NHS Herefordshire Clinical Commissioning Group

Wye Valley NHS Trust

Shared Care Guidelines

AZATHIOPRINE AND MERCAPTOPURINE

In Inflammatory Bowel Disease

INTRODUCTION

Azathioprine is an immuno-modulatory agent that is used to induce and maintain remission in Ulcerative Colitis and Crohn's Disease. Azathioprine is a pro-drug, which is cleaved rapidly in the liver to 6-mercaptopurine. Although unlicensed to treat these indications, their use is widely established in Inflammatory Bowel Disease (see BNF Section 1.5). The main toxic effect is myelosuppression, although hepatotoxicity is also well recognised.

DOSE AND ADMINISTRATION

Azathioprine
The initial oral dose is 50mg once daily for 2 weeks, and then gradually increased in 50mg increments every 2 weeks to 2 – 2.5 mg/kg daily, if tolerated.

Mercaptopurine
The initial oral dose is 25mg once daily for 2 weeks, and then gradually increased in 25mg increments every 2 weeks to 1 – 1.5 mg/kg daily, if tolerated.

Clinical response can usually be expected in 6-12 weeks.

ADVERSE EFFECTS

- Nausea, diarrhoea, vomiting anorexia, and abdominal discomfort.
- Hepatotoxicity (hepatic necrosis, biliary stasis)
- Bone marrow suppression (leucopenia, thrombocytopenia) and therefore increased risk of infection.
- Oral ulceration, rarely gastrointestinal ulceration?
- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hyptotension, dizziness)
- Rarely pancreatitis, interstitial nephritis.
- Alopecia

See BNF 8.2.1 for comprehensive list.

The patient should be advised to report any signs of bone marrow suppression (i.e. infection, fever, unexplained bruising or bleeding to the GP, this should then be reported to the hospital specialist clinician or IBD nurse.

CAUTIONS

- **Avoid prescribing Allopurinol in patients on Azathioprine/Mercaptopurine due to a clinically significant interaction that can lead to increased Azathioprine/Mercaptopurine toxicity.**
- Increased risk of haematological toxicity with co-trimoxazole/trimethoprim.
- Patients should avoid 'live' vaccines such as oral polio, oral typhoid, MMR, BCG and yellow fever, whilst on immunosuppressive therapy. Contact hospital specialist for advice on any vaccinations if required.
- Patients should try to avoid contact with people who have active chickenpox or shingles and should report any such contact to their GP or hospital specialist.
- Anticoagulant effect of warfarin possibly reduced by Azathioprine/Mercaptopurine.
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breast-feeding. Consult hospital specialist clinician or IBD nurse.

CONTRAINDICATIONS

- Moderate/severe renal or liver impairment
- Significant haematological impairment
- Thiopurine methyltransferase (TPMT) deficiency
- Hypersensitivity to Azathioprine/Mercaptopurine

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MONITORING STANDARDS FOR AZATHIOPRINE/MERCAPTOPURINE AT HEREFORD HOSPITALS NHS TRUST		
Record all blood results in the patient held record book.		
Pre-treatment Monitoring	FBC, U&E's, LFT's, CRP, TPMT phenotype	
Subsequent Monitoring	FBC	Every week for 2 months then monthly for 4 months, then if stable 3 monthly thereafter.
	LFT's	Every week for 2 months then monthly for 4 months, then if stable 3 monthly thereafter.
	CRP	As required to assess response to treatment.

ACTION AND ADVICE FOR GP'S IN RESPONSE TO BLOOD MONITORING/SIDE-EFFECTS	
Blood Test Results	**Action**
Lymphocytes **<0.5 x 10^9/L (on more than 3 consecutive occasions)**	Discuss with IBD nurse or specialist hospital clinician.
Neutrophils **< 1.5 x 10^9/L** **< 1.0 x 10^9/L**	Discuss with IBD nurse or specialist hospital clinician. **Stop drug** and discuss with IBD nurse or hospital specialist clinician.
Platelets < 100 x 10^9/L	Discuss with hospital IBD nurse or hospital specialist clinician.
Liver function tests >2 fold rise in AST, ALT (from upper limit of reference range) > 4 fold rise in AST, ALT > 50% rise in Alk p'ase (from upper limit of reference range)	Contact IBD nurse or hospital specialist clinician. **Stop drug** and contact IBD nurse or hospital specialist clinician **immediately.**
Symptoms	**Action**
Rash (significant new)	**Stop drug and check FBC**. If FBC abnormal contact IBD nurse or hospital specialist clinician. Wait until rash resolved and consider restarting at reduced dose, providing no blood dyscrasias.
Severe or persistent infections, fever, chills **Persistent sore throat**	**Stop drug**, **check FBC** and contact IBD nurse or hospital specialist. Do not restart until results of FBC known. If sore throats, take FBC, and discuss with hospital specialist.
Abnormal bruising or bleeding	**Stop drug until recovery** and check FBC. Do not restart if blood test abnormal, contact IBD nurse or hospital specialist clinician.
Varicella	Consider passive immunisation if patient has no PMH of varicella infection.
Nausea	Advise patient to divide dosage and take with food. If no improvement, reduce dosage or stop and contact IBD nurse or hospital specialist clinician if reducing dose ineffective.

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SHARED CARE RESPONSIBILITIES

Consultant and/or IBD Nurse

1. Initiate treatment and supply the first month of treatment or until the patient is stabilised
2. Send a letter to the GP requesting shared care for this patient.
3. Routine clinic follow-up on a regular basis.
4. Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
5. Evaluate any reported adverse effects by GP or patient.
6. Advise GP on review, duration or discontinuation of treatment where necessary.
7. Inform GP of patients who do not attend clinic appointments.
8. Ensure that backup advice is available at all times.

General Practitioner

1. Monitor patient's overall health and well being.
2. Prescribe the drug treatment as described.
3. Monitor blood results (FBC, U+E's and LFT's, CRP) in line with recommendations from hospital specialist.
4. Report any adverse events to the hospital specialist, where appropriate.
5. Help in monitoring the progression of disease.
6. Complete blood monitoring details in Patient Held Record Book.

CONTACT NUMBERS FOR ADVICE AND SUPPORT

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics and British National Formulary.