help line (Mon-Fri 0900-1600)	(0114) 2713086 (option 3)
Dermatology help line (24 hour answering machine)	(0114) 2712018
Inflammatory Bowel Disease help line	(0114) 2712209 (RHH), (0114) 2269031 (NGH
Oral Medicine, Charles Clifford Dental hospital	(0114) 2268669
On call specialist via RHH switchboard:	(0114) 2711900
Neurology	(0114) 2711598

Patient information leaflets

These are provided to patient by secondary care, but can also be downloaded from - www.arthritisreasearchuk.org

These can be made available electronically to practices from Rheumatology and Gastroenterology.

A wide range of leaflets can also be downloaded from the British Association of Dermatologists website. There are specific leaflets here.

Information leaflets are also available from Crohn's and Colitis UK
http://www.crohnsandcolitis.org.uk/Resources/CrohnsAndColitisUK/Documents/Publications/Drug-Info/Azathioprine%20and%20Mercaptopurine.pdf

References

BSR DMARD guidelines
https://academic.oup.com/rheumatology/article/56/6/865/3053478

Full list of side-effects is given in the azathioprine / mercaptopurine summary of product characteristics (SPC), available from www.emc.medicines.org.uk

Current BNF:
https://www.medicinescomplete.com/mc/index.htm
UKMI Drug Monitoring Document:
https://www.sps.nhs.uk/wp-content/uploads/2017/12/Drug-monitoring-2017.pdf

IBD information:
http://www.crohnsandcolitis.org.uk/Resources/CrohnsAndColitisUK/Documents/Publications/Drug-Info/Azathioprine%20and%20Mercaptopurine.pdf

Green Book – shingles:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/357155/Green_Book_Chapter_28a_v0_5.pdf

NICE NG130 - Ulcerative colitis: management (May 2019)
https://www.nice.org.uk/guidance/ng130

NICE NG 129 - Crohn's disease: management (May 2019)
https://www.nice.org.uk/guidance/ng129

Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011. doi:10.1136/gut.2010.224154. Available from:
https://gut.bmj.com/content/60/5/571

Supporting information for unlicensed indications:

Kuks JB, Djojoatmodjo S, Oosterhuis HJ. Azathioprine in myasthenia gravis: observations in 41 patients and a review of literature. Neuromuscular Disorders. 1991;1(6):423-31.

Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology. 1998;50(6):1778-83.

Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, et al. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. European Journal of Neurology. 2006;13(7):691-9.

Costanzi C, Matiello M, Lucchinetti CF, Weinshenker BG, Pittock SJ, Mandrekar J, et al. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology. 2011;77(7):659-66.

Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. Neurology. 1998;51(4):1219-20.

Casetta I, Iuliano G, Filippini G. Azathioprine for multiple sclerosis. Cochrane Database of Systematic Reviews. 2007(4).

Saenz A, Ausejo M, Shea B, Wells G, Welch V, Tugwell P. Pharmacotherapy for Behcet's syndrome. Cochrane Database of Systematic Reviews. 2000(2).