SHARED CARE GUIDELINE FOR THE USE OF THIOPURINES IN ADULTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

INDICATION

The British Society of Gastroenterology Guideline for the management of inflammatory bowel disease in adults (2011) states: "Azathioprine (AZA) or mercaptopurine (MP) are widely used in ulcerative colitis and Crohn's disease as adjunctive therapy and as corticosteroid-sparing therapies although they are unlicensed therapies for IBD. Their slow onset of action precludes usage as sole therapy for active disease. Purine antimetabolites inhibit ribonucleotide synthesis, but the mechanism of immunomodulation is by inducing Tcell apoptosis by modulating cell (Rac1) signalling.140 AZA is non-enzymatically metabolised to MP, which involves loss of a nitro-imidazole side chain; this is thought to explain some of the side effects seen with AZA and which may be less of a problem with MP.141 142 MP is subsequently metabolised to 6-thioguanine nucleotides (6-TGN). 6-TGN has been used for treatment of IBD, but caution is appropriate because of potential hepatotoxicity.

Thiopurines are effective maintenance therapy for patients with ulcerative colitis who have failed or who cannot tolerate mesalazine and for patients who require repeated courses of steroids, although the data quality has been cited as poor in a recent Cochrane review and the evidence for using thiopurines in ulcerative colitis is weaker than in Crohns disease: probably the best study to date is Ardizzone et al which found steroid-free, clinical and endoscopic remission in 53% patients on AZA compared with 21% given 5-ASA (OR on ITT 4.78, 95% CI 1.57 to 14.5). Thiopurines are effective for both induction and maintenance of remission in Crohn's disease. A Cochrane review of the efficacy of AZA and MP for inducing remission in active Crohn's disease demonstrated a benefit for thiopurine therapy compared to placebo with an OR of 2.43 (95% CI 1.62 to 3.64). This equates to a number needed to treat (NNT) of about five and a number needed to harm (NNH) of 14. Their efficacy at maintaining remission is confirmed in another Cochrane review. The OR for maintenance of remission with AZA was 2.32 (95% CI 1.55 to 3.49) with a NNT of six. The OR for maintenance of remission with MP was 3.32 (95% CI 1.40 to 7.87) with a NNT of four. Higher doses of AZA improved response. Withdrawals due to adverse events were more common in patients treated with AZA (OR 3.74; 95% CI 1.48 to 9.45, NNH¼20) than with placebo"

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of a thiopurine can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Patients should only be prescribed thiopurines if the patient can be adequately monitored for toxic effects throughout the duration of the therapy. Particular care should be taken to monitor haematological response and to reduce the maintenance dosage to the minimum required for clinical response.

Specialist Responsibilities	
1	Discuss with the patient the benefits and side effects of the treatment and the importance of regular blood tests.
2	To check any interactions between thiopurines and the patient's medication of which they are currently taking and aware of.
3	Send letter to the GP requesting to take part in Shared Care Agreement.
4	Initiation and stabilisation of the treatment with supply of hospital prescriptions for suitable quantities to last until the transfer of the prescribing and monitoring responsibilities to primary care (up to three months)
5	To carry out all applicable baseline tests.
6	To regularly review the patient's condition and their response to the therapy.
7	To communicate to the GP the transfer of prescribing and monitoring under this Shared Care Agreement.
8	To notify the GP of any dose changes or if therapy is to be discontinued upon specialist review.
9	To inform GP of any patient who fails to attend outpatient appointments.
10	To ensure there is a clear arrangement for quick referral or for additional advice and support to the consultant.

General Practitioner Responsibilities	
1	To respond to the request for shared care as soon as is practicable.
2	To monitor the patients overall health and wellbeing.
3	To ensure the consultant is aware of any regular and acute medication.
4	To report and seek advice from the consultant on any aspect of the patient's care which is of concern to the GP and may affect the treatment.
5	To continue to prescribe for and monitor the patient as per shared care agreement after transfer of responsibility.
6	To report any adverse, significant or unexpected events to the consultant and also the MHRA via the yellow card scheme www.yellowcard.mhra.gov.uk
7	To adjust the dose or discontinue the therapy in accordance with the specialist teams instructions where necessary.

Patient's role (or that of carer)	
1	To alert healthcare professionals to the treatment when receiving any new medicines, either purchased or prescribed.
2	To agree to attend regular clinic appointments and to have regular blood tests.
3	To report any adverse effects to their consultant, IBD nurse and or GP.
4	To share any concerns in relation to their treatment with thiopurines.
5	To report to the consultant or the GP if they do not have a clear understanding of the treatment or there are changes which may affect disease management, e.g. pregnancy or exposure to chicken pox/shingles.
6	To read any written information given to them regarding their treatment including the Patient Information Leaflet.

SUPPORTING INFORMATION

Dosage and Administration

Tailoring or optimisation of thiopurine therapy can occur prior to or during treatment. The appropriate maintenance dose of AZA is 2-2.5 mg/kg/day and of MP is 0.75-1.5 mg/kg/day in both ulcerative colitis and Crohn's disease. The 'maximum' dose will differ between individuals and effectively means that level at which leucopenia develops.

If patients are deficient in thiopurine methyltransferase deficiency, the enzyme which metabolises the thipurines, the dosage used may be substantially reduced.

The SPC for azathioprine states "The tablet should be taken with at least a glass of liquid (200 ml)."

Monitoring

Initial monitoring under secondary care responsibility:

- Locally FBC, creatinine / calculated GFR, ALT and / or AST and albumin every 1-2 weeks for 8-10 weeks then 3 monthly FBC's, creatinine / calculated GFR, ALT and / or AST and albumin. Secondary care may check TPMT prior to initiation,and TGN/MMPN levels at 6-10 weeks and adjust dose accordingly.

Ongoing primary care responsibility:

- FBC, creatinine / calculated GFR, ALT and / or AST and albumin at least every 12 weeks

Contraindications

Hypersensitivity to the active substance (azathioprine or mercaptopurine) or to any of the excipients.

Cautions

- Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts.
- Co-administration of ribavirin and a thiopurine is not advised.
- In patients with renal and/or hepatic insufficiency, consideration should be given to reducing the dosage

Pregnancy and breast feeding

The SPCs suggest a careful assessment of the risks vs. benefit when considering the use of thiopurines in pregnancy therefore the patient should be discussed with/referred to their IBD team for pre-conception, pregnancy and breast feeding advice prior to any adjustments in thiopurine dose being made. European Crohns and Colitis consensus document supports involvement of the IBD team in all stages, from pre-conception to postpartum.

Side effects

Very common side effects include bone marrow suppression, leucopenia and thromobocytopenia.
Common side effects include nausea, vomiting, biliary stasis, hepatoxicity and pancreatitis.
Refer to SPCs for further information on adverse effects.

Interactions

- Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol, which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid.
- There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfazalazine) inhibit the TPMT enzyme.
- Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with thiopurines; therefore higher doses of the anticoagulant may be needed.
- Where possible, concomitant administration of cytostatic drugs, or drugs which may have a myelosuppressive effect, such as penicillamine, should be avoided.
- Azathioprine can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and can reduce the blockade produced by non-depolarising agents such as tubocurarine.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs:

Azathioprine	Mercaptopurine
Azathioprine 25mg Tablets x28 £2.01 **Azathioprine 50mg Tablets x 56 £2.21**	**Mercaptopurine 50mg Tablets x 25 £49.15**

References

Summary of Product Characteristics – Mercaptopurine - www.medicines.org.uk updated August 2016, accessed November 2016.

Summary of Product Characteristics – Azathioprine - www.medicines.org.uk updated October 2016, accessed November 2016.

Guidelines for the management of inflammatory bowel disease in adults - http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/ibd/ibd_2011.pdf Published 2011, accessed November 2016.

For current pricing www.drugtariff.nhsbsa.nhs.uk accessed November 2016.

Crohn's disease management: NICE Clinical Guideline CG152 www.nice.org.uk/guidance/CG152 Published October 2012, accessed November 2016.

Ulcerative Colitis: Management: NICE Clinical Guideline CG166 www.nice.org.uk/guidance/cg166 Published June 2013, accessed November 2016.

The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease: http://ecco-jcc.oxfordjournals.org/content/9/2/107, accessed November 2016

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