Oxford University Hospitals NHS
NHS Trust

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Clinical Commissioning Group

MERCAPTOPURINE
Shared Care Protocol

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

Background for Use

Mercaptopurine is used as a disease–modifying agent to help induce and maintain remission in ulcerative colitis and Crohn's disease. It is used in patients who require additional courses of corticosteroids, or in those in whom the condition relapses as steroids are withdrawn. It is increasingly used at a very early stage (within a few weeks of diagnosis) in some patients who are likely to have particularly troublesome disease. Such patients include young people who present with perianal or proximal small intestinal Crohn's disease, or have Crohn's disease in three or more locations. It is often referred to as a "steroid sparing agent" or "immunomodulator." Although **unlicensed to treat these indications**, its use has been widely established in Inflammatory Bowel Disease (IBD) over the past 50 years. If tolerated, patients are usually on mercaptopurine for about 5 years.

Mercaptopurine is usually initiated in IBD patients who are unable to tolerate azathioprine. Of the 30% of patients who are intolerant to azathioprine, two thirds will tolerate mercaptopurine.

Mercaptopurine should only be initiated by, or under the direction of, a hospital Gastroenterologist in the treatment of inflammatory bowel disease.

Supporting Information

- 70% patients can take mercaptopurine without any side-effects
- Steroid-withdrawal in 70% able to tolerate mercaptopurine
- Steroid-free remission maintained for more than a year in 70% tolerating mercaptopurine
- Reduces risk of post-operative relapse after resection for Crohn's disease by a factor of 4
- Protects against colorectal cancer in patients with extensive colitis for >10 years

Contraindications and Precautions

Contraindications	Action
Leucopenia	Avoid. See monitoring below
Porphyria	Avoid
Thiopurine Methyltransferase (TPMT) deficiency	Avoid
Concomitant therapy with Allopurinol	Avoid, or exceptionally reduce dose of mercaptopurine by 75% of original dose and use metabolite monitoring.
Cautions	**Action**
Moderate/Severe renal impairment	Monitor more closely and potentially reduce dose. • GFR ml/min 10 – 50: Reduce dose by 25%. • GFR ml/min <10: Reduce dose by 50%.
Liver impairment	Monitor more closely
Alcohol	Safe in moderation but may aggravate nausea.
Drugs that cause myelosuppression	Reduce dose (for allopurinol see above).
Pregnancy and breastfeeding	Patients who become pregnant on whilst on mercaptopurine should be referred to the IBD specialist and obstetric physician, so that the use of the drug can be discussed. Mercaptopurine is generally best continued, as active IBD in the mother is a greater risk of harm to the foetus than mercaptopurine. Evidence has shown that the benefits of breast feeding outweigh any theoretical risks of taking mercaptopurine (minimal or no evidence that drug metabolites can be detected in breast milk). The daily dose should be taken immediately after a feed.
Family Planning	Patients should be advised on adequate contraceptive precautions (for both males and females). Patients planning on becoming pregnant should discuss with the continued benefit of mercaptopurine with the Gastroenterologist.

Dosage
Inflammatory Bowel Disease:

- 1mg to 1.5mg/kg daily by mouth.
- The dose should be taken with or soon after food (it can cause stomach irritation).
- The maximum dose rarely exceeds 100mg.

Preparations available
Available as 50mg tablets. Tablets are scored so minimum dose adjustment is 25mg. The tablets disperse in water.

Time to Response
Up to 3 months.

Pre-Treatment Assessment
Baseline U&E's, LFTs, FBC and TPMT activity should be carried out prior to initiation of therapy by a hospital gastroenterologist. Mercaptopurine should not be taken if TPMT activity is deficient (very low or absent). Lower treatment doses should be considered if TPMT activity is below normal but not deficient[5]. This will be checked by the specialist before initiating treatment, TPMT results will also be available on the ePR for the GP to view.

Patients should be supplied with an information leaflet from the manufacturers and an in-house patient information leaflet from the Gastroenterology Unit (available on OxWeb).

Ongoing Monitoring
U&E's, LFTs and FBC should be performed 2 weeks after starting therapy or dose adjustment, then at 4 weeks, then every 3 months.

Patients should be counselled on recognising signs of illness or side effects such as unexplained bruising, bleeding, sore throat, fever or malaise, and contact their doctor/IBD service immediately.

They should also be advised to notify their GP if they have close contact with anyone who has chicken pox or shingles. The GP should reassure the patient that they are unlikely to come to any harm and check VZV antibody status to see whether they are already immune (usually done at diagnosis). If they are not immune, then liaise with virologists (Katie Jeffrey) about role of prophylactic anti-viral therapy, although this will rarely be indicated. If chicken pox/zoster do appear, then liaise with virologists about treatment (hyperimmune globulin rarely indicated) and **stop mercaptopurine**. Inform gastroenterology if this occurs.

Actions to be taken

Side Effects	Action
WBC < 3 x 10^9/L	Withhold and contact the relevant hospital gastroenterologist
Neutrophils < 1.5 x 10^9/L	Withhold and contact the relevant hospital gastroenterologist
Platelets < 130 x 10^9/L	Withhold and contact the relevant hospital gastroenterologist
AST/ALT > 3 x normal range	Withhold and contact the relevant hospital gastroenterologist
Significant reduction in renal function	Withhold and contact the relevant hospital gastroenterologist
Mouth or throat ulceration	Rare, withhold and re-challenge at a lower dose. Consider possibility of BMD.
Rash	Withhold until rash clear and re-challenge at a lower dose.
Unexplained bleeding/bruising	Withhold and check FBC. Contact the relevant gastroenterologist.
Fever	Withhold and contact the relevant hospital gastroenterologist
Upper abdominal or back pain	Withhold and contact the relevant hospital gastroenterologist
Alopecia	Rare. Stop if severe.
Recurrent sore throats, infections, fever or chills	Withhold and contact the relevant hospital gastroenterologist
Nausea and vomiting	Common, usually 2-3 weeks after starting therapy. Nausea may be relieved by taking the dose with/after food or in divided doses. Otherwise, stop and contact the relevant hospital gastroenterologist.
Diarrhoea	Common, as with nausea or vomiting (above). Contact the relevant hospital gastroenterologist.

In addition to absolute values for haematological indices, a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance. In order to monitor trends it is recommended that all blood test results are entered in patient held monitoring booklet/card.

Vaccination

Seasonal influenza vaccination is recommended, as well as standard vaccination strategy for any patient with IBD (H1N1) (swine-flu) vaccination, pneumococcal polysaccharide vaccine, HPV according to national guidance and hepatitis B for selected patients. Live vaccines must be avoided. Inactivated polio is available although sub-optimal response may be seen.

Notable Drug Interactions (Refer to BNF and SPC)

- When co-prescribed with allopurinol/oxipurinol/thiopurinol, the dose of mercaptopurine should be reduced to one quarter of the original dose.
- Trimethoprim & co-trimoxazole (increased risk haematological toxicity)
- Warfarin (reduced anticoagulant effect). Monitor INR more closely at initiation of treatment in patients taking warfarin.
- Aminosalicylate derivatives, e.g. olsalazine, mesalazine, sulfasalazine inhibit the TPMT enzyme. Combined prescriptions are common in ulcerative colitis, however caution is advised by the manufacturers.
- Ribavirin – avoid concomitant use

Back-up Information and Advice

John Radcliffe Hospital	01865 741166 (switchboard)
Professor Simon Travis (IBD Consultant)	01865 228753 or simon.travis@ndm.ox.ac.uk
Dr Oliver Brain (IBD Consultant)	01865 228760 or oliver.brain@ndm.ox.ac.uk
IBD Advice Line (useful point of contact)	01865 228772
Gastroenterology Registrar	Bleep 4084. Out-of-hours contact switchboard for on-call SpR
Sarah Cripps (Consultant Gastroenterology Pharmacist)	Bleep 1084

References

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